PROTOCOL NAME Human Lung Regional Ventilation Defect Severity Measured by Fluorine-19 Gas MRI

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List of Abbreviations

(e.g.)

CAMRD	Center for Advanced MR Development
CRF	Case Report Form
COPD	Chronic Obstruction Pulmonary Disease
CFR	Code of Federal Regulations
CT	Computed Tomography
DIAL	Duke Image Analysis Laboratory
DSMC	Data Safety and Monitoring Committee
DUMC	Duke University Medical Center
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GOLD	Global Obstructive Lung Disease
ICH	International Conference on Harmonization
IRB	Institutional Review Board
MRI	Magnetic Resonance Imaging
PFP	Perfluoropropane gas
PFT	Pulmonary Function Test
SF6	Sulfur Hexafluoride
SQUID	Scalable Query Utility and Image Database

1 Background

1.1 Investigational Agent

Perfluoropropane gas (PFP or C_3F_8) (Air Liquide, DMF #16400)

1.2 Preclinical Data

Various laboratories around the world have successfully used PFx gas mixtures to image morphology and function in animal lungs in vivo and in ex-vivo human lungs. Likely the first use of PFx gases in an animal study was in 1984 (20) where perfluoromethane mixed with oxygen was compared to Xenon ventilation CT studies in dogs. There was little additional activity in the field until 1998 when Kuethe's group demonstrated the use of perfluoroethane mixed with oxygen to image rat lungs using 19F MRI and respiratory triggered imaging (13). Two years later Schreiber's group demonstrated 'breath-hold' imaging of the lungs of ventilated pigs using SF6 and 'ultrafast' MRI (24). The same group evaluated dynamic imaging including wash-in/washout kinetics of pulmonary ventilation in 2001, again in ventilated pigs (23). Kauczor reviewed various strategies for lung ventilation assessment using MRI in 2002 and cited six animal studies using PFx gases for such purposes (11). Jacob et al. demonstrated imaging of ventilation and diffusion in diseased and healthy excised human lungs as well as in 7 excised canine lungs using perfluoroethane (9). Perez-Sanchez et al. used SF6 to create diffusion-weighted images in anesthetized rats as well as calculated apparent diffusion constant (ADC) maps in 2005 (18). The same group demonstrated the impact of pressure and air-SF6 composition on ADC maps in rats in 2005 (21). Schreiber's group demonstrated sub-second SF6 images in pigs in 2006 as well as static 3D and dynamic wash-in images (26). Conradi et al. expanded on previous work and evaluated hyperpolarized 3He in humans as well as PFx gases in excised healthy and emphysematous human lung using perfluoroethane and perfluoropropane (4). Most recently Schreiber's group has compared MRI of inhaled SF6 with respiratory gas analysis in anesthetized pigs and found correlations adequate for lung function analysis (22).

1.3 Risk/Benefits

There likely will be no direct benefits to the subjects, other than increased understanding of their COPD. There will be not direct benefits to the subjects without lung disease. The benefits resulting from this research includes a better understanding of COPD structure/function relationships and how these relate to clinical trajectories and therapeutic responses. This should translate into better-targeted therapies and more focused clinical trial designs.

1.3.1 Potential Risks

1. Pain and/or hematoma formation may occur at blood sampling site. This is not a serious complication.
2. Dizziness during blood sampling may occur.
3. Spirometry may exacerbate bronchospasm, but in our laboratory this has not been a

serious problem.
4. Ionizing radiation exposure from HRCT
5. The risks of participating in the MRI component of the study are considered minimal. MRI is a non-invasive imaging modality that involves no ionizing radiation. At the time of recruitment/consenting and again before the MRI session, all subjects will complete a standard questionnaire to screen for contraindications to MRI imaging (e.g. presence of metal in the eye).
6. The primary risk of the perfluorinated gases would be asphyxiation if breathed without oxygen present. This risk is minimized by obtaining the medical grade agents premixed with oxygen and with certificates of analysis. Further, as described in the preliminary data and research methods the source gas oxygen level is tested in the source gasbag prior to the study (510k cleared Oxygraf system) and the subject's oxygen saturation is monitored with pulse oximetry before, during and after the MRI. Any abnormal drop in oxygen saturation based on absolute levels ($SpO_2 < 90\%$) or levels observed relative to room air breath-hold maneuvers OR any indication of a problem will the source gas would cause termination of the procedure. In addition, the gas is delivered via a disposable mask with spirometer filters to isolate the subject from the gas delivery system. Further, we monitor inhaled and exhaled flow with MR compatible pneumotachometers (510k cleared).

