MRI as a Means to Measure Lung Function: Non-Invasive Imaging in Neonates and Young Children

NCT02163681

December 4, 2017

IRB-HSR PROTOCOL

Investigator Agreement

BY SIGNING THIS DOCUMENT, THE INVESTIGATOR CONFIRMS:

1. I am not currently debarred by the US FDA from involvement in clinical research studies.
2. I am not involved in any regulatory or misconduct litigation or investigation by the FDA.
3. That if this study involves any funding or resources from an outside source, or if you will be sharing data outside of UVA prior to publication that you will contact the Dean's office regarding the need for a contract and letter of indemnification. If it is determined that either a contract or letter of indemnification is needed, subjects cannot be enrolled until these documents are complete.
4. The proposed research project will be conducted by me or under my close supervision. It will be conducted in accordance with the protocol submitted to and approved by the IRB including any modifications, amendments or addendums submitted and approved by the IRB throughout the life of the protocol.
5. That no personnel will be allowed to work on this protocol until they have completed the IRB-HSR On-line training and the IRB-HSR has been notified.
6. That all personnel working on this protocol will follow all IRB-HSR Policies and Procedures as stated on the IRB-HSR Website http://www.virginia.edu/vprgs/irb/ and on the School of Medicine Clinical Trials Office Website: http://knowledgelink.healthsystem.virginia.edu/intranet/hes/cto/sops/sop_index.cfm
7. I will ensure that all those delegated tasks relating to this study, whether explicitly or implicitly, are capable through expertise, training, experience or credentialing to undertake those tasks.
8. I confirm that the implications of the study have been discussed with all Departments that might be affected by it and have obtained their agreement for the study to take place.
9. That no subjects will be recruited or entered under the protocol until the Investigator has received the signed IRB-HSR Approval form stating the protocol is open to enrollment
10. That any materials used to recruit subjects will be approved by the IRB-HSR prior to use.
11. That all subjects will sign a copy of the most current consent form that has a non-expired IRB-HSR approval stamp.
12. That any modifications of the protocol or consent form will not be initiated without prior written approval from the IRB-HSR, except when necessary to eliminate immediate hazards to the subjects.
13. Any significant findings that become known in the course of the research that might affect the willingness of subjects to enroll or to continue to take part, will be promptly reported to the IRB.
14. I will report immediately to the IRB any unanticipated problems involving risk to subjects or to others including adverse reactions to biologics, drugs or medical devices.
15. That any serious deviation from the protocol will be reported promptly to the Board in writing.
16. That any data breach will be reported to the IRB, the UVa Corporate Compliance and Privacy Office , UVa Police as applicable.
17. That the continuation status report for this protocol will be completed and returned within the time limit stated on the form.
18. That the IRB-HSR office will be notified within 30 days of a change in the Principal Investigator or of the closure of this study.

19. That a new PI will be assigned if the current PI will not be at UVA for an extended period of time. If the current PI is leaving UVa permanently, a new PI will be assigned PRIOR to the departure of the current PI.
20. All study team members will have access to the current protocol and other applicable documents such as the IRB-HSR Application, consent forms and Investigator Brochures.
21. Signed consent forms and other research records will be retained in a confidential manner. Records will be kept at least 6 years after completion of the study.
22. No data/specimens may be taken from UVa without a signed Material Transfer Agreement between OSP/SOM Grants and Contracts Office and the new institution. Original study files are considered institutional records and may not be transferred to another institution. I will notify my department administration regarding where the originals will be kept at UVa. The material transfer agreement will delineate what copies of data, health information and/or specimens may be taken outside of UVa. It will also approve which HIPAA identifiers may be taken outside of UVa with the health information or specimens.
23. If any member of study team leaves UVa, they are STRONGLY ENCOURAGED to use Exit Checklist found on IRB-HSR website at http://www.virginia.edu/provost/facultyexit.pdf.

The IRB reserves the right to terminate this study at any time if, in its opinion, (1) the risks of further experimentation are prohibitive, or (2) the above agreement is breached.

Investigators Experience

Y. Mike Shim, MD has been involved in the areas of COPD research for the past 10 years with a number of NIH and foundation grants. He is also the director of the COPD clinic, PFT laboratory and pulmonary rehabilitation in which he manages a large number of patients with complicated lung diseases including COPD. He has collaborated on a number of hyperpolarized gas imaging protocols.

Dr. Altes is a leader in the field of functional lung imaging using MRI. She is a pediatric radiologist at the University of Virginia, a Hartwell Center of Biomedical Research, who has pioneered novel applications of lung imaging using hyperpolarized gas MRI in children with cystic fibrosis. Dr. Altes has been working on fast MRI and gas delivery methods for imaging of babies and has extensive experience in applying functional imaging techniques in adults and older children with cystic fibrosis

Signatures

Principal Investigator

_____	_____	_____
Principal Investigator Signature	Principal Investigator Name Printed	Date

The Principal Investigator signature is ONLY required if this is a new protocol, a 5 year update or a modification changing the Principal Investigator.

Department Chair

BY SIGNING THIS DOCUMENT THE DEPARTMENT CHAIR AGREES:

1. To work with the investigator and with the board as needed, to maintain compliance with this agreement.
2. That the Principal Investigator is qualified to perform this study.
3. That the protocol is scientifically relevant and sound.

_____	_____	_____
Department Chair or Designee Signature	Department Chair or Designee Name Printed	Date

The person signing as the Department Chair cannot be the Principal Investigator or a sub-investigator on this protocol.
The Department Chair or Designee signature is ONLY required if this is a new protocol or a modification changing the Principal Investigator.

Brief Summary/Abstract

The purpose of this study is to further develop the techniques to permit the imaging of infant lungs with hyperpolarized helium-3 MRI including techniques for acquisition in free breathing infants and infants on a ventilator. We have developed fast imaging techniques and obtained proof-of-concept data in infants as young as 2 months old. Many pediatric lung diseases including CF, bronchopulmonary dysplasia (BPD) and asthma have their origins in infancy so it would be desirable to be able to image infants with hyperpolarized gas MRI. We focused on developing fast imaging techniques to, in essence, freeze lung motion in non-sedated infants. We feel the technique will be more widely adopted if clinically useful images can be obtained without sedating the infant. Some very rapid imaging techniques have been developed for conventional proton MRI for applications such as cardiac MRI that require very short acquisition time. We modified these techniques for use in hyperpolarized gas MRI and developed a technique that permits the acquisition of the entire lung volume of an infant in less than 1 second. These techniques would also be useful for imaging infants who are still on a ventilator with the hope of increasing our understanding of lung development and neonatal lung disease. This is a technical development and proof-of-concept study. From our prior experience developing new techniques for hyperpolarized gas MRI, we anticipate 60 subjects will be required for the sequence development portion of the study. An additional 30 subjects [10 healthy, 10 with CF, and 10 bronchopulmonary dysplasia (BPD)] will be imaged as part of the proof of concept study. As a Phase I pilot technology development and proof of concept study, no formal statistical analyses are planned.

NOTE: Infants (under one year of age) who are ventilator dependent will not be enrolled until more data is available on non-ventilator dependent infants (under one year of age). The infant data must be reviewed and approved by the IRB-HSR before ventilator dependent infants may be enrolled.

Background

1. Provide the scientific background, rationale and relevance of this project.

Development of Rapid Imaging Techniques for use in Infants: Today, there is a fundamental requirement for a safe, non-invasive method for assessing the character and severity of childhood obstructive lung diseases in early development. To meet this unmet need, we are developing rapid helium MRI of the lung in non-sedated infants and children. This innovation will make it possible for the first time to provide important insights for the clinical management of pediatric lung disease in this population at risk. In this regard, we propose to deploy our approach for measurement of lung function in healthy children, cystic fibrosis (CF) (a progressive disease that substantially alters lung function with substantially reduced life expectancy), and BPD (chronic lung disease of prematurity). While it is possible to identify babies with these diseases, there are essentially no tools available to evaluate the efficacy of therapies that may prevent irreversible damage to the lungs. This study will enable imaging of lung function at the earliest stages of lung disease to allow intervention at the earliest stages of disease.

Despite widespread newborn screening and significant improvements in the management of CF, the severity of the associated pulmonary disease increases with age, culminating in life-threatening complications. Fortunately, in recent years several promising new therapies have emerged. However, the greatest impediment to the clinically meaningful evaluation of treatment outcomes remains the lack of an adequate measure of lung function in neonates and young children.

With the advent of surfactant therapy, prenatal steroid treatment of mothers in premature labor, and changes in ventilator support of premature infants, the mortality from lung disease has substantially decreased but the incidence did not decrease. The current thought is that the development of the lung in premature infants is altered resulting in a disruption of alveolar development. Early intervention with a treatment that would improve alveolar development could greatly improve the lives of these children. Our hope is that if our technical development is successful, hyperpolarized helium-3 could be used as an outcome measure in clinical trials of such treatments.

Conventional measures of pulmonary function like spirometry and forced expiratory volume in 1 second (FEV1) (CF Registry 2008 Report, p. 8) are not very specific, as over 90% of 6 year old children with CF are reported as having normal lung function. Computed tomography (CT) has been proposed as an alternative imaging-based biomarker of the disease, since it has been shown to detect abnormalities like wide spread inflammation of the airways. Unfortunately, CT requires ionizing radiation; severely limiting its use in longitudinal studies (de Jong, Nakano et al. 2006; de Jong, Tiddens et al. 2008), as well as an assessment tool for developing neonates and young children, who are more radiation-sensitive than adults.

For non-invasive imaging of lung function in neonates and young children with CF, we propose the use of magnetic resonance imaging (MRI), which provides both morphologic and functional data, but does not use ionizing radiation. At UVA we have been a leader in the development of hyperpolarized gas MRI, and published the first report of the change in hyperpolarized gas MR image findings with treatment in CF (1). We also pioneered the use of a fast imaging technique called spiral imaging in hyperpolarized gas MRI (2). We performed a small proof-of-concept study in infants that has been submitted for publication.

This research will continue to optimize the fast imaging methods for neonates and young children and perform a larger pilot study in healthy infants, and infants with CF and BPD.

