Study Description
AAAQ8089
VAPE-Tox Study
Version 1.4 5/11/2017

Protocol Title: Ventilation and Pulmonary Endothelium Toxicities (VaPE-Tox) of E-cigarettes: A Randomized Crossover Pilot Study

1. Study Purpose and Rationale.

As e-cigarettes become increasingly popular, bolstered by claims that they are relatively safe, there is an urgent need for data on the safety of inhalation of e-cigarette vapor. Decades of research have demonstrated that the primary site of toxicity of conventional cigarettes is the lungs. However, years of exposure are required to affect most standard physiologic measures, and e-cigarettes have not been used for long enough to estimate reliably chronic effects. Recent advances in non-invasive, radiation-free imaging of the lung, developed in part by our group, provide sensitive, specific and reproducible measures to quantify acute pulmonary effects of e-cigarettes and to predict potential long-term harms. **The proposed study employs these measures and, thus, may be used to inform regulation.**

E-cigarettes may cause acute airway changes due a large number of airway irritants. Heated propylene glycol (PG), nicotine, and carbonyls – all commonly found in e-cigarette vapor – stimulate vagal C-fibers in the pulmonary epithelium that trigger neuropeptide release, inflammation, mucous production, bronchoconstriction, and, potentially, airway remodeling leading to chronic lung diseases. Consistent with this, e-cigarette liquid induces airway inflammation and hyper-responsiveness in mice and its use, in humans, increases airway impedance and peripheral airway resistance by oscillometry. However, e-cigarettes have not been proved to reduce lung function, possibly due to the insensitivity of spirometry. Hyperpolarized helium (^{3}He) magnetic resonance imaging (MRI) has been used to demonstrate the extent of ventilation defects in healthy persons with normal spirometry; to measure ventilation changes in asthmatics pre- and post-challenge with albuterol and methacholine; and to predict pulmonary hospitalizations in persons with COPD. Hence, **^{3}He MRI represents a promising but as-yet untested approach to detect, measure, and illustrate acute airway effects of e-cigarettes that may predict increased long-term risk of chronic lung disease.**

Nicotine and carbonyls such as acrolein have well-established effects on the endothelium, suggesting that e-cigarettes may cause acute pulmonary microvascular changes. E-cigarette vapor with and without nicotine causes endothelial barrier dysfunction *in vitro* and, in humans, has been associated with decreased exhaled nitric oxide, a major vasodilator and regulator of pulmonary microvascular tone. E-cigarette-related endothelial dysfunction may therefore decrease pulmonary microvascular perfusion, which is implicated in the pathogenesis of emphysema. Until recently, direct measures of pulmonary microvascular blood flow were lacking. **Our group has developed an innovative measure of pulmonary microvascular blood flow (PMBF) on gadolinium (Gd)-enhanced magnetic resonance imaging (MRI), which we found to be markedly abnormal in early chronic obstructive pulmonary disease (COPD) and emphysema, and associated with increased endothelial microparticles, a marker of endothelial apoptosis;** however, PMBF has never been used to assess e-cigarette effects.

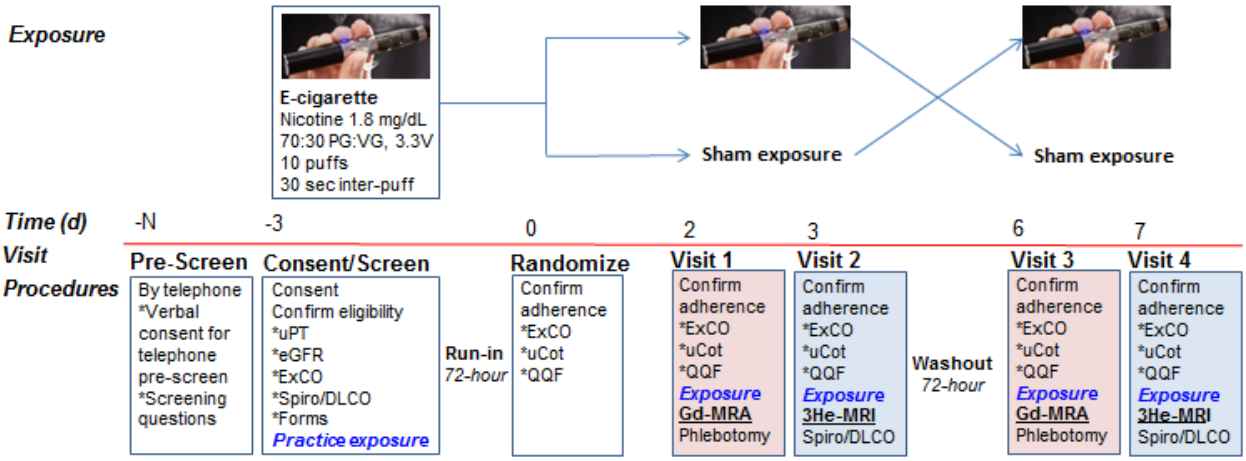
We therefore propose **to test the acute effects of a standardized e-cigarette exposure on pulmonary ventilation and perfusion in a randomized crossover design in 10 young, healthy, e-cigarette users.** We hypothesize that e-cigarette exposure will:

1. Increase global and regional ventilation defects on ^{3}He-MRI.
2. Decrease global and regional pulmonary microvascular blood flow.

This pilot work will provide **the experience and data to support subsequent funding applications powered to establish definitively the acute pulmonary effects of e-cigarette vapor** of various compositions (e.g., with and without nicotine, with and without flavoring) in persons with and without chronic lung diseases (e.g., asthma and COPD) with respect to ventilation and microvascular perfusion. Furthermore, **confirmation of our hypotheses in this modest sample would provide important, vivid preliminary data to inform regulatory decisions** regarding warning labels and public health education.

2. Study Design and Statistical Procedures.

We propose a randomized crossover clinical trial following a run-in period to test the acute pulmonary effects of a standardized e-cigarette exposure on ^{3}He-MRI/MRA measures among ten young, healthy intermittent e-cigarette users.



Pre-Screening

Potential participants will be pre-screened for eligibility by trained research assistants via telephone. A verbal consent script will be used and an information sheet will be provided. Participants found to be eligible on pre-screening will be referred for the first study visit for full written informed consent for study procedures and for additional screening (See **Figure 1**, "Consent/Screen"). Screening forms for those who are found to be ineligible (or for those who are pre-screened as eligible but do not, for any reason, sign written informed consent at the first study visit) will be abstracted, reviewed by the PI, and then discarded in a secure fashion such that no PHI is retained.

First Study Visit

All eligible participants will undergo written informed consent, additional screening procedures, and initial evaluation and then be entered into a run-in period to ensure their ability to abstain from non-study e-cigarettes and regular cigarettes for the duration of the study (**Figure 1**).

Randomization

Participants who are confirmed as adherent after the run-in period will be immediately assigned by random number generator in SAS to receive the e-cigarette exposure on days 2-3 or on days

6-7, with a 72-hour period between exposed and unexposed conditions**.** Allocation will be concealed until Day 2, when the first experimental exposure is administered.

Experimental exposure

For the experimental exposure, all participants will use identical, study-provided e-cigarette devices; however, these study devices will not be shared between participants. Each device will be labeled with the participant number and stored securely between participant uses. After a participant completes the study, that participant's dedicated device will be discarded by Environmental Health and Safety.

"Pen-style" e-cigarettes confirmed to be MRI-safe will be used. Cartomizers, batteries, and e-liquids will be obtained from commercial suppliers. The e-cigarette device will be loaded with 2 mL of flavorless e-liquid with a ratio of PG to vegetable glycerin of 70:30 and 1.8 mg/dL of nicotine. Please see **Section 5.3** for additional product details.

Consistent with prior literature, the study e-cigarette exposure will be 10 puffs with 30-second inter-puff intervals, as directly observed by a trained research assistant, using the standardized e-cigarette. This is anticipated to generate a plasma nicotine concentration of 19 ng/mL, similar to 10 puffs of a conventional cigarette. The exposure will be administered under a fume hood (Airtech Laminar Flow Workstation, Model ATG 220 UV Therapy Isolation Booth, http://www.airtechlaminarflow.com/atg-220.htm) at the enrollment visit in the CTSA and in the negative-pressure MRI scanner rooms at two of the four imaging visits.