1.3.2 Protection Against Risk

1. Pain and/or hematoma formation may occur at the blood drawing site. We have experienced coordinators and pulmonary function technologists certified in both arterial and venous blood sampling.
2. Dizziness during blood sampling may occur. Subjects will be supine during blood sampling to avoid this problem.
3. Spirometry may exacerbate bronchospasm, but in our laboratory this has not been a serious problem.
4. Subjects will stay on their prescribed oxygen levels while participating in the study. Please note, this includes all the imaging components (CT and MRI)
5. HRCT will be performed in accordance with all Duke Department of Radiology procedures to minimize unnecessary ionizing radiation. The risks of the delivered radiation (increased cancer risk) is described out in the required consent language and compared to other risks of everyday life (refer to section 1.3.4).
6. All data will be maintained in secured files within the Duke Research site or in the SQUID research image management system.
7. Subjects will be monitored as follows during the imaging procedures: (a) monitoring of SpO_2 before during and after the examination (any SpO_2 levels < 90% will cause the study to be terminated (b) monitoring of exhaled oxygen (%) and CO_2 (%) using a laser based capnograph. Further, we monitor inhaled and exhaled flow with MR compatible pneumotachometers (510k cleared).
8. Duke University has formal education and certification procedures regarding research ethics (www.irb.mc.duke.edu/certification.htm). All research personnel will complete these in full before entry into the protocol; the nature and risks of the study will be reviewed with each subject.
9. Each subject will be given the opportunity to read the consent form and ask questions.

After all questions by the study subject are answered, and before any protocol specified procedures are initiated, each subject will sign and date the consent form. A copy of the signed consent will be provided to the subject

1.3.3 MRI Risk

MRI uses a magnet and radio waves to make diagnostic medical images of the body. There have been no ill effects reported from exposure to the magnetism or radio waves used in this test. However, it is possible that harmful effects could be recognized in the future. A known risk is that the magnet could attract certain kinds of metal. Therefore, The technologist will carefully ask the subject about metal within the subject's body (this includes certain dyes found in tattoos). If there is any question about potentially hazardous metal within the subject's body, we will be excluding the subject from participation in this research study. We will also keep the exam room locked so that no one carrying metal objects can enter while the subject is in the scanner.

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

1.3.4 Computed Tomography (CT)

CT is a way to make x-ray images of the inside of the body. The CT scanner is a doughnut-shaped machine that uses x-rays to create computer pictures that show structures inside your body more clearly than regular x-ray pictures. During the procedure, a technologist will take the subject into the CT scan room where the subject will lie down on the table (usually on the subject's back) inside of the CT machine. The subject should get comfortable because it is very important the subject does not move during certain parts of the test. CT examinations differ depending on the part of your body being studied. For example, if your abdomen is being studied, a series of pictures will be taken from your lower chest to your lower pelvis. During the study, the subject will be asked to hold their breath so that the pictures will not be blurred. The machine will make some noise, and the table will move during the scan. Also, the subject may receive signals from the technologist or from the machine about their breathing.

If the subject is taking part in this research, the subject will have one or more medical imaging studies that use radiation. The tests or treatments the subject will have include lung CT scan (inhale/exhale). The radiation dose from this research is about 4 millisievert. To give subject an idea about how much radiation will get, we will make a comparison with an every-day situation. Everyone receives a small amount of unavoidable radiation each year. Some of this radiation comes from space and some from naturally occurring radioactive forms of water and minerals. This research gives your body the equivalent of about 1 extra year's worth of this natural radiation. The radiation dose we have discussed is what you will receive from this study only, and does not include any exposure you may have received or will receive from other tests.

A possible health problem seen with radiation exposure is the development of cancer later in life. This extra cancer risk is higher at younger ages and for girls and women. The extra lifetime risk of dying of a fatal cancer due to the radiation exposure from this research may range from about one in 8,000 to about one in 3,000. At such low radiation exposures, scientists disagree about the amount of risk. These estimates are very uncertain, and there may be no extra risk at all.

We can compare this possible extra cancer risk to other risks (over a lifetime) that everyone is subject to in everyday life. For example, the chances of a person dying of cancer with no extra radiation exposure are about one in 4. The chances of dying in a car crash are about one in 82, and the chances of being killed by a car while crossing the street are about one in 730.

1.4 Dose Rationale

Each subject will receive PFP as a contrast agent to visualize the airway and alveolar spaces in their lungs using magnetic resonance imaging of inert gas/oxygen mixtures.

