Increased Lung Volume as Rescue Therapy for Asthma

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The University of Vermont Committees on Human Research

For Committee Use Only
PROTOCOL NUMBER

Human Subjects Research Protocol

The Common Human Subjects Protocol Cover Form **must** be completed and **attached** to the front of this form. This Protocol form should be completed for any human subjects research proposal that does not have a specific "protocol," such as a grant application. This form must be submitted along with a copy of the complete grant proposal and all the information in this form **must** be consistent with that proposal. This protocol form, once IRB approved, will be the working protocol for that research. **When completing this document, do not refer to page numbers within your grant**. If revisions are necessary during the course of the research, amendments should refer to this protocol form, not the grant proposal. Enter responses for all sections. Check N/A if the section does not apply.

PROTOCOL SUMMARY

Project Title:	Protocol Version Date:
Increased Lung Volume as Rescue Therapy for Asthma	05 March 2018

Principal Investigator: Anne Dixon

Grant Sponsor: NIH Grant Number: R01HL130847-01

(For grants routed through UVM, indicate the OSP Proposal ID # located at the top of the OSP Routing Form)

Lay Language Summary: *(Please use non-technical language that would be understood by nonscientific IRB members to summarize the proposed research project. The information must include: (1) a brief statement of the problem and related theory supporting the intent of the study, and (2) a brief but specific description of the procedure(s) involving the human subjects. Please do not exceed one single-spaced 8 ½ X 11" page.)*

The purpose of this study is to test the effect of increasing lung volume with a simple hand-held device to both prevent, and also to relieve, airway constriction in people with asthma and a BMI ≥ 30 kg/m^2.

We will recruit 20 people who have late onset non-allergic asthma and a BMI of ≥ 30 kg/m^2. We will test the efficacy of elevating lung volume on both preventing and reversing bronchoconstriction in these people. We will elevate lung volume by having patients breathe out against a small level of resistance.

The ultimate purpose of this research is to develop a new treatment for asthma that occurs in the setting of obesity.

PURPOSE AND OBJECTIVES

Purpose: *The importance of the research and the potential knowledge to be gained should be explained in detail. Give background information.*

We propose a study to investigate whether PEEP can prevent and/or reverse bronchoconstriction in obese asthmatics.

Obesity is a major risk factor for the development of asthma, with about 250 000 new cases of asthma in the United States per year related to the obesity epidemic.[1] Not only is obesity a risk factor for the development of asthma, but these patients tend to have more severe disease (with a nearly 5-fold risk of hospitalization); a recent survey study found that more than 50% of severe asthmatics in the U.S. are obese.[2-5] Our group has contributed to major advances in the understanding of this disease.[6-8] We have found a novel form of asthma: late-onset non-allergic disease that develops consequent to obesity. Understanding the pathogenesis of airway disease in this late-onset non-allergic group is the focus of the current proposal. There is a critical need to understand this form of disease as obese patients do not respond as well to conventional asthma medications, [4,5,9] likely because all treatments for asthma have

been developed to treat early-onset allergic disease in lean patients. **There is a critical need to understand the pathophysiology of airway disease in late-onset, non-allergic obese asthmatics, in order to develop therapies to target this disease.**

Airway hyperresponsiveness (AHR) is a defining characteristic in asthma. In early-onset allergic asthma, AHR is caused by lymphocyte-driven allergic inflammation which leads to remodeling in the airway and causes hyperresponsivenss of airway smooth muscle; airway narrowing results from constriction of smooth muscle, inflammatory thickening of the airway wall, and secretion of mucus and inflammatory mediators into the airway lumen. In stark contrast, we have found minimal inflammation in obese late-onset asthmatics.[7] Indeed, lung function tests are more suggestive of distal airway closure rather than airway narrowing as a cause of hyperresponiveness in these patients (see preliminary data and our recent publication in Respirology[10]). We have also found that obese individuals who develop this late-onset non-allergic asthma tend to have more collapsible lung peripheries than obese individuals who do not develop asthma.[8] This closure manifests largely in the small airways because their narrow lumens are particularly susceptible to occlusion by mucus plugs compared to larger airways (although closure can potentially occur anywhere throughout the airway tree).

The above findings from our laboratory lead us to the overarching hypothesis that **the AHR of non-allergic obese asthma reflects enhanced closure of small airways secondary to more compliant airway walls.** One of the most important and exciting implications of this hypothesis is that it suggests an immediate therapy: if late onset asthma in obesity is related to a tendency of airways to close, it should respond to therapies designed to keep airways open, such as Positive End-Expiratory Pressure (PEEP), an intervention that can be applied easily and cheaply with small light-weight valves.

The purpose of this proposal is to investigate the efficacy of PEEP on prevention and reversal of bronchoconstriction in obese people with asthma.