Blinding

The "unexposed" condition will be breathing from the study e-cigarette with the battery off (or, if this is not feasible, completing the prescribed "puff" maneuvers using only room air). To assess the adequacy of blinding, participants will be interviewed at the end of study regarding whether they were able to guess correctly their allocation assignments.

Imaging

Gadolinium-enhanced MRI will be performed on days 2 and 6, ensuring >48-hour clearance of gadolinium, and ^{3}He-MRI for ventilation will be performed on days 3 and 7.

ΔFEV_1	Δ VDP	80%	90%	95%
1%	0.34	66	88	108
2%	0.68	24	32	39
3%	1.02	15	20	24
5%	1.70	10	12	15

ΔSI	80%	90%	95%
-.05	189	252	311
-.10	47	63	77
-.15	22	28	34
-.20	13	17	20

Statistics

As this is a randomized crossover trial, statistical procedures will consist mainly of permutation tests. The proposed study is designed to generate preliminary data rather than definitively to confirm or rule out acute pulmonary toxicities of e-cigarettes, although the proposed sample may be adequate to detect large effects (**Table 1**). We will have 60% power at an alpha of 5% in two-tailed significance testing to detect the 1.02 increase in ventilation defect percentage (VDP) that may be predicted based on prior literature showing an approximately 3% FEV_1 decline with e-cigarettes and additionally assuming that prior associations between FEV_1 and VDP are linear. Based on published associations between secondhand smoke, endothelial microparticle concentrations, and pulmonary microvascular measures such as signal intensity (SI) we might anticipate a 5% decrement in PMBF from secondhand smoke exposure alone; however, the effect is likely to be larger for e-cigarette vapor given its much higher nicotine yield.

3. Study Procedures

Pre-screening

After providing verbal consent for participation in the telephone screening questionnaire, which will be administered by a trained research assistant or a study investigator, participants will answer 18 questions relating to major inclusion/exclusion criteria for ongoing involvement in the study (see attached document).

Main study procedures
All participants will provide written informed consent prior to enrollment using the appropriate, approved consent form with signature obtained by one of the investigators or staff listed as such in the Personnel section.

The timing of procedures is schematized in **Figure 1**. The procedures are as follows:

1. Questionnaires: Questionnaires will be administered to all study participants covering respiratory symptoms, medical (including exacerbations) history, cigarette/e-cigarette use, and MRI and spirometry exclusions (including pregnancy).
2. Physical Assessment: Blood Pressure will be measured following the MESA protocol. Height and Weight will be measured with a scale and stadiometer. Resting and exercise oxygen saturation will be measured non-invasively with a pulse oximeter.
3. Phlebotomy: At the enrollment visit and at Imaging Visits 1 and 3, non-fasting venous blood samples will be collected to measure creatinine, oxygen tension, complete blood count, and serum nicotine. A maximum of 60 ml (4 tablespoons) will be collected at a given visit. Samples will also be banked for future analyses.
4. Urine collection: urine will be collected at all study visits for cotinine measurement (uCot) and pregnancy test (uPT) for all women. Urine will also be banked for future analyses.
5. Exhaled carbon monoxide (ExCO): Participants will exhale into a portable monitor, which will indicate whether the participant has recently smoked conventional cigarettes.
6. Spirometry (Spiro): All participants will undergo uniform, standardized spirometry at the enrollment visit and prior to and after 3He-MRI scanning. Spirometry will be performed using a SensorMedics model 1022 rolling-barrel spirometer and/or the NDD EasyOne in accordance with American Thoracic Society (ATS) guidelines.
7. Diffusion Capacity (DLCO) and lung volumes: These non-invasive tests are similar to spirometry, but involve less effort. Diffusion capacity may be measured by the rebreathing technique in which the participant will be asked to breathe through a closed circuit while the flow and volume of inspired and expired gas are measured following ATS guidelines. This will be performed at the enrollment visit and before and after 3He-MRI scanning by NDD EasyOne Pro.
8. Exhaled breath condensate (EBC): Participants will be asked to breathe into an EBC collection device (Rtube System, Respiratory Research Inc, Charlottesville, VA) for up to 10 minutes. EBC will be aliquoted and stored for subsequent analyses.
9. E-cigarette exposure: This will be completed as described in (2) and (5) at the enrollment visit in the CTSA and at two out of the four imaging visits (days 2-3 or 6-7, depending on randomization).
10. Magnetic Resonance Imaging
    a. Ventilation Scan (3He-MRI): this exam will be used to examine the size and function of the lungs. For this exam, the participant will lie on a table inside of the MRI for about 30 minutes. Before having the MR exam, participants will be asked