1.5 Trial Design

An open label study in 250 subjects over five years. We are planning 130 subjects with COPD (varies stages of GOLD I-IV) and 120 normal subjects (non-smokers, ex smokers and current smokers with normal PFT's).

1.6 Literature

Gas trapping by HRCT

Air trapping can be detected by CT (14) (11) at suspended or full expiration with straightforward analysis of the image density in the lung field usually by counting pixels below a threshold value, e.g. <-856 in the COPDGene protocol. Air trapping using HRCT has been shown in recent work associated with the COPDGene project to be perhaps the only clinical phenotype to identify the several genotypes of COPD (http://www.copdgene.org/ats-abstracts-2010) (17) (7). We will focus on measuring such trapping in Aim 1.1 as well as washout using temporal measures of PFx image intensity in Aim 1.

Preliminary Studies

1. **IND and Mixed Gases from Air Liquide/Scott Medical Products**

Before the initiation of these studies we received a full FDA safety review and obtained IND 104,917 (Evaluation of Regional Ventilation in Normal Subjects and Subjects with Airway and Lung Disorders Using 19F Magnetic Resonance Imaging of Inert Perfluorinated Gases mixed with Oxygen (SF6, and PFP): A Phase 1 Study). We provided this information to our IRB in support of local approval of the protocol. Our shipments of gas mixtures have undergone microbial limit testing under USP <1111>, USP <61> and USP <62> as required by the FDA Note that these gases are supplied at low pressure to insure that the dense gas component remains in the gaseous state. Example calculations follow: The gas mixture is formulated to have a 'dew point' of 0°C, i.e. it will not 'condense' above 0°C. The vapor pressure of PFP at 0°C is 60.41 psi. In order to determine the overall pressure of the mixture we divide the vapor pressure by the concentration in the mix to get the corresponding mix pressure (at 0°C). Then multiply by 294/273 (°Kelvin to °C conversion) to find the pressure at 21°C/70°F (assumed room temperature). So, for 79% PFP mix, it is: 60.41 / 0.79 = 76.46 psia @ 0°C x 294/273 = 82.35

psia @ 21°C - 14.7 = 67.65 psig @ 21C.

2. **Initial Human Images and Physiological Monitoring**

We have initiated a proof of concept study under IND 104,917 and with local IRB approval (Evaluation of Regional Ventilation in Normal Subjects and Subjects with Airway and Lung Disorders Using 19F Magnetic Resonance Imaging of Inert Perfluorinated Gases mixed with Oxygen (PFP): A Phase 1 Study). We have consented 44 subjects minus one withdrawal, screened 43 subjects in the study with the characteristics described in Table 1 and scanned 30 subjects (reasons for non scanning of subjects: 1 voluntary withdrawal prior to any study participation, 5 body habitus (too obese), 4 screen fails, 4 MRI contraindications).

Disease Status	Number of Subjects Screened (F/M)
Normal	13 (5/8)
COPD	11(7/4)
COPD, Emphysema	4 (1/3)
COPD Emphysema, Asthma, Small Airway Disease	1(1/0)
COPD Asthma, Small Airway Disease	1 (1/0)
Asthma	2 (2/0)
Asthma, small airway Disease	2 (2/0)
Cystic Fibrosis	5 (4/1)* all with lung transplant
Lung Transplant	2 (1/1)
Small Airway Disease	1 (1/0)
Unknown Etiology	1 (0/1)
Total	43 (25/18)

Table 1: Disease profiles of screened subjects in the phase 1 proof of concept study

2 Trial Objectives

The proposed study will determine regional qualitative and quantitative lung function information in the context of the clinical trajectory of COPD defined by the cross sectional cohort components. Due to the long time-frame of this disease we are using a modified case control design that allows a cross-sectional evaluation of the proposed measures in aims 1-2 to identify putative markers that could later be tested as prognostic factors in longitudinal studies. In the case of these PFx/oxygen mixtures, the availability of multi-liter quantities allows for wash-in/wash-out image acquisition and analysis allowing direct measures of gas trapping in a manner not easily achieved with any existing modality.

3 Trial Design

The central hypothesis and current observation is that PFx gases used as contrast agents provide functional images of the lung airways including important regional ventilation information such as ventilation defect severity and gas trapping. We will test the central hypothesis and accomplish the overall objective by addressing the following specific aims:

3.1 Primary Study Aims/Secondary Aims

Aim 1: Determine quantitative measures of lung ventilation performance in terms of direct measures of gas trapping measured during washout of the perfluorinated gas mixture.