***References**. Include references to prior human or animal research and references that are relevant to the design and conduct of the study.*

1 Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. Am J Respir Crit Care Med 2007; 175:661-666
2 Vortmann M, Eisner MD. BMI and health status among adults with asthma. Obesity (Silver Spring) 2008; 16:146-152
3 Dixon A. The treatment of asthma in obesity. Expert Rev Respir Med 2012; 6:331-340
4 Peters-Golden M, Swern A, Bird SS, et al. Influence of body mass index on the response to asthma controller agents. Eur Respir J 2006; 27:495-503
5 Boulet LP, Franssen E. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. Respir Med 2007; 101:2240-2247
6 Dixon AE, Pratley RE, Forgione PM, et al. Effects of obesity and bariatric surgery on airway hyperresponsiveness, asthma control, and inflammation. J Allergy Clin Immunol 2011; 128:508-515 e501-502
7 Sideleva O, Suratt BT, Black KE, et al. Obesity and asthma: an inflammatory disease of adipose tissue not the airway. Am J Respir Crit Care Med 2012; 186:598-605
8 Al-Alwan A, Bates JH, Chapman DG, et al. The nonallergic asthma of obesity. A matter of distal lung compliance. Am J Respir Crit Care Med 2014; 189:1494-1502
9 Sutherland ER, Goleva E, Strand M, et al. Body mass and glucocorticoid response in asthma. Am J Respir Crit Care Med 2008; 178:682-687
10 Chapman DG, Irvin CG, Kaminsky DA, et al. Influence of distinct asthma phenotypes on lung function following weight loss in the obese. Respirology 2014
11 Finucane MM, Stevens GA, Cowan MJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet 2011; 377:557-567
12 Camargo CA, Jr., Weiss ST, Zhang S, et al. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. Arch Intern Med 1999; 159:2582-2588

13 Consortium LWGftL, Belle SH, Chapman W, et al. Relationship of body mass index with demographic and clinical characteristics in the Longitudinal Assessment of Bariatric Surgery (LABS). Surg Obes Relat Dis 2008; 4:474-480
14 Schatz M, Hsu JW, Zeiger RS, et al. Phenotypes determined by cluster analysis in severe or difficult-to-treat asthma. J Allergy Clin Immunol 2014; 133:1549-1556
15 American Lung Association-Asthma Clinical Research Centers' Writing C, Dixon AE, Castro M, et al. Efficacy of nasal mometasone for the treatment of chronic sinonasal disease in patients with inadequately controlled asthma. J Allergy Clin Immunol 2014
16. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *The European respiratory journal* 1999; 14: 902-907.

Objectives: *Clearly state the primary and secondary objective(s) of the study.*

<u>Objective</u>: To establish the efficacy of increased lung volume as a *rescue* therapy for the asthma of obesity.

- We will determine the effect of PEEP on *preventing* the increase in respiratory system impedance in response to methacholine.
- We will determine the effect of PEEP on *reversing* the increase in respiratory system impedance in response to methacholine.

METHODS AND PROCEDURES

Study Design: *Describe the research design, including a description of any new methodology and its advantage over existing methodologies.*

We will determine the effect of volume elevation produced by PEEP on reversing bronchoconstriction in obese asthmatics. We will initially perform a conventional methacholine challenge test to determine the PC_{20} to methacholine (the concentration of methacholine producing a 20% fall in FEV1, the standard clinical measure of airway responsiveness). We will also perform testing to assess the compliance of the airways in the lungs, to determine if this predicted response to lung elevation.

A) We will ask participants to return for 2 visits in which we will administer methacholine concurrently with varying levels of PEEP (using PEEP to prevent bronchoconstriction).
B) Subject will return for another 2 visits in which we will determine the effects of PEEP subsequent to methacholine challenge (using PEEP to reverse bronchoconstriction).

The reason to test both short-term time points is to assess:

A) whether PEEP has any value as an intervention that will prevent the immediate development of bronchoconstriction (i.e. bronchoprotection, analogous to using rescue therapy prior to exercise to prevent bronchoconstriction), and
B) if PEEP will reverse established bronchoconstriction (i.e. bronchodilation, as a form of rescue therapy after onset of symptoms).

These studies will be completed over 5 visits. If necessary, participants may be asked to return for an additional visit if some of the lung function tests were not completed at the regularly scheduled visits, if the lung function testing was completed, but did not produce consistent and accurate results, or if there is a longer than expected gap between study visits, which creates a need to calculate a new PC_{20} dose for the participant through an additional methacholine challenge.

Procedures: *Describe all procedures (sequentially) to which human participants will be subjected. Identify all procedures that are considered experimental and/or procedures performed exclusively for research purposes. Describe the types, frequency and duration of tests, study visits, interviews, questionnaires, etc. Include required screening procedures performed before enrollment and while on study. Please provide in table, list or outline format for ease of review. (describe and attach all instruments)*

Note: A clinical research protocol may involve interventions that are strictly experimental or it may involve some aspect of research (e.g., randomization among standard treatments for collection and analysis of routine clinical data for research purposes). It is important for this section to distinguish between interventions that are experimental and/or carried out for research purposes versus those procedures that are considered standard therapy. In addition, routine procedures performed solely for research purposes (e.g., additional diagnostic/follow-up tests) should be identified.

