Human Subjects Research Protocol

The Common Human Subjects Protocol Cover Form **must** be completed and accompany 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. All materials must be submitted electronically to the IRB via InfoEd. Proper security access is needed to make electronic submissions. Visit the InfoEd Resource Materials page for more information.

PROTOCOL SUMMARY

Project Title:	Protocol Version Date:
MitoQ for the treatment of Metabolic Dysfunction in Asthma	07/13/2022

Principal Investigator: Anne Dixon

Grant Sponsor: NIH Grant Number: HL137619

(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.)*

This study will be a 14-week, randomized, placebo-controlled, double-masked clinical trial in 40 obese patients with poorly controlled asthma.

The intervention is Mitoquinol (MitoQ), which is an antioxidant oral supplement.

The primary aim of this pilot study is to determine if MitoQ improves airway reactivity in obese patients with asthma.

Procedures involved in this study include randomization to MitoQ versus placebo, lung function testing, collection of blood, sputum, exhaled breath, questionnaires (pertaining to general health and asthma), collection of nasal cells, nasal strip, and nasal lavage.

PURPOSE AND OBJECTIVES

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

Nearly 60% of patients with severe asthma in the U.S. are obese. [1] Obese asthmatics do not respond as well to standard therapy as lean asthmatics.[2] Obese asthmatics with earlier-onset disease and increased markers of inflammation tend to have the most severe asthma, with a 6-fold risk of ICU admission compared with lean asthmatics.[3] Therefore, there is an urgent need to find therapies for these patients.

The mechanisms causing asthma in obesity remain unclear, but we have data suggesting it might relate to mitochondrial dysfunction. This trial will study the efficacy of targeting mitochondrial reactive oxygen species (mROS) for treatment of obese asthma using a mitochondrial targeted antioxidant, MitoQ.

MitoQ has been extensively studied in animal models of disease, with efficacy in models of Parkinson's disease, sepsis, steatohepatitis, ischemia-reperfusion injury, and diabetic kidney disease.[4-6] Based on these studies, the efficacy of MitoQ has also been investigated in human diseases. For example, in one study 128 patients with Parkinson's Disease were enrolled in a 3-arm, randomized, double-masked trial of two doses of MitoQ compared with placebo over 12 months.[7] The drug was well tolerated; the only significant side-effect being a dose-dependent risk of nausea and vomiting. The intervention did not have clinical efficacy in this patient population, likely because participants already had established, irreversible, neurologic injury. In a separate study of hepatitis C (involving 30 participants), MitoQ was found to reduce serum alanine transaminase and aspartate aminotransferase, and markers of acute inflammation.[8] Combined, these studies support the safety of MitoQ for use in humans, and suggest potential efficacy in disease with active inflammation related to mROS, such as obese asthma.

We have preliminary data in a mouse model of house dust mite (HDM)-induced airway disease indicating that administration of MitoQ decreases airway inflammation and airway hyperresponsiveness to methacholine. Hence, MitoQ is an exciting potential therapy for the treatment of obese asthma.

Completion of this trial will provide critical preliminary data on the effects of directly targeting mROS in people with obese asthma, a patient population with very severe disease that is currently very challenging to treat.

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

1. Schatz M, Hsu JW, Zeiger RS, et al. Phenotypes determined by cluster analysis in severe or difficult-to-treat asthma. *The Journal of allergy and clinical immunology.* 2014;133(6):1549-1556.
2. Dixon A. The treatment of asthma in obesity. *Expert review of respiratory medicine.* 2012;6(3):331-340.
3. Holguin F, Bleecker ER, Busse WW, et al. Obesity and asthma: an association modified by age of asthma onset. *The Journal of allergy and clinical immunology.* 2011;127(6):1486-1493 e1482.
4. Kelso GF, Porteous CM, Coulter CV, et al. Selective targeting of a redox-active ubiquinone to mitochondria within cells: antioxidant and antiapoptotic properties. *The Journal of biological chemistry.* 2001;276(7):4588-4596.
5. Ramsey H, Wu MX. Mitochondrial anti-oxidant protects IEX-1 deficient mice from organ damage during endotoxemia. *Int Immunopharmacol.* 2014;23(2):658-663.
6. Smith RA, Murphy MP. Animal and human studies with the mitochondria-targeted antioxidant MitoQ. *Ann N Y Acad Sci.* 2010;1201:96-103.
7. Snow BJ, Rolfe FL, Lockhart MM, et al. A double-blind, placebo-controlled study to assess the mitochondria-targeted antioxidant MitoQ as a disease-modifying therapy in Parkinson's disease. *Mov Disord.* 2010;25(11):1670-1674.
8. Gane EJ, Weilert F, Orr DW, et al. The mitochondria-targeted anti-oxidant mitoquinone decreases liver damage in a phase II study of hepatitis C patients. *Liver Int.* 2010;30(7):1019-1026.