Sub-aim 1.1: Compare gas trapping from aim 1 with air trapping by HRCT using conventional analysis procedures.

Sub-aim 1.2: We will accomplish this aim (as well as Aim 2) in a well-characterized cohort of subjects with COPD and subjects with normal global pulmonary function tests (non-, ex- and current smokers). This cohort will provide the basis for the cross sectional evaluation of the imaging markers in all aims with respect to disease severity (e.g. GOLD status) and risk factors (e.g. smoking)

Aim 2: Determine ventilation defect severity by comparing regional gas signal during wash-in of the perfluorinated gas mixture to steady state in the same cohort.

The outcomes of the work proposed in the aims is expected to demonstrate a novel quantitative approach for ventilation defect and gas trapping evaluation of regional lung function in humans that would be easily deployed for multi-center studies. It should also provide a set of biomarkers that could better inform evaluation of new treatments.

3.2 Trial Treatment

Each subject will receive PFP gas as a contrast agent to visualize the airway and alveolar spaces in their lungs using magnetic resonance imaging of inert gas/oxygen mixtures. The subjects will receive the gas by breathing normoxic mixtures of the gas using a 6500 V2 Disposable oral-nasal mask and a standard Douglas Bag system. No additional drug products, investigational or otherwise will be provided in this study. The subject will be monitored with a MRI compatible pulse oximeter as well as exhaled % oxygen and carbon dioxide.

3.3 Duration

3.3.1 Screening (V0)

1. Obtaining Informed Consent from each subject
2. History and Physical exam. The history will focus on onset of symptoms, co-morbidities, and smoking/occupational/environmental history. Also included:
    a. An assessment of patterns of exacerbations (mild = use of oral antibiotics and/or steroids for an acute change in respiratory status; moderate = hospital admission for a change in respiratory status; severe = requirement for mechanical ventilation for a change in respiratory status).
    b. A measurement of the body mass index (BMI).
    c. A medication history (oral steroids, chronic bronchodilator use, oxygen use) with an emphasis on whether adherence was adequate.
    d. Assessment of gastro-esophageal reflux disease (10)
    e. Epworth Sleepiness Scale as a marker of sleep disordered breathing

   f. Estimate of daily physical activity (25)
3. Pulmonary function tests will include spirometry, plethysmographic lung volumes, and corrected carbon monoxide diffusing capacity (DLCO). All procedures will be done in accordance with ATS/ERS standards (3) (15) (17).
4. High resolution computerized scans of the chest (HRCT). Emphysema scores will be calculated per COPD Gene protocol (7). We will also explore novel approaches to quantifying airway structures (5) (16)
5. A six-minute walk test with monitoring of pulse oximetry and heart rate will be conducted in accordance with ATS standards (1)
6. Vital Signs will be measured and recorded (temperature, heart rate, blood pressure and respiratory rate)
7. Pulse oximetry will be measured and recorded.
8. Weight and height will be recorded.
9. Quality of Life (QOL) will be assessed using the St George self-administered instrument
10. A serum pregnancy test will also be performed in women with child bearing potential.

MRI will be collected at the study visit 1 after the screening visit. Where possible the screening visit (V0) and MRI visit (V1) will be accomplished on the same day for the convenience of the subject. In all cases, the MRI will be followed-up immediately following the MRI procedure for any adverse events. Finally, all subjects will be contacted 24 hours post-MRI by phone for follow-up regarding any adverse events.

3.3.2 Visit 1: MRI

Visit 1 will include a rescreening for MRI safety by the MR Technologist, (if not performed at screening), the MRI exam, Vital signs (temperature, heart rate, blood pressure, respiratory rate and pulse oximetry) will be collected at pre and post imaging examination. A urine pregnancy test will be performed on female of child-bearing potential if the screening serum test was given 48 or more hours earlier. They must have a negative result to further participate in the study.

Additionally, subjects will be carefully observed for any signs of hypoxia before, during, and after the MRI exam using pulse oximetry. Any SpO2 reading < 90% will result in termination of the study.
Subjects will stay on their prescribed oxygen treatment, while participating in the study. Please note, this includes both imaging components (CT and MRI)

3.3.3 Twenty-four Hour Follow-up

Twenty-four hours post V1 (and subsequent imaging visits) the subjects will be contacted by phone and questioned regarding any post MRI adverse events. (Refer to Table 2 for the scheduled of events.)