All procedures will be performed exclusively for research purposes.

- Baseline Medical History: we will obtain a baseline medical history and record all medications
- Baseline anthropometrics (BMI, waist and hip circumference, as well as temperature and blood pressure)
- Asthma Questionnaires: participants will complete a validated questionnaire to assess asthma control.[16]
- Berlin Sleep Questionnaire (modified version)
- Blood draw: We will draw 10 cc of blood; this will go to the UVMMC laboratory for measurement of complete blood count and differential, and IgE levels (these are used as measures of allergic status). IgE will not be repeated if tested previously.

- Blood draw: We will draw 16cc of blood, this will go to Dr. Dixon's UVM laboratory for measurement of serum biomarkers (used to detect circulating anti-inflammatory markers)
    - Subjects consenting to store leftover blood samples and data for future research on asthma and obesity will have sample stored in a bio-repository under CHRMS: 16-636.
- Spirometry without bronchodilator will be performed per standard clinical protocol.
- Urine pregnancy test will be performed at all visits.
- Lung Volumes will be measured per standard clinical protocol (by plethysmography).
- Methacholine challenge test (conventional): this will be performed per standard clinical protocol. Participants will inhale increasing doses of methacholine to identify the concentration of methacholine producing a 20% decrease in FEV_1 or FVC (the PC_{20} dose); this concentration will be used in the subsequent single dose methacholine challenge testing.
- Chest CT: A chest CT will be performed with images at different lung volumes, and with PEEP at a setting of 10 cmH_2O, to assess changes in airway diameter during breathing (if participant has not had this performed previously as part of protocol 15-327 or protocol 16-061).
- Single breath nitrogen wash out: the participant will take a single deep breath of 100% oxygen, and then exhale through a one way valve. (if participant has not had this performed previously as part of protocol 15-327 or protocol 16-061).
- Multiple breath nitrogen wash out: the participants will breathe 100% oxygen for approximately 7 minutes (normal tidal breathing). (if participant has not had this performed previously as part of protocol 15-327 or protocol 16-061).
- Single dose methacholine challenge test at PEEP 0 or PEEP 10 with forced oscillation: The experimental protocol will consist of having the subject breathe a fixed concentration of methacholine aerosol for four and a half minutes; we will use the dose of methacholine that produces a 20% fall in FEV_1. We will measure airway impedance by the forced oscillation technique before, during and after the inhalation of methacholine. Subjects breathe, taking normal breaths, through a conventional plastic mouthpiece attached to a specialized apparatus that measures respiratory impedance by pressure changes related to a variable airflow during normal breathing.

Study Visits:

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Baseline history	*				
IgE level / CBC with differential	*				
Serum Biomarker	*				
Pregnancy Test[1]	*	*	*	*	*
Asthma Control Questionnaire	*	*	*	*	*
Berlin Sleep Questionnaire	*				
Conventional methacholine	*				
Lung Volumes	*				
SBNW[2]	*				
MBNW[2]	*				
Training for CT breathing[2]	*	*			
CT imaging[2,3]		*			
PEEP + methacholine together		*	*		

Methacholine prior to PEEP				*	*
PEEP level (cmH_2O)		0	10	0	10

[1]For women of child-bearing potential
[2]Participants who have not previously completed these procedures as part of a related research protocol only.
[3] CT imaging may be performed at any of visits 2-5, at convenience of participant

Study Visits:

There will be five regularly scheduled study visits, with some participants asked to complete a screening visit, as follows:

*Screening Visit: Participants who have not had a serum IgE level drawn/results are not available will be asked to attend a screening visit. The research staff will provide participants with full details of the study. Participants who sign a consent form will have blood drawn for measurement of IgE and Complete blood count with differential (assesses allergy, and required for eligibility assessment), and for serum anti-inflammatory biomarkers. In addition, the eligibility criteria for the study will be reviewed with the participants, which may involve a height and weight measured to test for BMI eligibility.

Visit 1: This visit will take approximately 3 hours. The research staff will provide participants with full details of the study. Participants who sign a consent form will undergo the following procedures/ assessments. Past medical history, asthma control questionnaire, Berlin Sleep Questionnaire, urine pregnancy test, measurement of height, weight, blood pressure, waist and hip circumference, as well as temperature. Eligible participants will undergo spirometry and lung volumes measurements. Participants who have not previously had the following tests will undergo a single-breath (SBNW) and multi-breath (MBNW) nitrogen (N_2) washout methods to assess functional residual capacity (FRC), closing volume, closing capacity, lung clearance index (number of FRC turnovers required to reduce N2 concentration to 1/40 of its initial value), and lung heterogeneity (reflected in the washout parameters Sacin and Scond).

Participants will undergo a standard methacholine challenge for measurement of PC_{20}, a standard measurement of airway reactivity. Using the medical records we will screen for methacholine challenge results performed in the past two weeks.