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

The objective of this proposal is to conduct a pilot clinical trial with the mitochondrial-targeted antioxidant MitoQ.

<u>Primary Outcome</u>

The primary outcome will be change in airway reactivity, based on our preliminary data suggesting that MitoQ affects airway reactivity.

Secondary outcomes

- Change in mitochondrial reactive oxygen species in nasal epithelial cells.
- Change in sputum, nasal lavage, serum and exhaled breath 8-isoprostanes.
- Change in induced sputum cell counts.
- Changes in asthma control documented with daily asthma diaries (including symptoms, rescue medication use, and peak flow measurements).
- Adherence monitored in daily asthma diary cards and by pill counts.
- The Asthma Control Test (ACT), a 4-week recall questionnaire that measures asthma control.
- The Marks Asthma Quality of Life Questionnaire (Marks AQLQ), an asthma-specific quality of life questionnaire.
- The Asthma Symptom Utility Index (ASUI), a 2-week utility-weighted asthma symptom questionnaire.
- Anthropometrics will include height and weight, and hip and waist measurements.
- Spirometry with bronchodilator will be performed to measure FEV1 and FVC in accordance with ATS/ERS standards.
- Forced oscillation (with methacholine testing) will be used to measure impedance, detect changes in the periphery of the lung.
- Adverse effects will be assessed by open-ended questions at each visit and rated in severity.
- Interval health history will be recorded at each clinic visit.
- Baseline questionnaires and exam will be administered to ascertain demographics, including self-reported ethnicity and race, general health, co-morbid conditions, asthma symptoms, and medication use.
- Exit questionnaires will be administered at the last visit to determine global assessments of treatment, adequacy of informed consent procedures, satisfaction with study procedures and personnel, and opinions about the intervention.

METHODS AND PROCEDURES

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

A 14 week, randomized, double-masked, placebo controlled trial in 40 participants.

This study will be performed at the University of Vermont and Duke University. Two centers will facilitate recruitment, and improve generalizability of findings to inform any decision to proceed with a full-scale, appropriately powered multi-center trial.

Background Asthma Care
Participants will be treated in accordance with asthma guidelines and best practices using materials already developed at our centers. All participants will be prescribed controller medication that includes inhaled corticosteroids and additional add-on treatments as needed.

Rationale for study duration: We based the duration of the study on the likely time needed to improve asthma control, and to determine the tolerability of the supplement over several weeks.

Source of Study Medication

MitoQ capsules and placebo will be provided by MitoQ Ltd.

Rationale for dose of active supplement:
The dose of supplement will be 40 mg per day, which is based on tolerability and efficacy findings in prior human studies (references 6-8 listed above). Participants will be started on 20 mg a day for at least the first three days and will then be escalated to 40 mg if well tolerated.

Randomization and blinding:
Treatment assignments will be stratified by center and the allocation ratio will be (1:1). Randomization will be accomplished by reviewing and confirming eligibility data; after verification of eligibility, a treatment assignment number corresponding to a unique study kit will be assigned. Study kits will be labeled with two-part tear-off labels with unique identifiers. The tear-off label will be affixed to a study form when the kit is assigned to a participant and the information will be keyed into data system to verify that assigned treatment was given to the participant.

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.

Due to COVID-19 some of these procedures may not occur until guidelines allow it.
COVID testing and other precautions will be conducted according to current institutional guidelines.