Review of Adverse Events in Pediatric Subjects who Underwent Helium MRI at UVa

As part of this 5-year protocol update, we reviewed the AE data from all pediatric subjects who underwent a helium MRI at UVa from the beginning of our first protocol that included pediatric subjects through March 2017. During this period, we performed both investigator-initiated and industry-sponsored research.

- As described in more detail below, in the investigator initiated trials, 121 children were imaged and there were 6 AEs (5.0%) that were possibly/probably/definitely related to the helium, a rate less than that found in adult subjects. All possibly/probably/definitely related AEs were mild and not serious.
- In the Vertex Pharmaceuticals trial 5 children were imaged and there was one AE in one subject that was considered possibly related to the helium. This was a sore throat that developed 8 days following imaging with helium.
- In the TEVA sponsored trial, between June 2016 and March 6, 2017, 14 subjects were imaged on multiple study visits. In these 14 subjects, there were 7 AEs considered possibly/probably/definitely related to the helium. In addition in this trial, the manual of procedures required expected, mild, transient side effects of the helium inhalation be recorded as adverse events. In our other trials, such side effects are recorded in our case report form and tabulated in our yearly report to the FDA under our IND.

Investigator Initiated Trials: Under this protocol and other investigator-initiated protocols at UVA, 121 children aged 1 month to 17 years underwent hyperpolarized helium MRI between July 2001 and March 2017. Of these, 43 had asthma, 42 were healthy, 25 had a history of BPD, 10 had CF, and 1 had a congenital lung lesion. An additional 5 children were enrolled in studies but were not dosed with hyperpolarized helium due to inability to cooperate with the exam (ages 3, 4, 5, 6, and 7 years). No children on ventilators have been enrolled. In the 121 children imaged, there were 6 AEs (5.0%), a rate less than that found in adult subjects. All AEs were mild and not serious. Details of the possibly/probably/and definitely related AEs are given in Table 1.

		Diagnosis/Indication							
Age Ranges	# Subjects Imaged	Asthma	CF	BPD	Healthy	Other	# AEs Not Related to Helium	# AEs Possibly/Probably /Definitely Related to the Helium	Descriptive Summary AEs Possibly/Probably/Definitely Related to Helium Gas
Age < 1year	5	0	3	1	1	0	0	1	One AE in a 10 month old male with cystic fibrosis, on the day after imaging, began vomiting in the middle of the day, due to increased mucus. The AE resolved within a few hours after treatment with some suctioning. The family reported that he has a history of these type of episodes, with the last one about 6 weeks ago. This AE is considered, mild, not serious, expected and possibly related to the helium gas.
Ages 1 - 6 years	41	15	4	8	14	0	1	3	Three AEs in three subjects were considered mild, not serious, expected, and possibly related to helium gas and include chest soreness in a 5 year old, a sore throat and headache in a 6 year old, and a fever in a 2 year old that developed two days after imaging; The subject with a fever was treated by their parents with an antipyretic. All others recovered without treatment.
Ages 7-15 years	66	22	1	16	26	1	1	2	Two AEs in two subjects were considered mild, not serious, expected, and possibly related to helium gas and include dizziness in a 14 year old which resolved without treatment; and warm to the touch and a cough in a 11 year old who underwent a clinical bronchoscopy on the same day as imaging. The 11 year old was treated by her mother with tylenol and symptoms resolved by the following morning.
Ages 16-17 years	9	6	2	0	1	0		None	
Total	**121**	**43**	**10**	**25**	**42**	**1**	**2**	**6**	

Table 1: Enrollment data and Adverse Events (AE) for pediatric subjects who underwent hyperpolarized helium MRI in investigator initiated studies from July 2001 to March 2017.

Industry Sponsored, Vertex Pharmaceuticals:
In addition, in an industry sponsored trial (sponsor: Vertex), 5 children were imaged. There was one AE of a sore throat occurring 8 days after imaging with helium in one subject that was considered possibly related to the helium as detailed in Table 2.

		Diagnosis/Indication							
Age Ranges	# Subjects Imaged	Asthma	CF	BPD	Healthy	Other	# AEs Not Related to Helium	# AEs Possibly/Probably/ Definitely Related to the Helium	Descriptive Summary AEs Possibly/Probably/Definitely Related to Helium Gas
Age < 1year	0	0	0	0	0	0	0	0	
Ages 1 - 6 years	0	0	0	0	0	0	0	0	
Ages 7-15 years	4	0	4	0	0	0	1	1	One AE was considered mild, not serious, expected and possibly related to the helium gas and included a sore throat that began 8 days after the imaging study.
Ages 16-17 years	1	0	1	0	0	0	2	0	
Total	**5**	**0**	**5**	**0**	**0**	**0**	**3**	**1**	

Table 2: Enrollment data and Adverse Events (AE) for pediatric subjects who underwent hyperpolarized helium MRI in the Vertex sponsored study from October 2010 to February 2013.

Industry Sponsored, TEVA:
In a second industry sponsored trial (sponsor: TEVA), 14 children have been imaged as of March 6, 2017. The study protocol includes 4 imaging time points, and is currently still enrolling. In the Manual of Procedures for this study, common, mild, expected side effects of the helium MRI were specifically required to be reported as AEs: "*Symptoms and side effects associated with helium-3 that are noted on the Helium Dosing Assessment will be documented on the AE CRF and reported to the FDA as part of the annual report, except in cases where expedited reporting is required (i.e. serious and unexpected events)*." For clarity, below we separately report the symptoms/side effects (e.g. transient decrease in pO2 or lightheadedness following helium inhalation) from AEs. Nine of 14 subjects had symptoms/sides effects from the helium MRI, all of which were mild and transient. This is typical in our experience. In other protocols, side effects from the inhalation of the helium are recorded in our case report forms and report to the FDA in our yearly report. Table 3 details the number of side effects and AE's reported for each subject in this trial. All of the possibly/probably/definitely related to helium AEs required no treatment.

Subject Number*	Age at First Study Visit (years)	# Side Effects**	# AEs Not Related to Helium	# AEs Possibly/Probably/ Definitely Related to the Helium	Descriptive Summary AEs Possibly/Probably/Definitely Related to Helium Gas
EXP001	9	6	2	0	
EXP002	6	9	2	1	1 episode of nausea after breathing in the helium gas on only one of the study visits. This study visit occurred directly following a Xolair injection, and the child had not eaten anything, so this was most likely related to having an empty stomach. The nausea subsided quickly.
EXP003	15	9	6	0	
EXP004	11	7	0	1	1 episode of nausea after breathing in the helium gas on only one of the study visits. This event was transient in nature - subject felt better within a minute.
EXP005	7	0	0	0	
EXP006	12	2	5	1	1 episode of a headache considered moderate, not serious, expected and possibly related to the helium gas. Headache could have been related to helium-3 or the child's underlying illness
EXP007	15	6	0	2	2 mild, unexpected, not serious AEs, occurring on one study visit, including transient disorientation for a few seconds following the first helium dose and resoving prior to the administration of the second helium. The subject also experienced tiredness after the initial dose of helium. The subject had an URI infection at the time of the visit, which had started 2 days before the study appointment, and may have contributed to his tiredness.
EXP008	15	3	0	1	1 episode of shortness of breath following dosing with helium gas. This was transient, and resolved less than 10 seconds after the dose. SOB occurred with the first helium dose only. Subject also withheld medications as part of study protocol which may have contribued to the shortness of breath.
EXP009	10	0	0	0	
EXP010	15	1	0	0	
EXP011	9	0	1	1	1 episode of a headache following first full dose of helium, which resolved prior to administration of the second dose
EXP012	7	1	0	0	
EXP013	9	0	0	0	
EXP014	10	0	1	0	
Totals		**44**	**17**	**7**	

*In this protocol, each subject undergoes 4 helium MRIs on 4 different study visits over a several month period

**The 44 reported side effects included 21 instances of transient pO2 drop following the inhalation of the helium gas; 13 instances of lightheadedness following the inhalation of the helium gas; 1 instance of shortness of breath during the MRI; and 9 instances of change in spirometry following dosing with helium gas.

Table 3: Enrollment data and Adverse Events (AE) for pediatric subjects who underwent hyperpolarized helium MRI in the TEVA sponsored study from June 2016 to March 6, 2017.

Hyperpolarized Helium-3 MRI: Hyperpolarized helium-3 (3He) gas magnetic resonance (MR) imaging is a relatively new technique for evaluating the lungs. With this test the lung airspaces are directly visualized by inhaling the hyperpolarized gas. Preliminary studies have shown the potential of visualizing the small airways after inhalation of relatively small quantities of gas, allowing assessment of ventilation abnormalities (3-5). More recent developments including our own have shown that with this technique, an indirect measurement of the lung airspaces, may be obtained by measuring the diffusion of the helium-3 gas in the lungs (6). Preliminary studies have shown that hyperpolarized helium lung MR can potentially be used to assess diffuse lung diseases such COPD (7-10), asthma (11), cystic fibrosis (12). However, the full extent of this technique in evaluating these diseases is yet to be established.

Hyperpolarization of the Helium 3 gas:

1. Original polarizer:

    - The method for polarizing the helium-3 gas uses the technique of spin-exchange optical pumping. The polarization process is performed in a glass cell filled with helium-3 gas and a few milligrams of alkali metal (rubidium).
    - The glass cell is heated to vaporize the alkali metal, and the cell is then illuminated for approximately 10-12 hours with circularly polarized laser light, allowing the helium-3 to become polarized through a process called spin exchange.
    - The alkali metal is needed to facilitate the transfer of spin from the laser light to the helium-3 atoms.
    - After polarization is complete, the cell is cooled down to allow the alkali metal to return to the solid state, and it condenses on the inside of the glass cell.
    - The polarized helium-3 gas is then released from the cell and passes through a 20-micron adsorption filter that removes any residual alkali-metal vapor.
    - The filtered gas is dispensed into a bag and inhaled by the study subject through the mouth for imaging of the lungs, or through the nose for imaging the sinuses using H3He MRI.

2. Second helium polarizer: Built under the direction of Dr. Gordon Cates in the physics department and Dr. Wilson Miller in radiology, it generates larger batch volumes with higher net polarization than our original helium polarizer.