Participants will also have blood drawn at visit 1, which will go to Dr. Dixon's UVM laboratory for measurement of serum biomarkers. If this blood draw cannot happen at visit 1 for logistical reasons, then it may be performed at visits 2-5.

Visits 2-5 will be conducted in random order using a schema provided by the biometry facility at the University of Vermont.

Visits 2 & 3: Participants will be questioned about their interim history to asses for adverse events and will be asked to complete the asthma control questionnaire. In addition, participants will undergo a methcholine challenge, while we continuously measure their lung function by forced oscillation.

We will administer a single dose of methacholine (as determined by their PC_{20} dose, the dose of methacholine required to produce a 20% decreased in FEV1), and measure respiratory system impedance with the forced oscillation system while concurrently applying either PEEP 0 or PEEP 10.

Visit 4 & 5: Participants will be questioned about their interim history to assess for adverse events, and will be asked to complete the asthma control questionnaire. In addition, participants will undergo a methcholine challenge, while we continuously measure their lung function by forced oscillation.

We will administer a single dose of methacholine (as determined by their PC_{20} dose, the dose of methacholine required to produce a 20% decreased in FEV1), and measure respiratory system impedance with the forced oscillation system, *after* the single dose of methacholine, we will apply either PEEP 0 or PEEP 10.

Participants who have not had a chest CT as part of protocol 15-327 will undergo a protocolized non-contrast chest CT. Images will be taken at full inspiration, resting expiration (FRC), full expiration (residual volume), and resting expiration with PEEP10cmH_2O. Images will be recorded using standardized procedures, and analyzed using commercially available software for quantification of airway diameter, airway thickness, and lung attenuation at standardized locations in both lung fields. These measurements will allow us to directly quantify changes in the large airways (diameter and wall thickness), and also airway trapping (degree of attenuation) through the normal respiratory cycle.

Additional Visit: Some participants may be asked to return for an additional visit if some of the lung function tests were not completed at the regularly scheduled visits, if the lung function testing was completed, but did not produce consistent and accurate results, or if there is a longer than expected gap between study visits, which creates the need to calculate a new PC_{20} dose with an additional methacholine challenge.

This additional visit may involve spirometry, lung volume measurements, single-breath nitrogen washout, multiple-breath nitrogen washout, a methacholine challenge, or the forced oscillation procedure with a single dose of methacholine, depending on the need for the specific participant.

If methacholine is needed during the additional visit, the participant's blood pressure will be assessed. In addition, women of childbearing potential will be required to undergo a urine pregnancy test prior to methacholine testing.

For research involving survey, questionnaires, etc.: *Describe the setting and the mode of administering the instrument and the provisions for maintaining privacy and confidentiality. Include the duration, intervals of administration, and overall length of participation. (describe and attach all instruments)*

☐ ***Not applicable***

Baseline medical and asthma control questionnaires will take 5- 10 minutes to complete, will be completed at the Medical Office Building, in a private office. Questionnaires are in paper format, and will be completed by the participant.

Statistical Considerations: *Delineate the precise outcomes to be measured and analyzed. Describe how these results will be measured and statistically analyzed. Delineate methods used to estimate the required number of subjects. Describe power calculations if the study involves comparisons. Perform this analysis on each of the primary and secondary objectives, if possible.*

We will compare changes in respiratory system impedance across the 2 levels of PEEP for participants being exposed to methacholine prior to PEEP (visit 4-5) and methacholine simultaneously with PEEP (visits2-3), separately.

We will also measure symptom scores using the Borg scale; symptom scores in the obese are related to lung reactance, and we anticipate that symptom scores will be decreased by the PEEP intervention and that this will correlate with decreases in measures of impedance.

The primary statistical analysis will be to compare changes in measures of impedance at PEEP 0 versus 10 cmH_2O using paired t-tests. If normal distribution assumptions are not met, variables will be appropriately transformed. We will compare data from visits 2-3, and visits 4-5 as separate experiments, as they address different scientific questions. We will also compare symptom scores (Borg scale) and, FRC at the two different levels of PEEP.

Power Analysis: Based on the preliminary data shown in Figs. 10 & 11 obtained with a PEEP of 10 cmH_2O, we anticipate that a PEEP of 10 cmH_2O will lead to a 50% attenuation in the increase in resistance in response to methacholine compared to the increase in resistance at PEEP 0, which will be our primary outcome of interest. From our prior work using a commercially available forced oscillation system in obese asthmatics,

we anticipate that the baseline resistance of the respiratory system at a frequency of 5 Hz will be 7.02 ± 1.80 $cmH_20.s/L$, and that this will increase to 10.50 ± 2.20 $cmH_20.s/L$ with a PC_{10} dose of methacholine at PEEP = 0. Examination of the change in resistance in response to methacholine for PEEP = 0 compared to PEEP = 10 using a paired t-test with a 2.5% Type I error level and r = 0.50 within subject correlation indicates that a sample size of n = 10 LONA subjects will provide 99% power to detect the postulated within subject change. An independent comparison using a 2.5% Type I error level for the change in resistance prior to methacholine using the smaller effect sizes would require a sample size of n = 15 to achieve a 78% power. An adjusted 5% Type I error level was used to compensate for the two separate comparisons conducted for testing the resistance changes. We will increase this to 20 participants to allow for potential drop-outs and any technical difficulties participants experience with completing any of the study visits.