Table 2: Scheduled of Events

Protocol Activities	Screening (V0)	Study Visit (V1)	Follow Up (24 hours by phone)
Informed Consent	X		
General Medical History	X		
Physical Exam	X		
HRCT [1]	X		
Weight and Height	X		
Concomitant Medication	X		
Pregnancy Test (serum and urine) [2]	X		
Quality of Life Assessment	X		
MRI Screening Form	X	X	
Vital Signs Assessment	X	X	
Pulse oximetry	X	X	
Six Minute Walk Test	X		
Thermally Polarized Gas MRI		X	
Pulmonary Function Test	X		
Adverse Event Assessment		X	X
[1] depending on scheduling, the HRCT will be performed at screening (V0) or between screening (V0) – study visit (V1)			
[2] Females of child–bearing potential who had a blood pregnancy tests performed, will have a urine pregnancy test if blood test was given 48 or more hours earlier			

3.4 Product Accountability

In accordance with ICH, we will have proper documentation with regards to product accountability. The documentation will include the following information: the gas type, dates (e.g. order, receive, certification and expiration), ALHCH Lot (or Cylinder #), and ALHACH park #.

The Cylinder # (ALHCH lot) and gas type will be included on each subject's CRF for product accountability purpose.

3.5 Data Identification

According to ICH and FDA guidance, the following data will be considered source and will be recorded directly into each subject's CRFs.

- Screening (V0)
    - Informed Consent date
    - General Medical History
    - Physical Exam
    - Weight/Height
    - Concomitant Medications
    - Quality of Life Assessment
    - Vital Signs
    - Pulse Oximetry
    - 6 Minutes Walk
    - PFT First section
- Study Visit (V1)
    - Vital Signs (pre and post imaging)
    - Pulse Oximetry (pre and post imaging)
    - For Women of child bearing potential
    - Date of the results of the pregnancy test
    - Adverse Events (post imaging)
- 24hr Follow up phone call
    - Adverse Event
    - Follow-up

The following data will be considered source but will not be recorded directly into each subject's CRFs. This data will likely be found in the subject's research folder (paper) and/or electric medical record.

- Informed Consent
- For Women of child bearing potential
    - Result of pregnancy test
- MRI screening Form
- HRCT reading
- PFT Testing results

The CRFs, the MR/HRCT images and PFT testing results will serve as source documents for this study.

4 Selection of Subjects and Withdrawal/Discontinuation

4.1 Inclusion/Exclusion Criteria for Subjects with COPD

Inclusion criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the

trial

1. Outpatients of either gender, age > 18.
2. Willing and able to give informed consent and adhere to visit/protocol schedules. (Consent must be given before any study procedures are performed.)
3. Women of childbearing potential must have a negative serum pregnancy test. This will be confirmed before participation in this investigational protocol.
4. Clinical diagnosis of COPD confirmed by Spirometry demonstrating FEV1/FVC <0.70.

Exclusion criteria

Subjects presenting with any of the following will not be included in the trial:

1. Abuse of alcohol or illicit substances.
2. Medical conditions, which, in the opinion of the investigator, will significantly affect five-year survival.
3. Medical or psychological conditions which, in the opinion of the investigator, might create undue risk to the subject or interfere with the subject's ability to comply with the protocol requirements.
4. Conditions that will prohibit MRI scanning (metal in eye, claustrophobia, inability to lie supine, renal insufficiency with eGFR < 60 mL/min/1.73 m2)

4.2 Inclusion/Exclusion Criteria for Normal Subjects

Inclusion criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the trial

1. Outpatients of either gender, age > 18.
2. Willing and able to give informed consent and adhere to visit/protocol schedules. (Consent must be given before any study procedures are performed.)
3. Women of childbearing potential must have a negative serum pregnancy test. This will be confirmed before participation in this investigational protocol.
4. Normal PFT determined by spirometry.
5. Non-smoker, ex-smoker, or current smoker.

Exclusion criteria

1. Abuse of alcohol or illicit substances.
2. Conditions that will prohibit MRI scanning (metal in eye, claustrophobia, inability to lie supine).

4.3 Subject Withdrawal and/or discontinuation

The reason for a subject discontinuing from the trial will be recorded in the CRF. A discontinuation occurs when an enrolled subject ceases participation in the study, regardless of the circumstances, prior to completion of the protocol. The investigator must determine the primary reason for discontinuation.

When a discontinuation is due to a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined below.

4.4 Treatment of Subjects

4.4.1 MRI

At the study visit (V1), MRI 'studies' will be performed using the same MR scanner (a 3.0-Tesla (T) TRIO MRI system (Siemens Medical Systems)). Lung morphology and function will be acquired using conventional ^{1}H MRI followed by ^{19}F MRI with a gaseous contrast agent mixed with oxygen for the ^{19}F MRI study. For both series the subject will lie down in a supine position on the magnet bed inside a transmitter and receive (T/R) coil for imaging of the human torso.