    - The operating principles of the new polarizer are identical to those of the original polarizer. In both systems, helium polarization is carried out in a heated glass cell filled with helium gas and a few milligrams of alkali metal (rubidium and/or potassium). After polarization is complete, the cell is cooled down to allow the alkali metal to return to the solid state. The polarized helium gas is then released from the cell, mixed with medical-grade nitrogen, and dispensed into a dosing bag for inhalation by the subject. All tubing and valves used for handling and dispensing the helium gas were manufactured according to oxygen-clean standards, which is the most stringent cleaning specification for gas-handling systems.

- The only functional difference between the two polarizers is that rubidium is the only alkali metal used in the original polarizer, whereas a mixture of rubidium and potassium is used in the new polarizer. The safety procedures used in the original polarizer, which ensure that none of the alkali metal in the cell escapes into the dispensed helium, are duplicated in the new polarizer:

    - The cell temperature is monitored continuously during the cooling process, and we wait until the cell temperature has been below 40°C (104°F) for at least 30 minutes before dispensing the polarized helium. This ensures that there is enough time for the rubidium and potassium vapor to condense out of the gas phase.

    - The polarized helium is released from the main body of the cell through a capillary stem that precedes the cell valve. The capillary stem provides additional surface area for any residual alkali vapor to condense onto, and ensures that virtually all of the rubidium and potassium remains behind in the glass cell.

    - For good measure, the dispensed helium passes through a 20-micron filter at the outlet port. This filter would remove any solid alkali metal if it happened to escape from the cell, although tests of unfiltered gas show that this step is probably not necessary.

- To verify the effectiveness of these safety measures, helium was polarized according to standard operating procedures, and a standard human dose was dispensed into a gas-sampling bag. This bag was sent to an independent laboratory (Element One, Wilmington, NC) for analysis. The gas sample and the inside surface of the bag were both tested for the presence of rubidium, potassium, and silicon, using exactly the same type of analysis (ICP-MS) that was performed on gas from our original polarizer. No traces of these elements were found at the machine detection limits.

3. Third method for Helium Polarization: As interest in hyperpolarized gas imaging has increased, there is a need to develop a method for providing polarized helium gas to sites that are not equipped with an onsite polarizer.

    - With this third method, the polarization of the helium gas will occur in a polarization device at our industry partner, Xemed, LLC in New Hampshire. As with the two methods described above, helium polarization is carried out in a heated glass cell filled with helium gas and a few milligrams of alkali metal (rubidium and/or potassium). After polarization is complete, the cell is cooled down to allow the alkali metal to return to the solid state. The polarized helium gas is then transferred to a glass cell for transport to the site. At the site the polarized helium gas will be dispensed from the glass cell into tedlar (a type of plastic) bag. It may be mixed with medical-grade nitrogen to achieve the appropriate volume for inhalation by the subject. All tubing and valves used for handling and dispensing the helium gas are manufactured according to oxygen-clean standards, which is the most stringent cleaning specification for gas-handling system. As above, the gas from this method was sent for purity testing and no traces of other elements were found at the machine detection limits. A purity report of the dispensed helium gas is attached.

    - The gas transportation system: The helium gas is polarized offsite at Xemed. Then, it is pumped into a 1 L iron-free glass transport cell and placed in a metal container with a permanent shielded

(0.8 mT) magnet to protect against stray external magnetic fields (pictured below). The filling pressure of the gas allows 1 L of useable gas when released. The container is then shipped to the imaging center where is its transferred to the tedlar bags and administered to the subject. This system has been previously tested successfully in Europe and Australia. (21, 22)

Hypothesis to be Tested

The purpose of this study is to further develop the technique of rapid hyperpolarized helium-3 MRI for use in infants, and perform a pilot study in infants who are healthy and infants with CF, BPD, and asthma.

Study Design: Biomedical

1. Will controls be used? No.

2. What is the study design?
Pilot.

3. Does the study involve a placebo?
No.

Human Participants

Ages: _1 month -65 years old___
Sex: _Both___
Race: _All___

Subjects- see below

1. **Provide target # of subjects (at all sites) needed to complete protocol.** 110.
2. **Describe expected rate of screen failure/ dropouts/withdrawals from all sites.** 10%.

3. How many subjects will be enrolled at all sites? 121.
4. How many subjects will sign a consent form under this UVa protocol? 121**.**
5. Provide an estimated time line for the study. We expect to complete this study in 5 years.

Inclusion/Exclusion Criteria

1. List the criteria for inclusion

We confirm that this protocol includes two arms: 1) one that enrolls adults and children age >1 month to fine tune the details of the MRI sequence acquisitions and 2) a pilot study that enrolls infants and young children age >1 month with either healthy or diseased lungs. Some of the subjects in arm 2 may be on a ventilator and ready to wean.

<u>MRI sequence development (n=60):</u>
Healthy subjects and patients with CF, BPD, asthma, COPD, a history of smoking or other lung diseases will be used in the development of the rapid imaging techniques. These subjects will be age 1 months to 65 years old. Healthy subjects can have no history of chronic respiratory disease. The subjects with CF, asthma, or BPD must have a physician diagnosis of their respective disease.

<u>Pilot Study (n=50):</u>
Twenty healthy infants, 10 infants with CF, and 20 infants with BPD age 1-24 months will be imaged in the proof-of-concept study. Healthy infant must have had an uncomplicated term birth and have no history of chronic respiratory symptoms. Infants with BPD must have a physician diagnosis of BPD. The patients with CF must have a physician diagnosis of CF and be at their baseline clinical status on the day of imaging. In order to enroll infants with normal lungs who are being ventilated, we will include infants with a perinatal hypoxic ischemic event (HIE) as healthy subjects.

Some subjects may be invited to return for an additional MR imaging visit and the subsequent follow up (as described below) after approximately 5 months from their first visit. Before this is done, the participant will sign the consent form again.

If a child is on a ventilator, they must either meet the criteria for being ready to be weaned from the ventilator or clinically stable on a home ventilator. An MRI compatible ventilator will be used while the patient is in the scanner.

2. List the criteria for exclusion

- Any condition for which a MRI procedure is contraindicated.
- Presence of any non-MRI compatible metallic material in the body, such as pacemakers, metallic clips, etc.
- Likelihood of claustrophobia.
- Chest circumference greater than that of the helium MR coil.
- Pregnancy, by report of subject. Clinically in the Department of radiology at UVA, self-report is used when screening patients for MR scans as well as CT scans and fluoroscopy studies. If the subject

reports there is any chance of their being pregnant, a urine pregnancy test will be performed prior to any imaging.

3. List any restrictions on use of other drugs or treatments.
Inhaled medications such as short acting beta-2 agonists should not be administered within 4 hours prior to the hyperpolarized helium-3-MRI.

Statistical Considerations

1. **Is stratification/randomization involved?** No.

2. What are the statistical considerations for the protocol?
The goals of this project are to further develop the technique of hyperpolarized helium-3 MRI for use in infants and to perform a small pilot study in 30 infants to demonstrate the technique could be expanded to a larger clinical trial. No formal statistical analyses are planned. For the images obtained as part of the proof-of-concept study, we will measure conventional metrics of image quality such as signal-to-noise ratio (SNR) to quantify the image quality obtained with our technique. However, no comparison with our historical data in cooperative, older subjects is planned. In addition, we will calculate as a measure of disease severity, the percent of the lung volume that is poorly ventilated.

3. Provide a justification for the sample size used in this protocol.
The sample size for the MRI sequence development portion of this study is derived from our long experience in developing new techniques for hyperpolarized gas MRI. Best guess estimates are initially used for the sequence parameters but the sequences must be tested and refined in human subjects because the complex interactions of the lung microstructure, the hyperpolarized gas signal characteristics, and sequence parameters are difficult to predict, so much trial and error is used in the development. The sample size for the proof-of-concept trial is the smallest number to demonstrate that the technique is both feasible and robust in both healthy infants and infants with lung disease.

4. What is your plan for primary variable analysis?
No formal statistical analyses will be required, and none are planned.

5. What is your plan for secondary variable analysis?
We will compare the measures of image quality and disease severity between the 10 healthy infants, the 10 infants with CF, and the 10 infants with BPD. However, we do not expect there to be significant differences between these two groups with this low number of subjects**.**

6. Have you been working with a statistician in designing this protocol? No.

7. Will data from multiple sites be combined during analysis? No.

Biomedical Research

1. What will be done in this protocol?

All study procedures, including MR imaging, will take place at the Snyder Building at Fontaine Research Park or the main radiology department in the hospital.

- A medical history will be taken defining any present and past history of respiratory illnesses, medications, and hospitalizations and the ability to have MR imaging.
- A urine pregnancy test will be done for women of childbearing potential, who report the possibility that they might be pregnant.
- If needed, a practice bag filled with room air will be given to the subject as a teaching tool to teach the subjects the breathing technique used during the administration of hyperpolarized helium gas.
- Before and after MR imaging, a physical exam, spirometry (if subject able to perform test), and a baseline %PO2 will be performed.
- During the MR imaging procedure, the subject's heart rate and blood oxygen saturation will be monitored using an MR compatible pulse oximeter when possible.
- Once positioned in the MR scanner, the free breathing MR imaging will be performed.
- Then, the hyperpolarized helium 3 imaging will be performed.
    - Subjects who are infants will be bundled or held to restrain motion while in the MRI scanner
    - Infants will be placed in the MR coil such that their head is supported in a neutral position. Imaging occurs very quickly so the total time the subject is expected to be in the scanner is less than 15 minutes.
    - For infants with BPD, a physician from the research team will be present at all imaging sessions to monitor the subject. Imaging will be terminated if the physician feels the baby is being unusually stressed in any way.
    - Imaging will be terminated and oxygen given if the subject's pO2 on pulse oximetry drops by 10% or more or if there is a sustained low heart rate over one minute of less than 100 bpm heart rate. We have experience with MR imaging of young infants for clinical brain MRI and most infants tolerate imaging of the brain MRI well. We expect infants to tolerate the lung imaging well particularly since the duration of imaging will be less than brain MRI.
    - If the subject is not on a ventilator, the subject will inhale the hyperpolarized gas which may be mixed with medical grade nitrogen through a small plastic tube connected to a plastic bag containing the hyperpolarized gas mixture or through a face mask or other gas delivery device. If the subject is on a ventilator the hyperpolarized gas mixture will be introduced into the ventilator circuit just before the endotracheal or tracheostomy tube.
    - Rapid MR imaging will be performed during inhalation/exhalation and/or breath-hold. Depending upon the availability of gas and the quality of images obtained, the helium-3 inhalation and MR imaging may be repeated.
    - Oxygen by nasal cannula or mask may be administered immediately before and after gas inhalation.
    - The dedicated transmit/receive MR coils used for the gas imaging is an investigational, non-FDA approved device. However, the manufacturer considers it a non-significant risk device. In addition, non-standard MR pulse sequences are used for hyperpolarized gas imaging. In general these sequences require much lower power depositions than conventional MR imaging and therefore include no significant risk.