Confidentiality Measures and Secure Storage of Data or Tissue: *Describe how the data/tissue will be collected. Will there be identifiers or will the data/tissue be coded? Describe where the data/tissue will be stored and how it will be secured. Describe who will have access to the data/tissue or the codes. If subject data/tissues with identifiers will be released, specify to whom. Describe what will happen to the data/tissues when the research has been completed.*

☐ ***Not Applicable***

- Research material obtained from participants will include results of lung function testing, and medical history obtained from direct patient interview.
- People having access to protected data will be the investigators participating in this study and appropriate regulatory authorities.
- Documents containing identifiable information will be kept in a locked file cabinet at the Vermont Lung Center. All participants will be assigned a unique study ID, which be kept in this locked file cabinet. Study specimens will be labeled with the study ID, and not identifiable information. Our study database will be password protected, and participants will be identified in the database only by their unique participants ID.
- Optional Leftover blood samples and data for future research on asthma and obesity will be stored frozen in Dr. Dixon's UVM laboratory bio-repository (CHRMS: 16-636). The samples will be identified with the unique study ID and date only.

Risks/Benefits: *Describe any potential or known risks. This includes physical, psychological, social, legal or other risks. Estimate the probability that given risk may occur, its severity and potential reversibility. If the study involves a placebo or washout period, the risks related to these must be addressed in both the protocol and consent. Describe the planned procedures for protecting against or minimizing potential risks and assess their likely effectiveness. Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Discuss the potential benefits of the research to the subjects and others. Discuss why the risks to the subjects are reasonable in relation to the anticipated benefits to subjects and others. Discuss the importance of the knowledge gained or to be gained as a result of the proposed research and why the risks are reasonable in relation to the knowledge that reasonably may result. If there are no benefits state so.*

Risks

Lung Function tests (spirometry and lung volumes, and single breath and multiple breath wash out tests):
These tests involve taking a very deep breath and breathing out fast, the main risk of this is that it can be tiring. We will give the patients as much time as they need to complete this testing.

Standard Methacholine challenge:
This test involves the inhalation of an agonist to induce bronchoconstriction and may induce the symptoms of an asthma exacerbation (chest tightness, dyspnea, coughing). The procedure is performed in a closely monitored clinical environment, with availability of bronchodilator. This procedure has been safely used in many previous studies in our division and nationwide, we will only perform this procedure if the baseline FEV_1 is > 60% predicted.

Bronchodilator (albuterol/salbuterol):
This medication will be available to be administered only if the participant is uncomfortable from the effects of the methacholine challenge test. These drugs can lead to tremor, nervousness, tachycardia, palpitations

and headache – these reactions are transient and rare (<5%) with the proposed doses used for this study, and if they occur, we will monitor the patient until they return to baseline. High doses may cause arrhythmias and hypokalemia: these are very unlikely with the doses used for this study.

Modified Methacholine with Flexivent.
Some subjects may feel discomfort from the slight oscillation of air in their mouth while they breathe, we will minimize this by using the dose of methacholine required to produce a 20% fall in FEV_1. We will perform this test with positive airway pressure at visit 3. The positive airway pressure is likely to be well tolerated, similar levels are conventionally used in the treatment of sleep apnea.

Chest CT
Computed tomography (CT scan): This is a routine imaging procedure used in pulmonary medicine. We plan to perform limited scans of your lungs. The scan results in a radiation dose of up to 3.0 mSv. This is equivalent to the exposure from natural background radiation in our surroundings over 6 months.

For comparison, the maximal permissible whole-body occupational radiation dose set by the federal government for people who work with radiation or volunteer for medical research is 50 mSv per year.

Abnormality detected during study procedures: if we detect an unexpected abnormality on the chest CT, or in the participant's lung function testing, we will communicate this with the participant, and with their permission, the participant's physician. If the participant has no regular physician, we will help them schedule an appointment with an appropriate health care provider.

Venipuncture (Blood Draw): We will collect a total of 26cc of blood for analysis of IgE and a complete blood count (10cc) as markers of allergic inflammation, and (16cc) serum for circulating anti-inflammatory bio-markers.

Confidentiality
The study also includes a risk of loss of confidentiality. We will follow Health Insurance Portability and Accountability Act guidelines on confidentiality and minimize these risks by assigning unique identifiers to health information, maintaining all records in a locked storage area, and using password protected electronic devices.

Potential Benefits of the Proposed Research to the Subject and Others
There are no direct benefits to patients from participating in this trial other than accurate diagnostic evaluation of any airway disease.

Importance of Knowledge to be gained
The benefit to others is to increase our understanding of the link between asthma and obesity, and potentially identify therapeutic strategies for treating asthma associated with obesity – two diseases which are at epidemic levels in the United States.