questions about their medical history and any exclusion criteria. Approximately 250-400 mL of hyperpolarized 3He mixed with 600-750 mL of nitrogen will be inhaled through a one-way valve in one inhalation starting approximately at residual volume. After a rest, inhalations may be repeated up to 3 times per session. Blood pressure, respiratory rate, pulse and oxygen saturation are monitored continuously during MRI procedures.

b. Perfusion Scan (Gd-MRA): this exam will be used to evaluate pulmonary perfusion and cardiac function. For this exam, the participant will lie on a table inside of the MRI for about 30 minutes. Before having the MR exam, participants will be asked questions about their medical history and any exclusion criteria. Gadolinium contrast will be injected into the antecubital vein through an 18-20 gauge IV. The type of gadolinium will be 0.03 mmol/kg bodyweight of dotarem (gadoterate meglumine). Participants will be coached to achieve and hold in expiration (FRC) phase, with several practice attempts prior to scan acquisition.

Participants will be asked to abstain from all tobacco products, with the exception of the study e-cigarette, from the first until the final study visit (11 days). Of note, tobacco product use will not be proscribed during the interval between the pre-screening telephone call and the first study visit.

4. Results Reports: No clinical reports will be generated for participants; however, a safety read will be performed as per CUMC policy.

5. Study Drugs or Devices:

(1) **Hyperpolarized helium**. IND 123,115 has been obtained from the FDA. The helium gas is supplied by Linde Healthcare, 6600 Peachtree Dunwoody Road, Embassy Row 400, Suite 300, Atlanta, GA 30328 Phone: Main 678-225-2940. The helium is hyperpolarized using the GE polarizer and administered by inhalation, as described in the IND application. There will be no charge to participants.

(2) **Dotarem (gadoterate meglumine)** will be used as the contrast agent for the Gd-MRA at a low dose of 0.03 mmol/kg bodyweight. It will be supplied by Guerbet, 120 West 7th Street, Suite 108, Bloomington, IN 47404-3835. Contacts include Toll Free: 877-729-6679; Phone: 812-333-0059; Fax: 812-333-0084.

(3) E-cigarette

- Planned e-cigarette device: We will obtain e-cigarettes from KangerTech (Building A1, No 66 West He'xiu road, Fuyong Town, Shenzhen,China; sales@kangeronline.com). The model will be the Kanger Top Evod.
  - Alternate E-cigarette: If e-cigarette #1 is unavailable or there are other logistical issues identified, our alternate (highly similar) product will be from Halo (Corporate**:** 7916 Evolutions Way Suite 200, Trinity, Florida 34655 United States; Manufacturing**:** 5909 NW 18th Dr., Gainesville, FL. 32653 United States; Customer Service: (888) 425-6649). We will use the “Triton” Variable Voltage Battery (adjustable voltage 3.3-4.8V, 900mAh, 10 seconds battery cut off time) “Triton” tank with 3.0-3.2 ohm coil.
- Study e-liquids: study e-cigarettes will be loaded with 2mL of flavorless e-liquid with a ratio of PG to vegetable glycerin (VG) of 70:30 and 1.8 mg/dL of nicotine (AVAIL Vapor, 820 Southlake Blvd, Richmond, VA 23236, contact Holly Kempf Lewis (804) 677-1588).

6. Study Questionnaires: See attached.

7. Study Subjects:

Inclusion criteria: Age of 21-35 years at time of enrollment and self-reported voluntary, recreational e-cigarette use (>1x/month but <daily).