For the gas mixture, the inert medical grade perfluorinated gas (PFP) will be present at 79% combined with 21% medical grade oxygen. The agents will be supplied in aluminum cylinders (MR compatible) at pressures to prevent phase change of the perfluorinated component to the liquid phase. For example, in an 8 inch by 52-inch aluminum cylinder, the same format cylinder of the 79% PFP/21% oxygen mixture will contain 137 liters of the mixture.

Subjects will rest in a supine position for breathing in normal air, and then switch to PFP by a passive Douglas bag system with 35 mm tubing with remote pneumatic switching between room air and PFP and MRI compatible pneumotachometers to allow flow rate and gas volume determinations. The subjects are monitored with an MRI compatible pulse oximeter as well as exhaled % oxygen and carbon dioxide. The subjects will then exit the MRI suite.

4.4.2 High Resolution Computerized Tomography

Chest CT Scan will be performed to assess for emphysema and airway disease in all subjects. An inspiratory chest CT scan will be performed with a radiation dose of 200 mAs in order to provide thorough assessment of small airway wall thickness and emphysema. An expiratory chest CT scan will be performed of lower dose (50 mA) to assess for air trapping.

4.5 Concomitant Medication

There will be no restriction on participation based on medication use. The following concomitant medication will be recorded.

- **Beta Adrenergic agents**
- **Non-selective agents**
    - Alprenolol
    - Carteolol
    - Levobunolol
    - Mepindolol
    - Metipranolol
    - Nadolol
    - Oxprenolol
    - Penbutolol
    - Pindolol
    - Propranolol
    - Sotalol
    - Timolol
- **β1-Selective agents**
    - Acebutolol
    - Betaxolol
    - Atenolol
    - Bisoprolol

- Metoprolol
- Amosulalol
- Tilisolol
- Nebivolol
- Landiolol

- **Mixed α1/β-adrenergic antagonists**
  - Arotinolol
  - Celiprolol
  - Carvedilol
  - Labetalol

- **Quaternary ammonium compound**
  - Ipratropium
  - Tiotropium

- **Inhaled Brochodilators**
  - Albuterol
  - Arformoterol
  - Metaproterenol
  - Salmeterol
  - Terbutaline
  - Formoterol
  - Levabuterol
  - Pirbuterol
  - Fenoterol

- **Inhaled corticosteroids**
  - Beclomethasone
  - Ciclesonide
  - Fluticasone Propionate
  - Triamcinolon
  - Budesondie
  - Flunisolide
  - Monetasone Furoate

- **Leukotriene blockers**
  - Montelukast
  - Zileutol
  - Zafirlukast

- **Inhaled Combos**
  - Albuterol and pratropium Inhalation
  - Budesonide and Formoterol
  - Fluticasone Propionate and Salmeterol
  - Formoterol and Mometasone

- **Mast Cell Blocker**
  - Chromolyn

- **Bronchodilator**
  - Oxtiphylline
  - Theophylline

- **Oral Steroids**
  - Prednisone
  - Prednisolone
  - Methyl-prednisolone

- **Phosphodiesterase type 4 (PDE-4)**
  - Roflumilast

- **Medical Gas**
  - Oxygen

5 Assessment of Efficacy

5.1 Efficacy Parameters

All of the protocols in this proposal will be approved by our Institutional Review Board and reviewed periodically (every 6-12 months). In addition, a local Data Safety and Monitoring Committee (DSMC) will be established. The committee members will be pulmonologists and radiologists with knowledge of COPD, imaging techniques and clinical research procedures. The frequency of monitoring depends on the progress of the study and will range between 3 and 12 months. Any adverse event will be reported to the IRB and DSMC, and serious adverse events will be reported within 24 hours. An annual progress report (or more frequently, if requested) will be submitted to the IRB and DSMC.

5.2 Adverse Event Reporting

Any adverse event will be reported to the IRB and DSMC, and any other regulatory agents, and serious adverse events will be reported within 24 hours. An annual progress report (or more frequently, if requested) will be submitted to the IRB, DSMC and any other regulatory agents.