- Conventional proton images of the thorax may also be obtained to define the lung boundaries for subsequent image analysis.
- May use an inline flow meter to measure the airway flow and gas volumes during dosing with practice bags outside of the scanner and with dosing bags while in the scanner.
- The total time of the MR image acquisition is limited typically less than 20 seconds. The total study visit duration is expected to be 3-4 hours.

Subjects will be contacted from 1-5 days via telephone or email after imaging to assess for side effects and adverse events.

NOTE: Gadolinium will not be used for this study.

2. List the procedures, in bullet form, that will be done for RESEARCH PURPOSES as stipulated in this protocol.
All procedures are being done for the research study.

3. Do you confirm that, except for blood draws through a peripheral site, that all invasive procedures will be performed by a licensed health care provider under the supervision of an MD? Yes.

4. Will you be using data/specimens in this study that were collected previously, with the use of a research consent form, from another research study? No.

5. Will any of the procedures listed in item # 2 have the potential to identify an incidental finding? This includes ALL procedures, assessments and evaluations that are being done for RESEARCH PURPOSES that may or may not be considered investigational. Yes.

►IF YES, *check one of the following two options:*

__X__ The examination(s) utilize(s) the same techniques, equipment, etc., that would be used if the subject were to have the examination(s) performed for clinical care. **There exists the potential for the discovery of clinically significant incidental findings.** (limited physical exam, spirometry, urine pregnancy test, if needed, vital signs)

- The PI takes full responsibility for the identification of incidental findings:
- The PI will inform the subjects verbally of all incidental findings that are of clinical significance or are of questionable significance**.**
- A follow-up letter describing the finding should be provided to the subject with instructions to either show the letter to their PC or if the subject has no PCP, the subject should be instructed to make an appointment at UVa or at the Free Clinic**.**

__**X**__ This examination(s) utilizes non-standard/investigational, technique, equipment, etc. It is impossible to determine the significance of such results, therefore abnormalities will not be shared with the subject because the meaning of the exam is not yet proven and is of unknown clinical benefit. (Helium MRI)

6. Do any of the procedures listed above, under question # 2, utilize any imaging procedures for <u>RESEARCH PURPOSES</u>?Yes.

IF YES, list procedures:
MRI with helium.

__**X**___This imaging research examination utilizes non-standard/investigational imaging modality, techniques, equipment, scanning sequences, etc. It is impossible to determine the significance of such images, therefore abnormalities will not be shared with the subject because the meaning of the exam is not yet proven and is of unknown clinical benefit.

7. Will you be using viable embryos? No.

8. **Will you be using embryonic stem cells?** No.

9 Are any aspects of the study kept secret from the participants? No.

10. Is any deception used in the study? No.

11. If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study.
NA, study does not involve a treatment.

12. Will your study involve measures (C-SSRS/BID/SCID etc.) used to assess for depression and/or suicidality <u>for research purposes?</u> No.

13. **Where will the study procedures be done?**
Check One:
__X__ UVA medical center facilities (In patient or outpatient)
__X__ UVa , but not medical center facilities: LIST specific location Snyder Building

14. If the study involves medical risk and study procedures will be done outside of the UVa Medical Center what is your plan to protect the subjects in case of a medical emergency?
__X___ Study coordinator onsite during procedures
__X___ Individual trained in CPR on site during procedures
__X___ AED and Individual trained to use it onsite
__X___ Call 911

Specimens

<u>Specimen Information</u>
1. Describe the type of specimen to be used: urine

2. Will the specimen be obtained BEFORE a subject has signed a consent form? No

3. Will you be using discarded specimens? No

Specimen Labeling

1. What information/ HIPAA identifiers will be on the specimen label when it is given to the study team (from clinical labs or other source outside the study team) and/or what information will you put on the specimen?
none, specimen will be processed at point of care

2. If the specimen is given to the study team with information on the label will you delete any of the information on the specimen label?
Not applicable

3. Will any additional data be linked to the specimen by way of a code? No

4. Will the analysis on the specimen be done soon (within 24 hours) after it is collected? Yes

Specimen Shipping
1. Do you plan to ship any specimens outside of UVA? No

Data and Safety Monitoring Plan

1. Definition:

1.1 How will you define adverse events (AE)) for this study?

_X____An adverse event will be considered any undesirable sign, symptom or medical or psychological condition **even if the event is not considered to be related** to the investigational drug/device/intervention. Medical condition/diseases present before starting the investigational drug/intervention will be considered adverse events only if they worsen after starting study treatment/intervention. An adverse event is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research. Adverse events also include any problems associated with the use of an investigational device that adversely affects the rights, safety or welfare of subject s.

1.2 How will you define serious adverse events?

__X___A serious adverse event will be considered any undesirable sign, symptom, or medical condition which is fatal, is life-threatening, requires or prolongs inpatient hospitalization, results in persistent or significant disability/incapacity, constitutes a congenital anomaly or birth defect, is medically significant and which the investigator regards as serious based on appropriate medical judgment. An important medical event is any AE that may not result in

death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions of SAEs.

1.3 What is the definition of an <u>unanticipated problem?</u>

Do not change this answer

An unanticipated problem is any event, experience that meets ALL 3 criteria below:

- Is unexpected in terms of nature, severity or frequency given the research procedures that are described in the protocol-related documents AND in the characteristics of the subject population being studies
- Related or possibly related to participation in research. This means that there is a reasonable possibility that the incident may have been caused by the procedures involved in the research study.
- The incident suggests that the research placed the subject or others at greater risk of harm than was previously known or recognized OR results in actual harm to the subject or others

1.4 What are the definitions of a protocol violation and/or noncompliance?

Do not change this answer

A **protocol violation** is defined as any change, deviation, or departure from the study design or procedures of research project that is NOT approved by the IRB-HSR prior to its initiation or implementation. Protocol violations may be major or minor violations.

Noncompliance can be a protocol violation OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulation**s**. Noncompliance may be serious or continuing.

<u>Additional Information:</u> see the IRB-HSR website at http://www.virginia.edu/vpr/irb/HSR_docs/Forms/Protocol_Violations_%20Enrollment_Exceptions_Instructions.doc

1.5 If pregnancy occurs how will this information be managed?

__X___ Unanticipated Problems- will follow Unanticipated Problem recording and reporting procedures outlined in section 3.

1.6 What is the definition of a Protocol Enrollment Exception?

__X_ Protocol has a sponsor outside of UVa. An enrollment exception is the sponsor's prospective approval for the enrollment of a research subject that fails to meet current IRB-HSR approved protocol inclusion criteria, or falls under protocol exclusion criteria. Enrollment exceptions only apply to a single individual. Such a request should be rare and justified in terms of serving the best interests of the potential study participant.

1.7 What is the definition of a data breach?

Do not change this answer

A data breach is defined in the HITECH Act (43 USC 17932) as an unauthorized acquisition, access, or use of protected health information (PHI) that compromises the security or privacy of such information.

Additional Information may be found on the IRB-HSR Website: Data Breach

2. Identified risks and plans to minimize risk

2.1 What risks are expected due to the intervention in this protocol?

Expected Risks related to study participation.	**Frequency**

Risk of Inhaling Hyperpolarized Helium 3 gas	
• The most common respiratory related symptoms include sore, dry or scratchy throat; tickle in throat; and cough • Additional non-respiratory related symptoms have also occurred and include headache and lightheadedness	☒ Occurs frequently, ☐ Occurs infrequently ☐ Occurs rarely ☐ Frequency unknown
• Other respiratory related symptoms include wheezing, chest tightness or chest pain and a decrease >10% in %PO2	☐ Occurs frequently, ☐ Occurs infrequently ☒ Occurs rarely ☐ Frequency unknown
• A small amount of the element rubidium is used to hyperpolarize the helium gas. The quantity used is less than 1/1000 of the amount that would poison a rat, though it is in a chemical form that a small droplet would cause a heat releasing reaction.	☒ Has never occurred

Risk of Magnetic Resonance Imaging	
• If you have metal shards or clips in your body, they may interfere with the magnetic field and give burns	☐ Occurs frequently, ☐ Occurs infrequently ☒ Occurs rarely ☐ Frequency unknown
• Claustrophobia: It is possible to feel a sensation of being confined or caged when in the MRI machine.	☐ Occurs frequently ☒ Occurs infrequently ☐ Occurs rarely ☐ Frequency unknown

Risks related to the investigational coil	

• This coil, which is necessary to obtain the MR images of the lungs with the hyperpolarized gas, transmits and receives radio waves at much lower power than used with most standard MRI techniques. The coil is considered by the manufacturer a non-significant risk device, but it has not been approved by the FDA.	☐ Occurs frequently, ☐ Occurs infrequently ☒ Occurs rarely ☐ Frequency unknown

Risk related to Spirometry	
• Since spirometry requires blowing hard several times, the subject may cough or feel short of breath during or after the test.	☒ Occurs frequently, ☐ Occurs infrequently ☐ Occurs rarely ☐ Frequency unknown

Risk to a fetus	
• For females: At present, the safety of hyperpolarized gas to a fetus has not been established. If you are pregnant or nursing you may not participate in this study.	☐ Occurs frequently, ☐ Occurs infrequently ☐ Occurs rarely ☒ Frequency unknown
• For males: You should not father a baby while you are in this study or for one month after your participation in the study ends	☐ Occurs frequently, ☐ Occurs infrequently ☐ Occurs rarely ☒ Frequency unknown

Risk of Transport	
• Risk of dislodgement of the endotracheal tube • Unplanned extubation	☐ Occurs frequently, ☐ Occurs infrequently ☐ Occurs rarely ☒ Frequency unknown

2.2 List by bullet format a summary of safety tests/procedures/observations to be performed that will minimize risks to participants:

- Medical History questionnaire
- Pre and post inhalation measurement of spirometry
- Pre and post inhalation measurement of oxygen saturation monitoring (pulsoximetry)
- For MRI scanning: Participants need to complete the standard MR questionnaire that is also used at the clinical sites to screen the individuals ineligible for MRI scanning: This screens for metallic foreign bodies, inner ear implants, pacemakers, claustrophobia, etc.