Therapeutic Alternatives: *List the therapeutic alternatives that are reasonably available that may be of benefit to the potential subject and include in the consent form as well.*

x	***Not Applicable***

Data Safety and Monitoring: *The specific design of a Data and Safety Monitoring Plan (DSMP) for a protocol may vary extensively depending on the potential risks, size, and complexity of the research study. For a minimal risk study, a DSMP could be as simple as a description of the Principal Investigator's plan for monitoring the data and performance of safety reviews or it could be as complex as the initiation of an external, independent Data Safety and Monitoring Board (DSMB). The UVM/UVM Medical Center process for review of adverse events should be included in the DSMP.*

Three physician scientists who are active in asthma research outside of Vermont will participate in a Data

Safety Monitoring Panel (DSMP). The panel will convene annually, primarily to review safety, and also to review the integrity of the data, and will provide recommendations regarding continuation of the studies.

During the study period if there is a primary reason to halt this study related to concerns regarding safety we will stop the protocol in the event of the following.

1. Serious Adverse Events:
The protocol will be stopped for any serious adverse event that is definitely or probably related to the study protocol. The protocol will be stopped in the event that there are two events that are thought to be possibly related to the study protocol.

2. Adverse Events:
For adverse events that are not within the category of serious adverse events, the protocol will be stopped in the events that are 3 adverse event of grade 3 category that are thought to be definitely or probably related to the study protocol. The study will not be stopped for grade 2 or lower adverse events.

Stopping Rules for an Individual Participant/Cohort
A study participant will be discontinued from the study for:

- Any clinical adverse event, laboratory abnormality, intercurrent illness, other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- Development of any exclusion criteria may be cause for discontinuation.

Composition of the DSMP

Chair:
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Adverse Event and Unanticipated Problem (UAP) Reporting: *Describe how events and UAPs will be evaluated and reported to the IRB. All protocols should specify that, in the absence of more stringent reporting requirements, the guidelines established in the Committees on Human Research "Adverse Event and Unanticipated Problems Reporting Policy" will be followed. The UVM/UVM Medical Center process for review of adverse events and UAPs to subjects or others should be included in the DSMP.*

Evaluation of Events

Definition of an Adverse Event (AE)

An adverse event (AE) is any unanticipated or unintended medical occurrence or worsening of a sign or symptom (including an abnormal laboratory finding) or disease in a study participant, which does not necessarily have a causal relationship with the study condition, procedures or study agent(s), that occurs after the informed consent is obtained.

Pre-existing conditions or illnesses which are expected to exacerbate or worsen are not considered adverse events. A pre-existing condition that we anticipate may worsen is asthma.

Definition of a Serious Adverse Event (SAE)

Serious Adverse Event (SAE): A Serious Adverse Event is defined as an AE meeting one of the following outcomes:

- Death during the period of protocol defined surveillance
- Life Threatening Event (defined as a participant at immediate risk of death at the time of the event)
- Inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance
- Results in congenital anomaly or birth defect
- Results in a persistent or significant disability/incapacity

Any other important medical event that may not result in one of the above outcomes, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above

AE/SAE Grading and Relationship Assignment

Intensity (severity) Scale

Each adverse event will be assessed for severity and classified into one the categories below:

- **Grade 1 (Mild)**: event requires minimal or no treatment and do not interfere with the patient's daily activities.
- **Grade 2 (Moderate)**: event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Grade 3 (Severe)**: event interrupts a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- **Grade 4 (Life threatening)**: Any adverse drug experience that places the patient or participant, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.
- **Grade 5 (Death)**

Relationship Assessment

For all collected AEs, the clinician who examines and evaluates the subject will determine the adverse event's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below:

- **Definitely Related:** There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study visit.
- **Probably Related:** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the study visit, is unlikely to be attributed to concurrent disease or other drugs or chemicals.
- **Possibly Related:** There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events).
- **Unlikely:** A clinical event, including an abnormal laboratory test result, whose temporal relationship to study visit makes a causal relationship improbable (e.g., the event did not occur within a reasonable time) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).
- **Unrelated:** The AE is completely independent of study, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.
- **Expected Events Related to Disease Process:** Expectedness refers to the awareness of adverse events related to study.

Reporting

Adverse event reporting for this protocol will be as follows:

- The PI's will submit a completed serious adverse event report to the IRB, the Chair of the DSMP and the NHLBI within 48 hours after any potentially life-threatening (grade 4) serious adverse event that is possibly, probably or definitely related to the study.
- The PI's will submit a completed serious adverse event report to the IRB, Chair of the DSMP and the NHLBI within 48 hours after becoming aware of any Grade 3 (severe) adverse event that is possibly, probably or definitely related to the study.
- The PI's will report within 15 days on any other event or condition regardless of grade, which in their judgment represents an event reportable to the IRB and DSMP.
- A summary of all adverse events will be reported to the DSMP annually, and the IRB with annual continuing review submission.
- An unanticipated problem that is not a serious adverse event will be reported to the Chair of the DSMP, the NHLBI and the IRB within 14 days of the investigator becoming aware of the problem.