Significant morbidity and mortality are anticipated in these study subjects due to the nature of the disease. Deaths, exacerbations of COPD, and hospitalizations for any cause are outcome measures of the trial and will not be reported as adverse events. These outcomes will be monitored by the DSMC. In accordance with policies of the NIH, other serious events, including severe injuries and new diagnosis of potentially fatal or disabling medical conditions will be reported as serious adverse events of the study to the local IRB, the DSMC, and the NIH. The clinical investigator(s) will terminate the study immediately if the occurrence of serious adverse events that suggests unacceptable risk to the health of the subjects. All observed or volunteered adverse events, regardless of suspected causal relationship to the study procedure(s), will be recorded on the adverse events page(s) of the CRF's or worksheets. Events involving adverse experiences occurring during the study procedure(s) will be recorded.

5.3 Definitions

5.3.1 Adverse Events

Adverse event is any untoward medical occurrence in a clinical investigation by a subject who has been administered a product or medical device; the event need not necessarily have a causal relationship with the study procedures. Adverse events include the following:

- All suspected procedure-related adverse events.
- Apparently unrelated illnesses, including the worsening of a preexisting illness (see fifth bullet, below, regarding preexisting conditions).

- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (e.g., a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate adverse events. If an accident results in a subsequent adverse event (e.g., hip fracture secondary to the fall), both the accident and the subsequent event should be recorded in the adverse event CRF.
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation unless they are associated with an already reported adverse event. A test or an examination that is repeated to check a possible abnormality does not constitute an adverse event.
- Preexisting condition (i.e., a disorder present before the adverse event reporting period started and noted on the pretreatment medical history/physical examination form) should not be reported as an adverse event unless the condition worsens or episodes increase in frequency during the adverse event reporting period.

5.3.2 Serious and Unexpected Adverse Events

A serious adverse event is any untoward medical occurrence that:

- Results in death;
- Is life-threatening (i.e., puts the patient or clinical investigation subject at immediate risk of death; but not an event that, had it been more severe, might have created a risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

An unexpected adverse event is any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the study documents. In this case, “expected” does not include events that are anticipated based on pharmacological properties.

5.4 Adverse Event Follow-up

The investigator will document all directly observed adverse events and all adverse events spontaneously reported by the trial subject. In addition, each trial subject will be questioned about adverse events by phone at 24 hours post imaging. The question asked will be “Since your MRI examination, have you had any health problems?”

6 Statistical Plan

6.1 Statistical Methods and Subject Population for Analysis

We have three main methods to employ to characterize of clinical phenotypes using MR Imaging bases features.

One method is to estimate with reasonable precision the mean and standard deviation ventilation parameters from 19F gas imaging. So with 250 (5 groups) subjects we should be able using a t-test (or ANOVA) to detect a variation in defect volume of approximately 6% in the smallest sample (N = 26/group, GOLD III/IV) (alpha 0.05 and 90% power) and 5% in the reference groups (N=40/group). [Statmate Ver 2, GraphPad Software (La Jolla, Ca)].

Further, we wish to evaluate the diagnostic/prognostic ability of the MRI parameters to provide distinction among current 'phenotypes' and perhaps extend better discrimination with the MRI parameters from study aims. We will also use statistical modeling for this project to correlate the features obtained from the gas-probe MR imaging-based measures with one or more of the clinical assessment measures recorded in Aim 1.2, to better characterize disease phenotypes and identify the most promising prognostic indicators.

In a similar context, a recent study has shown such promise for certain CT imaging-based features (7). Thus, if the role of MR imaging-based measures can be established in a similar fashion then, associated with a link £, is some MR-defined variable Z which can define a biomarker, risk factor or phenotype R, resulting in the general linkage statement of R←£→GOLD+MRI. The makeup of this biomarker would contain information obtained from one or more measures Aims 1, 1.1 and 2 as well as other clinical status information X (as codified in the GOLD score or more generally some combination of the demographic, physiological and past history information, (Aim 1.2). This biomarker would then provide a more rapid and efficient means for deciding treatment strategies. We will examine the diagnostic/phenotyping ability of the MR imaging-based features (Aims 1 and 2) in terms of their ability to predict existing clinical phenotypes (GOLD) characterized and other clinical features (Aim 1.2). For this purpose, we will divide the predictors into two categories: a) clinical assessments features (Xa1, Xa2,…, Xak), obtained from existing clinical, physiologic, and HRCT imaging, measured under Specific Aims 1.1 and 1.2; b) features obtained from MR imaging (Xb1, Xb2,…, Xbl), identified under Aims 1 and 2. A generalized linear model of the form [1] will be fitted using the method of maximum likelihood:

$$g(Yt) = \beta a0 + \beta a1Xa1 + \ldots + \beta akXak + \varepsilon \quad [1]$$

The predictability of this model will be calculated using the Akaike Information Criterion (AIC) statistic (2), which balances the quality of fit (likelihood) against model complexity (8). Selection of the optimal subset of predictors will be achieved via a search over predictor space to identify the subset that maximizes the AIC statistic.