- For MR scanning with inhaled hyperpolarized helium-3. Individuals whose body habitus does not allow the person to fit in the special vest coils for imaging at the MR frequency of hyperpolarized helium-3 are excluded. In case of doubt the vest coil will be fitted around the participant outside the scanner to determine eligibility.
- Follow-up for adverse events is performed within 1 to 5 days post imaging by telephone or email contact.
- All NICU infants, whether or not they are on a ventilator, will be transported to MRI per standard clinical care procedures and NICU personnel will remain with the infant during imaging per standard care.

2.3 Under what criteria would an INDIVIDUAL SUBJECT'S study treatment or study participation be stopped or modified

__X___At subject, PI or sponsor's request

2.4 Under what criteria would THE ENTIRE STUDY need to be stopped.

__X___Per IRB, PI, DSMB, or sponsor discretion

2.5 What are the criteria for breaking the blind/mask?

__X___NA – Not blinded/masked

2.6 **How will subject withdrawals/dropouts be reported to the IRB prior to study completion?**

__X___IRB-HSR continuation status form

3. Adverse Event / Unanticipated Problem Recording and Reporting

3.1 Will all adverse events, as defined in section 1.1, be collected/recorded? Yes.

3.2 How will adverse event data be collected/recorded? Check all that apply

__X___Paper AE forms/source documents

__X___Spreadsheet: paper or electronic

__X___Database: IRB# 13389 Hyperpolarized Helium 3 Research Database

3.3. How will AEs be classified/graded? Check all that apply

_X____Mild/Moderate/Severe

_X_ Serious/Not serious Required for all protocols

3.4 What scale will the PI use when evaluating the relatedness of adverse events to the study participation? *Check all that apply.*

___X__The PI will determine the relationship of adverse events to the study

using the following scale:

Related:	AE is clearly related to the intervention
Possibly related:	AE may be related to the intervention
Unrelated:	AE is clearly not related to intervention

3.5 When will recording/reporting of adverse events/unanticipated problems begin?

__X___After subject begins study drug/ device placement/intervention /study-related procedure/specimen collection

3.6 When will the recording/reporting of adverse events/unanticipated problems end?

__X___ Subject completes intervention and follow up period of protocol

3.7 How will Adverse Events, Unanticipated Problems, Protocol Violations and Data Breaches be reported? Complete the table below to answer this question

Type of Event	To whom will it be reported:	Time Frame for Reporting	How reported?
Any internal event resulting in death that is deemed DEFINITELY related to (caused by) study participation *An internal event is one that occurs in a subject enrolled in a UVa protocol*	IRB-HSR	Within 24 hours	IRB Online and phone call www.irb.virginia.edu/
Internal, Serious, Unexpected adverse event	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event. *Timeline includes submission of signed hardcopy of AE form.*	IRB Online www.irb.virginia.edu/
Unanticipated Problems that are not adverse events or protocol violations This would include a Data Breach.	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. *http://www.virginia.edu/vprgs/irb/HSR_docs/Forms/Reporting_Requirements-Unanticipated_Problems.doc)*

Protocol Violations/Noncompliance *The IRB-HSR only requires that MAJOR violation be reported, unless otherwise required by your sponsor, if applicable.* **OR** **Enrollment Exceptions** *See definition- only allowed if there is a commercial sponsor or a DSMB that has granted the enrollment exception.*	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Violation, Noncompliance and Enrollment Exception Reporting Form *http://www.virginia.edu/vprgs/irb/hsr_forms.html* *Go to 3rd bullet from the bottom.*
Data Breach	The UVa Corporate Compliance and Privacy Office ITC: if breach involves electronic data Police if breach includes items that are stolen: Stolen on UVA Grounds OR Stolen off UVa Grounds- contact police department of jurisdiction of last known location of PHI	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified. IMMEDIATELY.	UVa Corporate Compliance and Privacy Office- Phone 924-9741 **ITC:** Information Security Incident Reporting procedure, http://www.itc.virginia.edu/security/reporting.html UVa Police-Phone- (434) 924-7166

OUTSIDE SPONSOR			
All Serious adverse events	Sponsor	Within 7 calendar days from the time the study team	***Insert name of form and method of reporting to the sponsor***

		received knowledge of the event	
External, Serious and Unexpected adverse event resulting in change to the protocol or consent..	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event. *Timeline includes submission of signed hardcopy of AE form*	IRB Online www.irb.virginia.edu/
For Device Studies: Unanticipated adverse devic effects (internal)	Sponsor	Within 10 day of the study team receiving knowledge of the event	***Email or phone call***
Unanticipated Problem	Sponsor	Within 7 calendar days from the time the study team received knowledge of the event. .	***Email or phone call***
Protocol violations	**Sponsor**	Within 7 calendar days from the time the study team received knowledge of the event	***Email or phone call***

UVa PI HELD IND#57866			
Life-threatening and/or fatal unexpected events related o possibly related to the use o the investigational agent.	FDA	Within 7 calendar days of the study team learning of the event	Form FDA 3500A (MedWatch) or narrative
Serious, unexpected and related or possibly related adverse events	FDA	Within 15 calendar days after the study team receives knowledge of the event	Form FDA 3500A (MedWatch) or narrative
For Device Studies: Unanticipated adverse devic effects (internal or external)	FDA	Within 10 working days of the study team receiving knowledge of the event	Form FDA 3500A (MedWatch) or narrative
All adverse events	FDA	Annually	IND annual report

4. **How will the endpoint data be collected/recorded.** Check all that apply

__X___Protocol specific case report forms

__X___Source documents

__X___Database: IRB#13389 Hyperpolarized Helium3 Research Database.

5. Data and Safety Oversight Responsibility

5.1. Who is responsible for overseeing safety data for this study?

__X___No additional oversight body other than PI at UVa Skip question 5.2

5.3. What items will be included in the aggregate review conducted by the PI?

___X__All adverse events

__X___Unanticipated Problems

_X____Protocol violations/Issues of noncompliance

__X___Audit results

_X____Application of study designed stopping/decision rules

__X___Early withdrawals

__X___Whether the study accrual pattern warrants continuation/action

__X___Endpoint data

5.4 **How often will aggregate review occur?**

__X___Annually

5.5. How often will a report, regarding the outcome of the review by the DSMB/DSMC, be sent to the UVa PI?

__X___NA- There is no DSMB/DSMC overseeing this study.

5.6. How will a report of the information discussed in question 5.4 OR 5.5 be submitted to the IRB?

__X___Part of IRB-HSR continuation status form

Payment

1. **Are subjects being reimbursed for travel expenses?** No.

2. **Are subjects compensated for being in this study?** Yes.

2a. What is the maximum TOTAL compensation to be given over the duration of the protocol?
$100.00

2b. Explain compensation to be given.
Participants, or their parents, for minors under the age of 10, will be paid $50.00 upon completion of their imaging session. If the study visit duration exceeds 2 hours, an additional compensation of $25

per additional hour to a maximum of $100. It is not anticipated that the study visits will routinely take more than 2 hours.

2c. Is payment pro-rated?

Yes, if the subject arrives for the study and it cannot be completed, subject will receive a minimum of $25.00.

2d. Is money paid from UVa or State funds (including grant funds) or will items such as gift cards be distributed through UVa?

Yes, UVa funds.

2d(i). How will the researcher compensate the subjects?

___X_ Check issued to participant via UVA Oracle or State system

__X__ Other type of compensation: Occasionally, subjects require an overnight stay at a local hotel in order to make it possible for them to participate in the study. This cost is covered by study funds on an as needed basis and is paid directly to the hotel.

2d(ii). Which category/ categories best describes the process of compensation?

__X___ All compensation will be made via check issued to participant via UVA Oracle or State system

Risk/ Benefit Analysis

1. What are the potential benefits for the participant as well as benefits which may accrue to society in There are no direct benefits to the subject. Fast MR lung imaging has the potential to improve our understanding of the pathophysiology of childhood of lung diseases and also has the potential to assist in diagnosis and treatment of a variety of other lung diseases. This may help society in general.

2. Do the anticipated benefits justify asking subjects to undertake the risks?

MRI is a long established, FDA-approved, clinical imaging modality with known risks, which will be explained carefully during the informed consent process. The risks to subjects posed by the study are low. The potential benefit of improved methods of lung ventilation imaging may increase understanding of the pathophysiology of different lung diseases and has the potential to assist in the diagnosis and treatment of lung diseases.

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APPENDIX: Legal/Regulatory

Recruitment

The following procedures will be followed:

- Finders fees will not be paid to an individual as they are not allowed by UVa Policy.
- All recruitment materials will be approved by the IRB-HSR prior to use. They will be submitted to the IRB after the IRB-HSR has assigned an IRB-HSR # to the protocol.
- Only those individuals listed as personnel on this protocol will recruit and or conduct the consenting process with potential subjects.

Retention Incentives

Any item used by the sponsor/ study team to provide incentive to a subject to remain in the study, other than compensation identified in the Payment section, will be submitted to the IRB for review prior to use. The IRB-HSR will provide the study team with a Receipt Acknowledgement for their records. Retention incentive items are such things as water bottles, small tote bags, birthday cards etc. Cash and gift cards are not allowed as retention incentives.