Outline of Study Visits							
Week	-2	0 +/- 3 days	3 days after V2 +3 days	2 +/- 3 days	6 +/- 10 days	1-10 days prior to V5b	12 +/- 10 days
Visit number	V1	V2	Phone call∞	V3∞	V4∞	V5a∞	V5b∞
Consent	*						
Baseline/interim history	*	*	*	*	*	*	*
Concomitant medication review	*	*		*	*	*	*
Collect and review diary cards		*		*	*		*
Treatment assignment (randomization)		*					
Drug distribution		*			*		
Drug titration			*				
Drug return/ Pill counts				*	*		*
Assess for adverse events		*	*	*	*	*	*
Spirometry	*¥	* €				*€	*€
Forced oscillation	*	*				*	*
Lung Volumes	*						
Induced sputum	*					*‡	
Exhaled breath condensate	*	*					*
Exhaled nitric oxide	*	*					*
Methacholine Challenge		*^					*
Nasal lavage & nasal brush	*	*					*
Nasal strip	*	*				*	*
Asthma Control (ACT)	*	*		*	*		*
Marks AQLQ	*	*		*	*		*
ASUI	*						
Anthropometrics	*	*		*	*		*
Temperature	*	*					*
Blood pressure	*	*				*	*
Blood draw†	*	Fasting		Fasting	Fasting	Fasting	
Urine sample	*	*		*	*	*	*
Pregnancy test*	*	*		*	*	*	*
Follow-up phone call			*				
End of study questionnaire							*
Follow-up visit+	*	*				*	*

*for women of child-bearing potential
¥V1 spirometry only will be performed pre and post bronchodilator
†fasting blood draw may be performed on a different day (±7 days of actual visit)
‡Induced sputum at V5 will be performed within 10 days prior to the other V5 procedures (induced sputum and methacholine cannot be done at same visit, both may cause bronchoconstriction)
^participants with a negative methacholine test will stop visit 2 early
+follow-up visits will be scheduled in the event that a lung test cannot be performed that day
€ spirometry is done as part of the induced sputum or methacholine procedure
∞Visit windows for the visits following visit 2 will be scheduled based off of the date the participant was randomized to study drug

Visit 1 (duration three to four hours)
We will obtain informed consent, a baseline medical history, concomitant medications, and measure blood pressure, temperature, height, weight, and waist and hip circumference. We will collect urine for research. Women of childbearing potential will perform a urine pregnancy test. Participants will have blood drawn for an IgE, CBC w/ differential, CMP, and collection of serum and plasma for research. We will perform spirometry with bronchodilator, lung volumes, forced oscillation, and then induce sputum spontaneously or with inhaled hypertonic saline. We will collect exhaled breath condensate and exhaled nitric oxide measurement. We will insert a nasal strip for sample collection, then perform nasal lavage, and collect nasal cells via nasal brush. Participants will complete questionnaires pertaining to asthma control and asthma quality of life. We will instruct participants how to fill out asthma diary cards.

Visit 2 (duration 2 to 3 hours)
Participants will have fasting blood drawn for blood glucose, CBC w/ differential, CMP, and collection of serum and plasma for research (this may also be scheduled within 7 days per participant preference), assess for adverse events, obtain weight, measure blood pressure, temperature, review concomitant medications, obtain interim medical history, collect and review diary cards, perform spirometry, and perform a methacholine challenge test (measuring response by both FEV1 and forced oscillation). If we are unable to obtain sputum from the participant at visit 1 we will see if the participant is able to produce sputum spontaneously during pulmonary function testing. We will collect urine for research. Women of childbearing potential will perform a urine pregnancy test. We will collect exhaled breath condensate and exhaled nitric oxide measurement. We will insert a nasal strip for sample collection, then perform nasal lavage, and collect nasal cells via nasal brush. Participants will complete questionnaires about asthma control and asthma quality of life. Participants will be randomized to study medication and study drug will be dispensed.

Follow-up phone call (duration 10 minutes)
We will assess for symptoms to determine if the participant should increase to two tablets (40 mg) of study drug a day, remain at 1 tablet (20 mg) a day, or withdraw from treatment. We will also assess for study drug adherence, assess if vaping and/or inhaling marijuana, and any other adverse events.

Visits 3 (duration 1 hour)
We will assess for any adverse events, obtain weight, review concomitant medications, and obtain interim medical history. We will collect and review diary cards and assess adherence to study medication (by pill count). Participants will have fasting blood drawn for blood glucose, CBC w/ differential, CMP, and collection of serum and plasma for research (this may also be scheduled within 7 days per participant preference). We will collect urine for research. Women of childbearing potential will perform a urine pregnancy test. Participants will complete questionnaires about asthma control and asthma quality of life.

Visits 4 (duration 1 hour)
We will assess for any adverse events, obtain weight, review concomitant medications, and obtain interim medical history. We will collect and review diary cards and assess adherence to study medication (by pill count). Study drug will be collected and new drug will be dispensed. Participants will have fasting blood drawn for blood glucose, CBC w/ differential, CMP, and collection of serum and plasma for research (this may also be scheduled within 7 days per participant preference).. We will collect urine for research. Women of childbearing potential will perform a urine pregnancy test. Participants will complete questionnaires about asthma control and asthma quality of life.