6.2 Termination Criteria

Premature termination of this clinical trial may occur because of a regulatory authority decision, change in opinion of the IRB, or at the discretion of the FDA. DUMC also reserves the right to discontinue the trial prior to inclusion of the intended number of subjects, but intends only to exercise this right for valid scientific or administrative reasons.

After such a decision, the investigator must contact all participating subjects within 4 weeks. All trial materials must be collected and all CRFs completed to the greatest extent possible

7 Direct Access to Source Data/Documentation

During trial conduct, DIAL will conduct periodic monitoring to ensure that the protocol and GCP are being followed. DIAL staff will review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow DIAL staff and appropriate regulatory authorities direct access to source documents to perform this verification.

8 Quality Control and Quality Assurance

The trial site (Duke) may be subject to review by IRB and/or to quality assurance audits performed by Duke, and/or to inspection by appropriate regulatory authorities from the US. It is important that the investigator(s) and their relevant personnel are available during these monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

9 Ethical Considerations

9.1 Institutional Review Board

It is the responsibility of the investigator to obtain prospective approval of the trial protocol, protocol amendments, informed consent forms, and other relevant documents, e.g., advertisements, if applicable, from the IRB. All correspondence with the IRB should be retained in the Investigator file. Copies of IRB approvals should be retained at Duke.

The only circumstance in which an amendment may be initiated prior to IRB approval is where the change is necessary to eliminate apparent immediate hazards to the subjects consistent with applicable regulations. In that event, the investigator must notify the IRB in writing in a time frame consistent with Duke policy and applicable regulations

9.2 Ethical Conduct of the Trial

The trial will be performed in accordance with the protocol, ICH, GCP guidelines, and applicable local regulatory requirements and federal laws.

9.3 Subject Information and Consent

The informed consent form must be approved by the Duke IRB and must be in compliance with ICH, GCP, local regulatory requirements, and federal laws. The investigator must ensure that each trial subject is fully informed about the nature and objectives of the trial and possible risks associated with participation. The investigator will obtain written informed consent from

each subject subject's before any study-specific activity is performed. The informed consent form used in this trial, and any changes made during the course of the trial, must be prospectively approved by the IRB before use. Additionally, the FDA will be notified of any changes prior to implementation as appropriate. The investigator will retain a copy of each subject's signed consent form.

The subjects will be asked to provide contact information for their primary care (or other physician) so that they can be notified if any potentially clinically relevant findings are obtained from standard clinical procedure (e.g HRCT or PFT's). This contact information will be kept in the subjects research record.

10 Data Handling and Record Keeping

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this trial. A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Duke and should not be made available in any form to third parties, except for authorized representatives of Duke or appropriate regulatory authorities, without written permission from Duke.

It is the investigator's responsibility to ensure completion and to review and approve all CRFs. CRFs must be electronic signed by the investigator or by an authorized staff member. These signatures serve to attest that the information contained on the CRFs is true. At all times, the investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs.

The CRFs, the MR and HRCT images and PFTs testing results will serve as source documents for this study.

10.1 Data Management

All patient data will be collected on a dedicated and encrypted Duke University server. The data entry system will check for out-of-range and other implausible data entries and immediately prompt the study coordinator to confirm or correct the entry. All patient data files will be de-identified.

10.2 Data Storage

All MRI images are stored in DIAL for QA/QC and image analysis; CAMRD will be notified of cases of unacceptable image quality to enable the rescheduling of scans accordingly. Subjects can be rescanned a maximum of one (1) time. The data will be de-identified and stored in the research image management system SQUID, a research image management system in DIAL.

10.3 Record Retention

As required by law and to enable evaluations and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (i.e., sufficient information to link records to identity), all original signed informed consent forms,

copies of all CRFs, other source documents, and detailed records of treatment disposition. The investigator according to International Conference on Harmonization (ICH), or federal, and local regulations should retain the records, whichever is longer.

If the investigator relocates, retires, or for any reason withdraws from the trial, the trial records must be transferred to an acceptable designee, such as another investigator at Duke. The investigator must obtain Duke's written permission before disposing of any records, even if retention requirements have been met.

11 Publication Plan

The conditions regulating dissemination of the information derived from this clinical trial are compliant with existing Duke policies.

12 Reference

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