Clinical Privileges

The following procedures will be followed:

- Investigators who are members of the clinical staff at the University of Virginia Medical Center must have the appropriate credentials and been granted clinical privileges to perform specific clinical procedures whether those procedures are experimental or standard.
- The IRB cannot grant clinical privileges.
- Performing procedures which are outside the scope of the clinical privileges that have been granted may result in denial of insurance coverage should claims of negligence or malpractice arise.
- Personnel on this protocol will have the appropriate credentials and clinical privileges in place before performing any procedures required by this protocol.
- Contact the Clinical Staff Office- 924-9055 or 924-8778 for further information.

Sharing of Data/Specimens

Data and specimens collected under an IRB approved protocol are the property of the University of Virginia. You must have “permission” to share data/ specimens outside of UVa other than for a grant application and or publication. This “permission” may come in the form of a contract with the sponsor or a material transfer agreement (MTA) with others. A contract/ MTA is needed to share the data outside of UVa even if the data includes no HIPAA identifiers and no code that could link the data back to a HIPAA identifier.

- No data will be shared outside of UVa, beyond using data for a grant application and or publication, without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.
- No specimens will be shared outside of UVa without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.

Prisoners

If the original protocol/ IRB application stated that no prisoners would be enrolled in this study and subsequently a subject becomes a prisoner, the study team must notify the IRB immediately. The study team and IRB will need to determine if the subject will remain in the study. If the subject will remain in the study, the protocol will have to be re-reviewed with the input of a prisoner advocate. The prisoner advocate will also have to be involved in the review of future continuations, modifications or any other reporting such as protocol violations or adverse events.

Prisoner- Individuals are prisoners if they are in any kind of penal institution, such as a prison, jail, or juvenile offender facility, and their ability to leave the institution is restricted. Prisoners may be convicted felons, or may be untried persons who are detained pending judicial action, for example, arraignment or trial.
For additional information see the OHRP website at http://www.hhs.gov/ohrp/policy/populations/index.html

Compensation in Case of Injury

If a subject requests compensation for an injury, the study team should notify the IRB-HSR (924-9634/2439847) the UVa Health System Patient Relations Department (924-8315). As a proactive courtesy, the study team may also notify UVa Health System Patient Safety and Risk Management (924-5595).

On request, the study team should provide the Risk Management Office with the following information/documents:

- Subject Name and Medical Record Number
- Research medical records
- Research consent form
- Adverse event report to IRB
- Any letter from IRB to OHRP

Subject Complaints

During a research study, the study team may receive complaints from a subject. If the study team is uncertain how to respond to a complaint, or is unable to resolve it with the subject, the study team may contact the IRB-HSR (924-9634/243-9847), the UVa Health System Patient Relations Department (924-8315).

Request for Research Records from Search Warrant or Subpoena

If the study team receives a request for research records from a search warrant or subpoena, they should notify UVa Health Information Services at 924-5136. It is important to notify them if information from the study is protected by a Certificate of Confidentiality.

APPENDIX: Drug Information

1 What is the drug name, manufacturer and IND# if available?
Helium-3, IND# 57,866, Produced at UVA

2. If IND application has been submitted to the FDA, who is the Principal Investigator on the IND?
Eduard E. de Lange, MD

3. What is the phase or stage of this study?
Pilot.

APPENDIX: Device Information: Non-Proton Coils

1. **List name of device**. Non-proton coils

2. **Describe pertinent animal data that is available regarding the toxicity/safety of this device**. None

3. **Describe pertinent human data that is available regarding the toxicity/safety of this device**. Over 1000 subjects have been enrolled in studies using the helium coils here at UVA. Of these, 2 subjects reported feeling a slight sensation of warmth which may have been related to the helium coil and one subject reported a dime size burns to her right elbow, which was not related to the coil.

4. **Have there been any human deaths associated with this device? None**

5. **In how many humans has this device been used previously?** Over 1000 at the University of Virginia have undergone hyperpolarized helium MR with the helium coils.

6. **If this protocol will be used in children describe any previous use of this device with children of a similar age range.** No adverse events related to the coils have been reported in this population.

7. **Is this device removable?** NA –the device is not implanted.

8. **Is this a post-marketing study? No**

9. **Does this device have an IDE# from the FDA? No**

►IF NO, do any of the criteria in the table below apply? No

►IF you did not check any item in the preceding table do you feel the device is non-significant risk? Yes. Additionally, the School of Medicine, Clinical Trials Office (SOM CTO) has reviewed the helium coils and considers them to be non-significant risk devices not requiring an IDE.

APPENDIX: Device Information: Helium Polarizers

1. List name of device. Gas Polarizers: the gas polarizes helium 3 for use as a contrast agent for MRI imaging. The hyperpolarized helium 3 gas is considered an investigational new drug by the FDA. The gas polarizer does not come in contact with the subject and is only used to polarize the helium 3 prior to the inhalation by the subject.

1. **Describe pertinent animal data that is available regarding the toxicity/safety of this device**. None available

2. **Describe pertinent human data that is available regarding the toxicity/safety of this device.** None available

3. **Have there been any human deaths associated with this device?** Not to our knowledge

4. **In how many humans has this device been used previously?** Over 1000 studies have been performed using the helium 3 gas polarized in our original polarizer without any adverse events related to the device.

5. **If this protocol will be used in children describe any previous use of this device with children of a similar age range.** No adverse events related to the polarizers have been reported in this population.

6. **Is this device removable?** N/A not implantable

7. **Is this a post-marketing study? No**

8. **Does this device have an IDE# from the FDA? No**

►**IF NO, do any of the criteria in the table below apply? No**

►**IF you did not check any item in the preceding table do you feel the device is non-significant risk**? Yes. Additionally, the School of Medicine Clinical Trials Office (SOM CTO) has reviewed the helium polarizer and considers them to be non-significant risk devices not requiring an IDE.

APPENDIX: Recruitment

1. How do you plan to <u>identify</u> potential subjects?

a._X___ Chart Review/ Clinic Schedule Review/ Database Review from a database established for health care operations (departmental clinical database) or an Improvement Project (*e.g. Performance Improvement, Practice Improvement, Quality Improvement*).
<u>If you plan to obtain data from the UVa Enterprise Data Warehouse (EDW) please see option b below.</u>

<u>DHHS:</u> Study team requests Waiver of Consent to identify potential subjects.

HIPAA: Allowed under Preparatory to Research if PHI to be accessed.

IMPORTANT
Keep in mind that PHI in the medical record may only be accessed by individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:
--a UVa student working in the UVa HIPAA Covered Entity*
--a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity*

b_X___ Review of a database that was established to keep data to be used for future research such as the CDR, departmental research database or use of data from a separate current active research protocol.

If you plan to obtain data from the UVa Enterprise Data Warehouse (EDW) you are required to submit your request to the CDR. The CDR staff will work with the EDW to obtain the data you need.

DHHS: Study team requests Waiver of Consent to identify potential subjects.

HIPAA: Allowed under Preparatory to Research if PHI to be accessed.

IMPORTANT
Keep in mind that PHI in the medical record may only be accessed by individuals who work under the UVa HIPAA covered entity; which means they who meet one of the following criteria:
--a UVa student working in the UVa HIPAA Covered Entity*
--a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity*

The information from which you are obtaining potential subjects must also have an IRB protocol approval. If this item is checked, enter the IRB # below.

IRB# __13889_____

If obtaining information from the Clinical Data Repository (CDR) insert IRB # 10797

c. _X___ Patients UVa health care provider supplies the UVa study team with the patients contact information without patients' knowledge.

DHHS: Study team requests Waiver of Consent to identify potential subjects.

HIPAA: Allowed under Preparatory to Research if PHI will be shared by the health care provider.

IMPORTANT

Keep in mind that PHI may only be given to individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:
--a UVa student working in the UVa HIPAA Covered Entity*
--a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity*

d. _X___ Patient obtains information about the study from their health care provider. The patient contacts the study team if interested in participating. (Health care provider may or may not also be the a member of the study team)

DHHS: NA
HIPAA: Allowed under Health Care Operations

If this choice is checked, check 3d-INDIRECT CONTACT below.

e. _X___ Potential subjects will not be directly identified. They will respond to an advertisement such as a flyer, brochure etc.

If this choice is checked, check 3d- INDIRECT CONTACT below.
DHHS & HIPAA: NA

If item # a, b or c is checked above and if this protocol involves the use of protected health information do you confirm the following to be true?

- The use or disclosure is sought solely to review protected health information as necessary to prepare the research protocol or other similar preparatory purposes.
- No PHI will be removed from the UVa covered entity.
- The PHI that the researcher seeks to use or access is necessary for the research purposes.

Yes.

2. How will potential subjects be contacted?

a._X___Direct contact of potential subjects by the study team via letter, phone, direct e-mail. Members of study team ARE NOT health care providers of patients. Information will not be collected from psychotherapy notes.

Note: Letter, phone, direct email scripts must be approved by IRB prior to use. See IRB-HSR Website for templates.

DHHS/HIPAA: Study team requests a Waiver of Consent and Waiver of HIPAA Authorization to contact potential subjects.

IMPORTANT:
Keep in mind that if PHI was collected during the identification phase that contact with potential subjects may only be performed by individuals who work

under the UVa HIPAA covered entity; which means they meet one of the following criteria:

- a UVa student working in the UVa HIPAA Covered Entity*
- a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity*

b. _X___Potential subjects will be approached while at UVa Hospital or Health Clinic by a person who is NOT a member of their health care team. Information will not be collected from psychotherapy notes.

DHHS & HIPAA: Study team requests a Waiver of Consent and a Waiver of HIPAA Authorization to contact potential subjects.

IMPORTANT:
Keep in mind that contacting individuals in a clinical setting may only be performed by individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:
a UVa student working in the UVa HIPAA Covered Entity*
a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity*

You should share the following information with the potential subject:

- Your name
- Who you are: physician, nurse etc. at the University of Virginia.
- Why you want to speak with them
- Ask if you have their permission to explain the study to them
- If asked about how you obtained their information use one of the following as an option for response.
    - DO NOT USE THIS RESPONSE UNLESS YOU HAVE OBTAINED PERMISSION FROM THEIR UVa PHYSICIAN: Your doctor, Dr. insert name wanted you to be aware of this research study and gave us permission to contact you.
    - We obtained your information from your medical records at UVa.
    - Federal regulations allow the UVa Health System to release your information to researchers at UVa, so that we may contact you regarding studies you may be interested in participating. We want to assure you that we will keep your information confidential.
- IF THE PERSON SEEMS ANGRY, HESITANT OR UPSET, THANK THEM FOR THEIR TIME AND DO NOT ENROLL THEM IN THE STUDY. YOU MAY ALSO REFER THEM TO THE IRB-HSR AT 924-9634.

c. __X__Direct contact of potential subjects by the study team by approaching in person at UVa or via letter, phone, direct e-mail. Members of study team contacting potential subjects ARE health care providers of patients.