Visit 5a (duration 1.5 hours)
We will schedule the induced sputum prior to other study procedures (within 10 days of V5). We will assess for any adverse events, measure blood pressure, perform forced oscillation, obtain spontaneous sputum or perform the induced sputum procedure, review concomitant medications, and obtain an interim medical history. We will insert a nasal strip for sample collection. We will collect urine for research. Women of childbearing potential will perform a urine pregnancy test. Participants will have fasting blood drawn for

blood glucose, CBC w/ differential, CMP, and collection of serum and plasma for research (this may also be scheduled within 7 days per participant preference).

Visit 5b (duration 3 hours)
We will collect and review diary cards and assess adherence to study medication (by pill count). We will collect all remaining study drug. We will perform nasal lavage, collect nasal cells via nasal brush, measure blood pressure, temperature, obtain weight, and hip and waist circumference. Participants will perform spirometry. We will insert a nasal strip for sample collection. We will collect urine for research. Women of childbearing potential will perform a urine pregnancy test. We will perform a methacholine challenge test with forced oscillation (measuring response by both FEV1 and forced oscillation). If we are unable to obtain sputum from the participant at visit 5a we will see if the participant is able to produce sputum spontaneously during pulmonary function testing. We will collect exhaled breath condensate and exhaled nitric oxide. Participants will complete questionnaires about asthma control and asthma quality of life, and an end of study participant questionnaire.

Additional visit:
Some participants may be asked to return for an additional visit if some of the tests were not completed at the regular scheduled visits or for unexpected events. This additional visit may involve spirometry, a methacholine challenge, or induced sputum depending on the need for the specific participant. The participant's blood pressure will be assessed if the methacholine challenge or induced sputum need to be performed. In addition, women of childbearing potential will be required to undergo a urine pregnancy test prior to 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***

Questionnaires described above will be administered in a private setting at the Vermont Lung Center.

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.*

Analysis Plan. Baseline comparability between the two randomized arms will be compared using demographic and outcome variables obtained at baseline to identify potential group comparison confounders. Primary outcomes assessed at the end of the study will be compared using a two-sample t-test and associated 95% confidence interval or a Kruskal-Wallis rank test and nonparametric confidence interval if distributional assumptions are of concern. This will be followed by a pre-post repeated measures mixed linear model to test for group specific baseline to follow-up differences, while for those measures observed at multiple time points, a linear mixed model incorporating time at discrete levels will be implemented. The previous t-test comparisons and the mixed models will be extended to covariance models using baseline mROS, age, sex, BMI, smoking history, duration of asthma and asthma medications, and a confounder score using all items. The effect of medications will be determined by using dummy variables for each class of medication, and by using the cumulative dose of inhaled corticosteroid and β agonist in the regression model. We will compare the rate of events describing any change in medications (whether an increase or decrease), including addition of new anti-asthma drugs and use of steroid tapers in the treatment and placebo groups. Missing data patterns from any lost to follow-up or incomplete data collection will be examined using standard approaches to assess missing at random or missing completely at random assumptions. If missing data is of concern, specific multiple imputation approaches for missing data will be implemented. Analyses using complete data and imputed data sets will be qualitatively compared and presented jointly.

Sample size. The sample size calculations are based upon estimates of clinically meaningful mean differences and standard deviations derived from our studies of obese asthmatics at the University of Vermont (although this is predominantly a Caucasian population compared with the Duke site, we have found that methacholine reactivity variability does not differ by race [or BMI] in prior studies of the ALA-ACRC). The analysis is based upon a repeated measures analysis of variance approach. The primary outcome is the methacholine responsiveness. We assume that after treatment with MitoQ, a 20% fall in FEV_1 will be detected using a mean methacholine dose of 4 mg/ml, an improvement over the baseline estimate of 2 mg/ml. It is assumed that those in the control group will show no improvement over baseline. Using a within-person standard deviation of 3.0, and the assumptions indicated above, 17 individuals per group would provide 80% power with a 5% significance level to detect a difference between patients assigned to active treatment versus placebo. We will inflate these numbers to allow for a 10% patient drop-out and plan to recruit 40 participants total. Pre- and post- changes in mean lung function (% predicted) and questionnaire scores will be compared for each group, and across groups as described previously.