Withdrawal Procedures: *Define the precise criteria for withdrawing subjects from the study. Include a description of study requirements for when a subject withdraws him or herself from the study (if applicable).*

Participants may withdraw at any time.

Sources of Materials: *Identify sources of research material obtained from individually identifiable human subjects in the form of specimens, records or data. Indicate whether the material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records or data.*

Prior results of lung function testing, and blood tests will be used, if available to assess for eligibility, either from the general medical record, or from prior testing at the Vermont Lung Center.
All other materials will be obtained directly from the participant

DRUG AND DEVICE INFORMATION

Investigators are encouraged to consult the UVM Medical Center Investigational Pharmacy Drug Service (847-4863) prior to finalizing study drug/substance procedures.

Drug (s) [x] ***Not applicable***

Drug name – generic followed by brand name and common abbreviations. Availability – Source and pharmacology; vial or product sizes and supplier. If a placebo will be used, identify its contents and source. (attach investigational drug brochure)

Preparation: Reconstitution instructions; preparation of a sterile product, compounded dosage form; mixing guidelines, including fluid and volume required. Identify who will prepare.

Storage and stability – for both intact and mixed products.

Administration – Describe acceptable routes and methods of administration and any associated risks of administration.

Toxicity – Accurate but concise listings of major toxicities. Rare toxicities, which may be severe, should be included by indicated incidence. Also adverse interactions with other drugs used in the protocol regimen as well as specific foods should be noted. Address significant drug or drug/food interactions in the consent form as well. List all with above details.

Is it FDA approved: (include FDA IND Number)

1. *in the dosage form specified? If no, provide justification for proposed use and source of the study drug in that form.*
2. *for the route of administration specified? If no, provide justification for route and describe the method to accomplish.*
3. *for the intended action?*

Device (s) [x] ***Not applicable***

Device name and indications (attach investigational device brochure)

Is it FDA approved: (include FDA IDE Number)

1. *for indication specified? If no, provide justification for proposed use and source of the device.*

Risk assessment (non-significant/significant risk) - PI or sponsor needs to assess risk of a device based upon the use of the device with human subjects in a research environment.

SUBJECT CHARACTERISTICS, IDENTIFICATION AND RECRUITMENT

Subject Selection: *Provide rationale for subject selection in terms of the scientific objectives and proposed study design.*

Rationale for Eligibility Criteria: Our prior experience suggests that, if obesity does affect airway compliance, it may take time to develop Accordingly, we exclude participants younger than 18 years old as well as participants with an asthma diagnosis at an age younger than 18 years old. We use IgE as a marker of active allergic disease.

Vulnerable Populations: *Explain the rationale for involvement of special classes of subjects, if any. Discuss what procedures or practices will be used in the protocol to minimize their susceptibility to undue influences and unnecessary risk (physical, psychological, etc.).*

[x] ***Not applicable***

Number of Subjects: *What is the anticipated number of subjects to be enrolled at UVM/UVM Medical Center and in the case of a multi-center study, with UVM/UVM Medical Center as the lead, the total number of subjects for the entire study.*

20 total participants are needed to complete the study.
We anticipate that we will need to screen up to 80 subjects to find 20 that are eligible for this study.

Inclusion/Exclusion Criteria: *Eligibility and ineligibility criteria should be specific. Describe how eligibility will be determined and by whom. Changes to the eligibility criteria at a later phase of the research have the potential to invalidate the research.*

Inclusion Criteria:

1. BMI≥ 30 kg/m^2

2. ages ≥ 18 years
3. ≤ 20 pack year smoking history
4. physician diagnosis of asthma at age≥ 18 years
5. IgE <100 IU/ml.

Exclusion Criteria:

1. Pregnancy
2. other significant lung disease
3. unable or unwilling to provide informed consent
4. FEV1 < 60% predicted
5. Asthma exacerbation (defined as a hospitalization, ED visit, urgent health care visit for asthma or new systemic corticosteroids for asthma) in the prior 6 weeks.

Inclusion of Minorities and Women: *Describe efforts to include minorities and women. If either minorities or women are excluded, include a justification for the exclusion.*

Women:
We plan to recruit both genders to this study.

Minorities:
We anticipate that we will recruit minorities in proportion to the local population. Vermont is predominantly Caucasian (96.4% Caucasian, 0.9% African American, 1.4% Hispanic), but we have had success in recruiting minorities with outreach to our local community health clinics and targeted advertising to community groups. We will not exclude any racial/ethnic group from this study.

Inclusion of Children: *Describe efforts to include children. Inclusion is required unless a clear and compelling rationale shows that inclusion is inappropriate with respect to the health of the subjects or that inclusion is inappropriate for the purpose of the study. If children are included, the description of the plan should include a rationale for selecting or excluding a specific age range of children. When included, the plan must also describe the expertise of the investigative team in working with children, the appropriateness of the available facilities to accommodate children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study.* ***If children are excluded*** *then provide appropriate justification. Provide target accrual for this population.*

Children are excluded as our disease of interest is late onset asthma, occurring after childhood.