If you are not approaching them in person but using a letter, phone call or direct email please note that the letter, phone, direct email scripts must be approved by IRB prior to use.
See IRB-HSR Website for templates.

DHHS: Study team requests a Waiver of Consent to contact potential subjects
HIPAA: Allowed under Health Care Operations.

d. _X___ Indirect contact (flyer, brochure, TV, broadcast emails, patient provided info about the study from their health care provider and either the patient contacts study team or gives their healthcare provider permission for the study team to contact them.)

The indirect method used (flyer, brochure, TV, broadcast emails) must be approved by the IRB prior to use. The IRB does not need to review any type of script to use when the potential subject responds to the indirect method.

DHHS & HIPAA: NA

e. ____ Potential subjects are not patients. The study does not include obtaining subjects health information. Subjects will be contacted directly via email, phone, letter or presentation in group setting with consent then obtained individually in a private setting.

If you are not approaching them in person but using a letter, phone call or direct email please note that the letter, phone, direct email scripts must be approved by IRB prior to use.
See IRB-HSR Website for templates.

DHHS: Study team requests a Waiver of Consent to contact potential subjects.
HIPPA: NA

3. **Will any additional information be obtained from a potential subject during "prescreening"?**
Yes.

IF YES, submit any documents that will be used to collect pre-screening information so that the IRB may confirm what questions will be asked.
NOTE: To comply with HIPAA regulations only the minimum necessary information may be collected at this time. This means that only questions pertaining to the Inclusion and Exclusion Criteria may be asked.

IF YES,
DHHS: study team requests a Waiver of Documentation of Consent for Pre-screening questions.

HIPPA:
HIPAA does not apply if:

--no PHI is collected or
--if PHI is collected from a potential subject by an individual from a department that is not part of the HIPAA covered entity.

HIPAA does apply if the collection occurs by individuals* who work in a department that is part of the HIPAA covered entity.

In this case the collection will be covered under Health Care Operations/

These individuals are those that meet one of the following criteria:
--a UVa student working in the UVa HIPAA Covered Entity*
--a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity*

IF YES, Will any of the questions involve health information? Yes.

IF YES, will you collect HIPAA identifiers with the health information? Yes.

IF YES, which HIPAA identifiers will be recorded?
Name, Date of birth

Do you confirm that health information with HIPAA identifiers will not be shared outside of UVa until a consent form is signed or only shared in a de-identified manner?
Yes.

4. **Do you plan to ask the subjects to do anything, other than answering questions, for the study prior to signing a consent?** No.

5. **How will the consenting process take place with either the prospective subject, the subject's legally authorized representative or parent/legal guardian of a minor (if applicable)?**

Prior to the study day or on the study day, the volunteer/subject will be given the consent form to review and will be given an opportunity to ask any remaining questions before signing the consent form. In addition, volunteers/subjects may be given a copy of the consent form to review at home prior to enrolling, if requested. The signing of the consent form will take place in a private study room located in the Snyder building (Fontaine Research Park).

6. **Will subjects sign a consent form for any part of the study?**

Subjects will sign a consent form for the entire study.

7. **Will the study procedures be started the same day the subject is recruited for the study?** No.

8. Is there the potential to recruit economically or educationally disadvantaged subjects, or other vulnerable subjects such as students or employees? Yes.

IF YES, what protections are in place to protect the rights and welfare of these subjects so that any possible coercion or undue influence is eliminated?
There are students, employees, and economically and educationally disadvantaged people among the patient population at the UVA Health System. We will review the consent form carefully and completely, and we will ask questions to ensure all participants, especially those who are more vulnerable, understand their participation is completely voluntary.

9. Do you need to perform a "dry run" of any procedure outlined in this protocol? No.

10. Is the study regulated by the Department of Defense (DoD)? No.

APPENDIX: Participation of Children

In the state of Virginia a person under the age of 18 is considered a child.

1. Explain why this research topic is relevant to children.
The purpose of this study is to further develop techniques to image the lungs of young children and apply these techniques to improve our understanding of childhood lung disease.

2. Is the knowledge being sought in this study already available for children or is it currently being acquired through another ongoing study?
UVA is uniquely well suited to pioneer these tech since we have the largest world experience in performing hyperpolarized gas MRI we know of no other sites that can duplicate our experimental set up.

3. Provide data that is available in adults in order that the IRB may judge the potential risk in children. If there is no adult data available, provide reasons why not. If this information is available in a sponsor's protocol, you may reference the section # here and not duplicate the information.
Please refer to safety data reported in Appendix Pharmacy-Investigational Drugs/Biologics. This safety data includes data from minors enrolled at UVa in previous studies.

4. **Is the potential subject population likely to include wards of the state or children who are more at risk for becoming a ward of the state?** Yes.

4a. Is the research is this protocol related to the childs' status as a ward of the state?
No.

4b. Is the research to be conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards? Yes.

4c. Are you aware of the following requirement? yes

If the consent form contains a signature line for both parents the study team will notify the IRB immediately, if at any time during the course of the research, it becomes known that a potential subject is a ward of the state or that a child already enrolled in this protocol becomes a ward of the state.

5. **Does this study involve a placebo arm?** No

6. **Will UVa researchers conduct the study outside the state of Virginia?** No.

APPENDIX: Pharmacy-Investigational Drugs/Biologics

1. What is the name of the investigational drug/biologic?
Helium-3, IND# 57,866, Produced at UVA-de Lange is holder

2. Where will the subjects be seen for the administration/dispensing of the drug?
__X___ Outpatient Unit: Snyder building, Fontaine Research Park

3. What dose will be utilized in this study?
Between approximately 50 and 300 cc of hyperpolarized helium 3 will be administered from a tedlar bag and inhaled by the subject immediately prior to the hyperpolarized helium 3 MR image. Patients will inhale the gas from a small plastic straw, through a facemask or other gas delivery device. Up to 10 doses of helium may be administered per imaging session.

4. What will be the frequency of dosing in this study?
Subjects will receive up to 10 bags of helium-3 gas per imaging session.

5. What will be the duration of dosing in this study?
Helium dosing will be performed during the imaging session which is expected to last between 30 to 60 minutes. The actual inhalation of each dose and breath hold lasts ~20 sec or less.

6. What route of administration will be utilized?
Inhalation.

7. Will drug need to be prepared by the UVa Investigational Drug Service (IDS)?
__X___ NO- Drug will be prepared and/or administered per package insert

**Note: helium-3 gas is prepared in a special polarizer by research staff. As helium-3 is experimental, there is no package insert.

8. Are there any special handling instructions mandated by the study (e.g. weighing hazardous materials)?
No.

9. Does the protocol provide provisions for dose titration, dose reductions, and or re-challenged (if drug is stopped), etc.? No.

10. How will missed doses be handled? Not Applicable.

11. Will a comparator (active or placebo) be utilized in the protocol? No.

12. Does this study involve research on a drug, biologic, supplement or food additive? Yes

►IF YES, is this study investigator initiated?

Yes.

13 Are you using a drug/supplement/ food additive in a manner not approved by the FDA? Yes.

13a. Describe pertinent animal data that is available regarding the toxicity/safety of this drug.
Animal data was provided directly to the FDA by Amersham Health for our IND application. Amersham Health considered this information confidential and we therefore have no copy of the animal data.

13b. Describe pertinent human data that is available regarding the toxicity/safety of this drug.
We completed a second analysis of the safety data for helium 3 gas for the period on June 1, 1999 – May 30, 2006. The following is a summary of the results.

- Inhalation of hyperpolarized helium-3 gas was safe, with AEs occurring in 78 (9.5%) of 818 studies.
- Most related/possibly related AEs were respiratory in nature such as chest pain, dry mouth, cough and tickle in throat.
- Most AEs were mild with the symptoms quickly resolving without treatment.
- Two AEs were severe. Both occurred in patients with lung disease. In one the symptoms occurred 7 days after 3He inhalation.
- Subjects with lung disease, and asthma in particular, did NOT have more AEs than those without lung disease and thus, the presence of a lung disease was NOT a significant risk.
- Inhalation caused only mild transient decreases in blood pO2 with the nadir <10% from baseline in most cases.
- None of the pre-to-post changes in vital signs, spirometry, blood chemistry, blood coagulation, urine analysis, and 12-lead ECG were considered clinically important.
- AEs occurred more frequently in women than men
- Children were NOT more likely to have an AE than adults.
- Subjects with an abnormal baseline spirometry were NOT more likely to have an AE.
- The only operational factors associated with AEs were duration of filter use and number of 3He studies performed per filter.
- There was a trend toward an increase in number of related/possibly related AEs with total volume of inhaled 3He and number of inhaled doses; however, the differences were NOT statistically significant.

The following conclusions were reached:

- 3He was safe and well-tolerated as an inhaled MR contrast agent for lung imaging.
- Subjects with lung disease, and asthma in particular, were NOT at greater risk for experiencing an AE compared to those without lung disease. This was true also for subjects with severely

compromised lung function (FEV1 < 40% of predicted)

- In two of the 818 studies (0.2%) a severe AE occurred, with each involving a patient with lung disease. In one the symptoms occurred 7 days after 3He inhalation, and therefore the relationship in this case between the AE and 3He inhalation is questionable.

There was association between the duration of filter use on the outflow valve of the 3He polarizer and the likelihood of a related/possibly related AE. Therefore, to minimize the risk of AEs the outflow filter should be frequently replaced.

13c. Have there been any human deaths associated with this drug? No.

13d. In how many humans has this drug been used previously?

Over 1000 human studies performed thus far at UVa, which is largest number in the world. Number of doses at other sites is unknown.