Exclusion criteria: any chronic major medical or psychiatric problems including current asthma; self-reported heavy snoring/sleep apnea; pre-bronchodilator FEV_1 or FVC <80% predicted or FEV_1/FVC < lower limit of normal[58]; MRI exclusions (pregnancy, claustrophobia, metal in body, gadolinium allergy, eGFR <60 mL/min/1.73m^2); MRI scan with contrast within the last 12 months or planned MRI with contrast in the next 6 months; use of any of the following in the prior 30 days: any conventional cigarettes, marijuana >10 days, any other illicit drugs, any daily medication (including inhalers) except hormonal contraceptives. Persons with an adverse symptomatic response to the study e-cigarette exposure (e.g., palpitations, shortness of breath, chest pain, headache, dizziness) will also be excluded.

8. Recruitment

Participants will be recruited from the local community and universities via fliers and word of mouth. There will be partial co-recruitment with the PI's related e-cigarette pilot studies AAAQ9965 and AAAR2000. Healthy volunteers may be drawn from CUMC/NYP personnel including residents/fellows/interns/staff. This latter recruitment will not be coercive as it is 100% voluntary and there is no recrimination for non-participation. CUMC/NYP personnel who report directly to the PI or co-I will not be recruited.

9. Informed consent and eligibility

Since the exclusion criteria for the VAPE-Tox Study are few but cannot be fully determined prior to the first study visit (Day -3), the participant will come into the clinic and first sign the informed consent and HIPAA forms. Participants will be invited to the Clinical and Translational Science Awards (CTSA) research suite, where they will be confirmed to meet all inclusion/exclusion criteria via questionnaires, exhaled CO (exCO), pre-bronchodilator spirometry, serum creatinine assay, urine pregnancy test for women, and a practice session for the study e-cigarette exposure under observation by a trained research assistant, before being asked to abstain completely from non-study e-cigarette use for the duration of the study. Eligibility will be confirmed by the PI in writing.

Adherent participants, defined on Day 0 as no interim self-reported e-cigarette use, <=10 ppm exhaled CO (exCO), and urine cotinine (uCot) <100 ng/mL, will continue immediately with randomization.

10. Confidentiality of Study Data

The consent form signed by the participant will provide written assurance that all individual data collected in the study will be kept confidential to the extent provided by the Privacy Act of 1974. Any personal identifiers will be maintained on limited-access, secure servers and never put on endpoint devices so that confidential data are not released.

Participants will be informed that: (1) the only people who will know that they are research participants are members of the research team and, if appropriate, their physicians or health care providers; (2) no individual identifying information about them will be disclosed to others, except if required by law; and (3) when the results of the study are published or

discussed in conferences, no information will be included that would reveal their identity.

Data identified by study ID and acrostic only may be transferred to the MESA COPD Reading Centers (John Hopkins University, University of Iowa, Hannover University, University of Wisconsin, Northwestern University). Coded research data will be stored on password-protected, secure servers hosted by the Division of General Medicine and certified by CUMC IT the CUMC Radiology PACS, and in locked filing cabinets in General Medicine, and potentially on endpoint devices that will, in all cases, be encrypted.

Identifiable data will be stored in the General Medicine Server described above and in locked filing cabinets in separately partitioned drives/cabinets. The linking file will be similarly protected with limited access.

11. Potential Risks

There are no direct risks or discomforts from participation in the questionnaire, anthropometry, blood pressure, oxygen saturation, urine collection, or exhaled breath condensate. The only possible risk from these components involves the social-psychological risk for the individual resulting from the **inadvertent disclosure of confidential medical information**.

Potential risks posed by the proposed study exposures and procedures are as follows:

1. **E-cigarette use**:
    a. Nicotine exposure: Side effects from products that contain nicotine can include sweating, lightheadedness, dizziness, nausea, and nervousness. These effects are unlikely in individuals who use nicotine-containing products regularly, but are more likely to occur in non-regular users. Regardless, these effects are transient and long-term adverse effects are not expected based upon the study exposure. Nicotine is also an addictive substance, therefore exposure to nicotine theoretically carries a risk of promoting addition; however, in the amounts and manner administered in the study, this is very unlikely to occur.
    b. Propylene glycol exposure: propylene glycol is contained in most e-cigarette liquids, and will make up 70% of the study e-cigarette liquid. It is often used to make "theater fog" and is considered relatively safe, but it has occasionally been associated with shortness of breath or bronchospasm, especially in people with a history of asthma.
    c. Unknown risks: The effects of e-cigarette use remain mostly unknown, which is the major motivation for this study. We are only recruiting young, healthy, adults who have already made the decision to use e-cigarettes intermittently, despite this uncertainty. A safety board will be monitoring the study.
2. **Claustrophobia**: A minority of individuals may be subject to psychological risks if they develop previously unknown claustrophobia inside the magnet. Claustrophobic episodes can be psychologically traumatic to participants; however, the trauma ceases upon removal of the subject from the scanner and does not have any known lasting effects.
3. **Magnet risks**: All MRI studies involve exposure to magnetic field strength, rate of change of magnetic field gradients, and RF power exposure within guidelines recommended by the Food and Drug Administration.
4. Risks relating to **gadolinium contrast**:
    a. **Nephrogenic Systemic Fibrosis** (NSF) is a rare fibrosing condition of the skin and organs that has been reported in association with gadolinium contrast agents and severe renal failure (GRF < 30 ml/min/1.73 m2). No reported cases have occurred above this level in patients with chronic renal impairment. Acute onset renal failure, hepatorenal syndrome, peri-hepatic transplant or kidney transplant represent additional risk factors. The clinical course of NSF is progressive and

may be fatal. The incidence in the high risk population (severe renal failure, stage 4-5, transplant, dialysis) is 2-6%.

   b. **Allergy**: there is a risk of allergic reaction after the gadolinium injection, with a less than one in 300,000 chance that this will be severe. Metallic taste in mouth, tingling in the arm, nausea, or headache occurs in less than 1% of people.
   c. **Discomfort**: Insertion of the needle to inject contrast may cause minor pain, bruising and/or infection at the injection site.
   d. **Deposition in brain tissue**: Gadolinium has recently been reported to deposit in a dose-dependent manner in the brain, although the significance of this is unknown and there is no evidence of harm.

5. Risks relating to **hyperpolarized helium contrast**:
   a. **Transient desaturation**: Although generally proved to be well-tolerated, hyperpolarized helium inhalation and the subsequent breath-hold maneuver have been found, in a subset of subjects, to cause a mean transient decrease of 4% in oxygen saturation, with recovery occurring within one minute.
   b. **Discomfort**: mild lightheadedness and headache have also been reported after 3He inhalation, although these resolved during or immediately after imaging sessions.
6. **Spirometry**: This is a non-invasive test that involves minimal risks, such as precipitating coughing or mild, transient dizziness.

For regular users of conventional or e-cigarettes, or other tobacco products, there is a risk of some discomfort during abstinence from e-cigarettes and nicotine during the study. Side effects from tobacco/nicotine abstinence can include irritability, anxiety and restlessness, excessive hunger, difficulty concentrating, and sleep disturbance. Though these potential side effects have not been characterized in e-cigarettes users, they are common abstinence symptoms in cigarette smokers. Though uncomfortable, these feelings are not medically dangerous.

The only alternative to agreeing to participate is to decline to participate.

12. Protections Against Risk

In addition to continuous monitoring by trained research assistants during all study procedures, the following specific protections will be provided against the potential risks posed by the proposed study procedures.

1. **Anthropometry, blood pressure and pulse oximetry:** There are no direct risks or discomforts from participation in the anthropometry, blood pressure or pulse oximetry to measure oxygen saturation.
2. **Questionnaires**: There is minimal risk related to questionnaires, this involves the social-psychological risk from the inadvertent disclosure of confidential medical information. We guard against this by maintaining study information identified by study number only in a filing system separate from the name and address files.
3. **Phlebotomy**: The risks associated with blood collection are minimal and include the potential to feel a little pain or get a bruise at the place where the blood is drawn. It is possible, but not likely, that there may be swelling or bleeding at the site.
4. **EBC** testing is non-invasive and involves minimal risks.
5. **Spirometry:** Spirometry is non-invasive and involves minimal risks. Spirometry can induce shortness of breath, coughing or chest tightness, and may cause the participant to feel lightheaded. It is very rarely complicated by syncope. No bronchodilators will be administered.