For protocols including the use of an investigational drug, indicate whether women of childbearing potential have been included and, if not, include appropriate justification.

Women of childbearing potential have not been included.

If HIV testing is included specifically for research purposes explain how the test results will be protected against unauthorized disclosure. Include if the subjects are to be informed of the test results. If yes, include the process and provision for counseling. If no, a rationale for not informing the subjects should be included.

x ***Not applicable***

Recruitment: *Describe plans for identifying and recruitment of subjects. All recruitment materials (flyers, ads, letters, etc) need to be IRB approved prior to use.*

We will send information to participants in prior studies to gauge their interest in this study.

We will recruit participants through IRB approved flyers.

We will inform patients of the study in the adult pulmonary clinic, and invite them to participate.

A research coordinator will also screen the bariatric clinic for patients that identify as possible participants in the study. The Vermont Lung Center coordinator will contact the clinic staff of potentially eligible patients. The provider or clinic staff will notify the patient that someone from the Vermont Lung Center is available to speak with them about a research study, if they are interested.

We will mail IRB-approved letters to patients in the adult pulmonary clinic along with pre-stamped opt-out postcards. The letters will be addressed from the Principal Investigator, Dr. Anne Dixon. Patients will be instructed to return the postcard if they do not want to be contacted about the study. We will wait two weeks

to receive the opt-out postcards before reaching out to patients.

We will post IRB-approved language on facebook, Craigslist, Front Porch Forum, and the UVM Events and Announcements page.

FINANCIAL CONSIDERATIONS

Expense to Subject: *If the investigation involves the possibility of added expense to the subject (longer hospitalization, extra studies, etc.) indicate in detail how this will be handled. In cases where the FDA has authorized the drug or device company to charge the patient for the experimental drug or device,* ***a copy of the authorization letter from the FDA or sponsor must accompany the application. Final approval will not be granted until the IRB receives this documentation.***
There are very limited circumstances under which study participants may be responsible (either directly or via their insurance) for covering some study-related expenses. If the study participant or their insurer(s) will be billed for any portion of the research study, provide a justification as to why this is appropriate and acceptable. For example, if the study involves treatment that is documented standard of care and not investigational, state so. In these cases, the protocol and the consent should clearly define what is standard of care and what is research.

none

Payment for participation: *Describe all plans to pay subjects, either in cash, a gift or gift certificate. Please note that all payments must be prorated throughout the life of the study. The IRB will not approve a study where there is only a lump sum payment at the end of the study because this can be considered coercive. The amount of payment must be justified. Clarify if subjects will be reimbursed for travel or other expenses.*

☐ ***Not applicable***

Participants who qualify for the study will be reimbursed $100 for completion of each study visit; participants who need to undergo a CT scan will receive an extra $50 (up to $550 total). We think this is reasonable as study visits will likely last up to 3 hours, and involve complicated testing.

If an additional follow up visit is required, participants will be reimbursed $50 for completion of the visit. We think this is reasonable because the additional follow up visit will likely only require one or two tests.

If a participant travels 40 miles round trip from their home to the Vermont Lung Center, we will pay mileage at standard UVM rates.

Collaborating Sites*. When research involving human subjects will take place at collaborating sites or other performance sites when UVM/UVM Medical Center is the lead site, the principal investigator must provide in this section a list of the collaborating sites and their Federalwide Assurance numbers when applicable. (agreements may be necessary)*

x ***Not applicable***

INFORMED CONSENT

Consent Procedures*: Describe the consent procedures to be followed, including the circumstances under which consent will be obtained, who will seek it, and the methods of documenting consent. Specify the form(s) that will be used e.g. consent (if multiple forms explain and place identifier on each form), assent form and/or HIPAA authorization (if PHI is included). These form(s) must accompany the protocol as an appendix or attachment.*

Note: Only those individuals authorized to solicit consent may sign the consent form confirming that the prospective subject was provided the necessary information and that any questions asked were answered.

Once a prospective subject is identified, the PI or research coordinators will initiate the informed consent discussion and answers questions presented by the subject. Consenting is typically done at the Vermont Lung Center in the testing room (open area with plenty of seating). Occasionally it may take place in the coordinators office or in the waiting room (providing no other non-family/representatives are present). Subjects are usually given a consent well in advance and asked to read it prior to arriving and to bring

any questions they may have with them to the first visit. The PI may or may not be present during the consenting process. If the PI is not present and the subject wishes to discuss anything further with the PI, the PI will be contacted for the subject. The Vermont Lung Center will record the consenting process in the subject's study chart using a form created based on the template provided by the IRB.

Information Withheld From Subjects: *Will any information about the research purpose and design be withheld from potential or participating subjects? If so, explain and justify the non-disclosure and describe plans for post-study debriefing.*

x ***Not applicable***

Attach full grant application, including budget information and/or any contract or draft contract associated with this application.