13e. If this protocol will be used in children describe any previous use of this drug with children of a similar age range.

We have imaged approximately 125 subjects age less than 18 years including normal minors and minors with cystic fibrosis, BPD and asthma. To date, the youngest child imaged with hyperpolarized helium-3 MR at UVA was 2 months old.

Two respiratory adverse events, sore throat and cough, occurred in two asthma subjects, ages 6 and 11. Both are considered mild, not serious, expected and possibly related to the helium gas. One 5 year old male with BPD had some chest soreness which was also considered mild, not serious, expected and possibly related to the helium gas.

Six non-respiratory adverse events occurred. Of these 2 were considered not related to the helium gas and included an upset stomach and increased gas. The remaining 4 were all not serious, mild or moderate, expected and possibly related to the helium gas: one 14 year old male asthmatic reported transient dizziness while in the MR scanner; one 6 year old asthmatic female developed a headache; one 2 year old asthmatic male developed a fever 2 days after the imaging study; and one 11 year old asthmatic female reporting feeling warm to the touch in the evening. This last subject also received a clinical bronchoscopy on the same day, after the helium imaging study.

14. Do the following criteria apply? Check all that apply

_____ The investigation is intended to be reported to FDA as a well-controlled study in support of a new indication for use or intended to be used to support any other significant change in the labeling for the drug;

_____ If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is intended to support a significant change in the advertising for the product;

_____ The investigation does involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

If Not checked- explain why you believe the risk to subjects is not increased:

Helium 3 gas is not approved by the FDA. This study is being conducted under IND#57866.

__X__ The investigation will be conducted in compliance with the requirements for institutional review set part in part 21CFR56 and with the requirements for informed consent set forth in part 21CFR50 ; and This item must be checked.

_X___ The investigation will be conducted in compliance with the requirements of 21CFR312.7 (Promotion and charging for investigational drugs)
This item must be checked.

15. Is this a post-marketing study? No.

Privacy Plan

The following procedures must be followed.

- The data will be secured per the Data Security Plan of this protocol.
- Only investigators for this study and clinicians caring for the patient will have access to data. They will each use a unique login ID and password that will keep confidential. The password should meet or exceed the standards described on the Information Technology Services (ITS) webpage about *The Importance of Choosing Strong Passwords.*
- Each investigator will sign the University's Electronic Access Agreement forward the signed agreement to the appropriate department as instructed on the form.

  If you currently have access to clinical data it is likely that you have already signed this form. You are not required to sign it again.
- UVa University Data Protection Standards will be followed http://www.virginia.edu/informationsecurity/dataprotection.
- If identifiable data is transferred to any other location such as a desktop, laptop, memory stick, CD etc. the researcher must follow the University's "Electronic Storage of Highly Sensitive Data Policy". Additional requirements may be found in the University's Requirements for Securing Electronic Devices.
- If identifiable data is taken away from the UVa Health System, Medical Center Policy # 0218 will be followed.
- Data will be securely removed from the server/drive, additional computer(s), and electronic media according to the University's Electronic Data Removal Policy.
- Data will be encrypted or removed if the electronic device is sent outside of UVa for repair according to the University's Electronic Data Removal Policy.
- If PHI will be faxed, researchers will follow the Health System Policy # 0194.
- If PHI will be emailed, researchers will follow the Health System Policy # 0193 and University Data Protection Standards .
- Data may not be analyzed for any other study without additional IRB approval.
- If you are using patient information you must follow Health System Policy # 0021.
- Both data on paper and stored electronically will follow the University's Record Management policy and the Commonwealth statute regarding the Destruction of Public Records.

If you have a question or concerns about the required security standards contact ISPRO at it-security@virginia.edu

Summary of Requirements to Comply with UVa Health System, Medical Center and University Policies and Guidance as noted above:

Highly Sensitive Data is:
-personal information that can lead to identity theft if exposed or
-data that reveals an individual's health condition and/or history of health services use.
Protected Data (PHI) a type of Highly Sensitive Data, is data combined with a HIPAA identifier
Identifiable Data under HIPAA regulations is considered to be *Highly Sensitive Data at UVa.*
A **Limited Data Set** (LDS) under HIPAA regulations is considered to be *Moderately Sensitive Data* at UVa. The only HIPAA identifiers associated with data: dates and or postal address information limited to town or city, state, and zip code.
Will not include subjects age if older than 89 or subjects DOB if older than 89.

Highly Sensitive Data (Identifiable Health Info per HIPAA)	**Moderately Sensitive Data (Limited Data Set and De-identified data per HIPAA)**
General Issues	*General Issues*
Discussions in private Do not share with those not on the study team or those who do not have a need to know.	Do not share with those not on the study team or those who do not have a need to know
Password protect	Password protect
Physically secure (lock) hard copies at all times if not directly supervised. If not supervised hard copies must have double protection (e.g. lock on room OR cabinet AND in building requiring swipe card for entrance).	Physically secure (lock) hard copies at all times if not directly supervised.
For electronic documents turn off File Sharing; turn on firewalls; use up to date antivirus and antispyware; delete data securely.	For electronic documents turn off File Sharing; turn on firewalls; use up to date antivirus and antispyware; delete data securely.
Encrypt See Encryption Solutions Guidance *Files on Health System Network drives are automatically encrypted. If not stored there it is study teams responsibility to make sure data are encrypted.*	
If device sent out for service or repair, encrypt or remove data AND contract for repair using a UVa Purchase order.	If device sent out for service or repair, encrypt or remove data AND contract for repair using a UVa Purchase order.
Store files on a network drive specifically designated for storing this type of data, e.g. high-level security server/drives managed by Information Technology Services or the “F” and “O” managed by Heath Systems Computing Services. You may access it via a shortcut icon on your desktop, but you are not allowed to take it off line to a local drive such as the desktop of your computer (e.g. C drive) or to an individual Use Device*. May access via VPN	
Do not share with sponsor or other outside group before consent is obtained or the IRB has granted appropriate approvals and contract/ MTA is in place	Do not share with sponsor or other outside group before consent is obtained or the IRB has granted appropriate approvals and contract/ MTA is in place
If collected without consent/ HIPAA authorization will NOT be allowed to leave UVa HIPAA covered entity unless disclosure is approved by the IRB and the disclosure is tracked in EPIC	If collected without consent/ HIPAA authorization will NOT be allowed to leave UVa HIPAA covered entity unless disclosure is approved by the IRB and an MTA is in place prior to sharing of data

Highly Sensitive Data (Identifiable Health Info per HIPAA)	**Moderately Sensitive Data (Limited Data Set and De-identified data per HIPAA)**
Electronic Data Collection & Sharing	*Electronic Data Collection & Sharing*
(e.g. smart phone app, electronic consent using tablet etc.) MUST consult with ISPRO or Health System Web Development Office: 434-243-6702 ▪ University Side: IT-Security@virginia.edu ▪ Health System: Web Development Center:	
Individual-Use Device	*Individual-Use Device*
Do not save to individual-use device* without written approval of your Department AND VP or Dean. If approval obtained, data must be password protected and encrypted.	
Do not save an email attachment containing HSD to an individual use device (e.g. smart phone)	
E Mail	*E Mail*
Do not share via email with Outlook Web/ or forward email using other email vendors like Gmail/ Yahoo	
Do not send via email on smart phone unless phone is set up by Health System	
Email may include name, medical record number or Social Security number only if sending email to or from a person with * HS in their email address. *NOTE: VPR & IRB staff do not meet this criteria!*	In addition to sharing LDS, may include initials if persons sending and receiving email work within the UVa HIPAA covered entity.**
FAX	*FAX*
Verify FAX number before faxing	Verify FAX number before faxing
Use Fax Cover Sheet with Confidentiality Statement	Use Fax Cover Sheet with Confidentiality Statement
Verify receiving fax machine is in a restricted access area	Verify receiving fax machine is in a restricted access area
Verify intended recipient is clearly indicated	Verify intended recipient is clearly indicated
Recipient is alerted to the pending transmission and is available to pick it up immediately	Recipient is alerted to the pending transmission and is available to pick it up immediately

Highly Sensitive Data (Identifiable Health Info Per HIPAA	**Moderately Sensitive Data (Limited Data Set and Deidentified data per HIPAA**
Electronic Data Collection & Sharing	*Electronic Data Collection & Sharing*
(e.g. smart phone app, electronic consent using tablet etc…) MUST consult with ISPRO or Health System Web Development Office: 434-243-6702 University Side: IT-Security@virginia.edu Health System: Web Development Center: Contract must include required security measures.	
May be Stored in Qualtrics MAY NOT be stored in places like UVaBOX, UVa Collab or QuestionPro May also NOT be stored I n non-UVA licensed cloud providers, such as Dropbox, Google Drive, SkyDrive, Survey Monkey etc..	May be stored in places like UVaBox, UVaCollab, Qualtrics May NOT be stored in non-UVa licensed cloud providers, such as Dropbox, Google Drive, SkyDrive, Survey Monkey, etc.
LOST OR STOLEN	*LOST OR STOLEN*
Must report in accordance with protocol in accordance with the Information Security Incident Reporting Policy Any data breach will also be reported to the IRB of record in the report meets the criteria of an Unanticipated Problem	Must report in accordance with protocol/ in accordance with the Information Security Incident Reporting Policy. Any data breach will also be reported to the IRB of Record if the report meets the criteria of an Unanticipated Problem.

** Individual Use Device – examples include smart phone, CD, flash (thumb) drive, laptop, C drive of your computer, **The UVa HIPAA covered entity is composed of the UVa VP Office of Research, the Health System, School of Medicine, School of Nursing, Nutrition Services (Morrison's), the Sheila C. Johnson Center, the Exercise and Sports Injury Laboratory and the Exercise Physiology Laboratory.*

APPENDIX: Sponsor

Sponsor Information

1. **Explain the sponsorship for this study.**
   - NIH grant, IRB#16325. Original grant awarded to Xemed LLC. UVa has a sub-award.
   - Department of Radiology funds

2. **Do you confirm that you will obtain a contract/ material transfer agreement with the sponsor via the School of Medicine Grants and Contracts Office or the Office of Sponsored Programs (OSP)** ospnoa@virginia.edu**?** Yes