6. **E-cigarette exposure**: We will only recruit young, healthy, current e-cigarette using adults. Since these subjects choose to use e-cigarettes recreationally, it is reasonable to infer that they have determined independently that they are willing to accept the mostly unknown risks associated with e-cigarette vapor. Nonetheless, we will mitigate any potential risks associated with the standardized study exposure – which will employ short-term exposure to publicly available e-cigarette products containing a standardized e-liquid with moderate nicotine content and without flavorings – by requiring a monitored "test run" of the study e-cigarette exposure at the enrollment visit. All persons with an adverse response (e.g., palpitations, shortness of breath, chest pain, headache, dizziness) will be excluded. We will also provide symptomatic and hemodynamic monitoring throughout the study procedures.
7. **Claustrophobia**: We include severe, known claustrophobia as a contraindication to participation in this project
8. **Magnet risks**: All subjects will be screened to exclude those with contraindications to MR, including those with pacemakers, aneurysm clips, cochlear implants or other implanted electronic devices. Subjects with a history of occupational exposure to small metallic projectiles will also be excluded. The MR scanner areas at the sites are equipped with standard medical emergency equipment for a hospital-based MR center.
9. **Gadolinium contrast**:
    a. **Nephrogenic Systemic Fibrosis** (NSF): Participants with high-risk conditions will be excluded. GFR will be measured within two weeks of imaging, and GFR < 60 ml/min/1.73 m^2 will be the cutoff for exclusion in this study.
    b. **Deposition in brain tissue**: We will mitigate against this risk by using a low dose of gadolinium (0.03 mmol/kg) and a type of gadolinium that is not believed to be associated with this problem.
10. **Hyperpolarized helium contrast**: Medical grade 3He is hyperpolarized and mixed with inert nitrogen gas using a commercial polarizer (manufactured by GE Healthcare). 3He-enhanced MRI has been performed in over a thousand patients by 2008 and probably another 1000 since then. Since all of the inhaled 3He is expired, it is well-tolerated by health controls and patients with severe lung disease alike. The major risk is transient hypoxemia following inhalation of the gas. The mean change in SpO2 in a series of 100 subjects (controls, smokers, and severe COPD) was 0 +/- 2%, with a range from -4 to 6%, although occasionally (<5%) a significant desaturation is observed (Lutey, Radiology 2008). These have all been asymptomatic and without sequelae, to our knowledge. Other minor symptoms reported after inhalation of 3He include occasional (<5%) cough, lightheadedness and headache (similar to spirometry). We have obtained an IND from the FDA and its production at CUMC to be used in this process.

Potential problems and adverse events will be monitored and evaluated as per the Data Safety Monitoring Plan, which includes a DSMB.

12. Plan for Incidental Findings

The imaging may reveal subclinical findings that require further testing or interventions, which may be harmful, costly or cause distress.

The MRI protocols are designed for research purposes and do not necessarily provide standard clinical information on, for example, cardiac structure or function. The information obtained is specific to particular protocols, such that specific regions of the heart or lungs may be visualized with poor or no visualization of other regions of these organs or of the chest or other parts of the body.

MRI of the lungs yields generally low-resolution images of the large airways and airspaces, respectively. Only large abnormalities (e.g., large bronchiogenic cancer) would be detected.

Dr Prince, co-I (Dept of Radiology, CUMC and WCMC), will read all scans in a timely fashion for participants.

IFs of Clinical Significance will be communicated to the participants verbally and in writing. Major abnormalities (eg carcinoma) will be reported; subtle alternations of unknown clinical significance (eg regional lack of ventilation in a patient without respiratory symptoms) will not.

13. Potential Benefits

Three are no direct benefits to participants expected from this study except for the feeling of being involved in an important study. The societal benefits from the information on the relationship between e-cigarette vapor inhalation and pulmonary ventilation and microvascular perfusion are potentially large.

15. Alternatives: None.

16. Data Safety and Monitoring Plan

Please see attached document and proposed Data Safety and Monitoring Board (DSMB) roster.

17. IND Holder Responsibilities