Data quality. Data Quality will be enforced through a variety of techniques, and in collaboration with Dr. Peter Callas in biostatistics at UVM. This includes the preparation of a detailed manual of operations, staff training and certification of key staff in study procedures, design of unambiguous self-documenting data collection forms, double data entry, audit of source documents against the central database, automated intra-form and inter-form data consistency checks, range and validity checks during data entry, and centralized eligibility checks and randomization assignments. We will have an in-person training meeting at the start of this clinical study for the Investigators and Coordinators at Duke and UVM.

Data quality will be reviewed and discussed at monthly conference calls. Drs. Dixon and Que will meet in person no less than three times a year at the Steering Committee meetings of the American Lung Association-Airways Clinical Research Center network.

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.*

Bronchodilator (albuterol):

This medication will be available to be administered for post-bronchodilator testing or if the participant is uncomfortable from the effects of the methacholine challenge test. Albuterol 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.

Exhaled breath condensate:

This involves breathing out into a refrigerated container – there are no risks involved.

Exhaled nitric oxide:

There are no risks to this procedure other than possible light-headedness if the participant breathes out too hard during exhalation.

Forced Oscillation:
This will be performed in conjunction with the methacholine testing and induced sputum procedure. There are no risks involved in this test. Some subjects may feel discomfort from the slight oscillation of air in their mouth while they breathe. This technique has been used safely in many studies, including those involving infants.

Induced Sputum:
This involves inhaling hypertonic saline which, may induce bronchoconstriction, and so we will administer albuterol prior, and monitor lung function during, but is generally well tolerated.

Methacholine challenge:
This test involves the inhalation of an agonist to induce bronchoconstriction and may induce the symptoms of asthma (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 FEV1 is ≥ 60% predicted and ≥ 1.5 Liters (which is one of the eligibility criterion for the MIMDA study). We will not perform if participants have uncontrolled hypertension (SBP > 200 or DBP > 100), known aortic aneurysm, history of heart attack or stroke in the last 3 months or current use of cholinesterase inhibitor for myasthenia gravis.

MitoQ:
This over the counter supplement is usually well tolerated. In previous studies the main side effect noted has been mild nausea (incidence 15% with 40 mg dose being proposed for this study), which appears dose related, and is most significant at doses of 80 mg per day and above.

Nasal Brush (Nasal epithelial cell isolation):
These are collected by scraping the back of the nose. This may cause a slight tickling sensation. On rare occasions (approx. 1%) it could cause some minor nasal bleeding, which is self-limited.

Nasal Strip:
We will place a small strip into the back of the nose and ask the participant to hold it in place against the inside of their nasal cavity to collect surface liniing fluid. The participant will need to breathe through their mouth while their nose is pinched shut, which they may find uncomfortable. This process will take approximately 1 minute. They may experience a mild discomfort, runny nose, or sneezing when the nasal strips are placed in their nose. There is a very small risk that you could experience a nose bleed.

Nasal Lavage:
There are no known risks associated with this procedure.

Spirometry:
This is a standard clinical test that may cause discomfort by breathing forcefully through a mouthpiece while wearing nose clips. Occasionally some subjects may feel lightheaded. All testing is done in a seated position under direct monitoring.

Lung volumes (Plethysmography):
This is a standard clinical test with no known risks. Participants may experience discomfort from sitting briefly in a confined space of clear Plexiglas the size of a phone booth, and breathing through a mouthpiece that is briefly occluded for 1-2 seconds during measurement of thoracic gas volume. The mouthpiece occlusion may be interrupted at any moment by a signal from the participant and the door of the body plethysmograph can be opened at any time as well.

Venipuncture:
We will draw 30 cc of blood at every visit except 5b, which does not involve a blood draw. This will be a total of 150 cc total over 12 weeks. The main risks of venipuncture are discomfort and bruising.

Urine:
We will collect approximately 5 cc of urine at every visit. There are no known risks with urine collection.

Confidentiality:
The study 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. Blood will be stored for genotyping only with specific patient consent.

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.*

☐ ***Not Applicable***

Participants will stay on their usual asthma medications per their asthma care provider. There are no medications specifically targeting obese patients with asthma. The alternative is not to participate in this study.

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.*

The DSMB will include 3 physician scientists (not from the University of Vermont or Duke University) who are active in asthma research.

Chair
Sandhya Khurana, M.D.
Associate Professor & Primary Co-Director, Mary Parks Center
University of Rochester Medical center
Strong Memorial Hospital
601 Elmwood Ave, AC-3
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Phone:585-275-4861
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Area of expertise: Pulmonary & Critical Care Medicine

The panel will convene prior to the start of clinical studies, then annually by teleconference, primarily to review safety, and also to review the integrity of the data, and will provide recommendations regarding continuation of the studies.

On a quarterly basis an AE/SAE table will be generated and circulated amongst the members for review. In the event that the DSMB finds an AE/SAE of interest the PI will be contacted by the chair for any possible follow-up/recommendations.

All SAE's will be looked at by a second physician for assessment of relatedness and severity.

Reporting mechanisms for changes or amendments to the protocol or consent form to the DMSB
Minor changes to the protocol and consent form will be reviewed at annual meetings of the DSMB. Significant changes, and any changes that affect participant safety, will be reviewed by the Chair of the DSMB, and by the full DSMB at the discretion of the Chair.

Conflicts of interest
COI's will be reviewed by the DSMB annually

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.*

We will assess for adverse events at every study visit, and encourage participants to contact the site with any adverse events outside of the time of a study visit.

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 any clinically significant abnormal laboratory finding as determined by the study physician) 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.

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 by the site investigator 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 site investigator 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.

Study Drug Action Taken
The site investigator will classify the study drug action taken with regard to the AE. The action taken will be classified according to the categories below:
- **Dose not changed:** study drug dose not changed in response to an AE
- **Dose reduced:** study drug dose reduced in response to an AE
- **Drug interrupted:** study drug administration interrupted in response to an AE

- **Drug withdrawn:** study drug administration permanently discontinued in response to an AE
- **Not applicable**: Action taken regarding study drug administration does not apply. "Not applicable" will be used in circumstances such as when the investigational treatment had been completed before the AE began and no opportunity to decide whether to continue, interrupt, or withdraw treatment is possible.

Adverse Event Outcome

An AE will be followed until the site investigator has determined and provided the final outcome or the participant has completed the study.

- **Recovered/resolved:** resolution of an AE with no residual signs or symptoms
- **Recovered/resolved with sequelae**: resolution of an AE with residual signs or symptoms
- **Not recovered/not resolved (continuing):** either incomplete improvement or no improvement of an AE, such that it remains ongoing
- **Fatal:** outcome of an AE is death. "Fatal" will be used when death is at least possibly related to the AE
- **Unknown:** outcome of an AE is not known (e.g. a subject lost to follow-up)

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, NIH and Chair of the DSMP 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, NIH and Chair of the DSMP 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, NIH and DSMP.
- A summary of all adverse events will be reported to the DSMP, NIH and IRB annually.

Reporting Mechanisms of IRB actions to NHLBI

Routine IRB actions will be summarized in annual reporting to the IRB.

IRB actions that involve significant safety issues will be reported to NHLBI within 15 days of the action.

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, we will ask the participant to consider completing questionnaires regarding asthma control, and quality of life and end of study questionnaire if they withdraw prior to the end of the study.

A study participant will be discontinued from the study for:

- Any clinical adverse event, clinically significant 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 in the opinion of the site investigator.
- Development of any exclusion criteria may be cause for discontinuation.
- Stops corresponding with study staff team, i.e., "lost to follow-up". Participants will be contacted at least three times by either e-mail or phone. These contact attempts will be recorded by study personnel. If the participant does not respond after the third attempt, they may be withdrawn from the study and considered "lost to follow-up".

Stopping rules

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 two serious adverse events that are definitely or probably related to the study protocol. The protocol will be stopped in the event that there are three 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 4 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.

Blinding and unblinding

1. *Blinding:*
   - All subjects (including caregivers/companions) and site personnel (including the investigator and study team) will be blinded to the treatment code.
   - Individuals who may be unblinded include only the following:
     - Any site personnel for whom this information is important to ensure the safety of the subject in the event of a life-threatening medical emergency
     - Any site personnel for whom this information is important to ensure the safety of the subject and her fetus in the event of a pregnancy
     - Biostastician preparing the final randomization list
     - MIMDA IDS pharmacy personnel
2. *Unblinding:*
   - At the initiation of the study, the study site will be instructed on the method of breaking the blind.
     - Site investigator to contact site IDS pharmacy personnel
       - In the situation that IDS pharmacy personnel is not available contact the study biostatistician.
     - The unblinder has permission to give verbal or written unblinding to site investigator
   - Unblinding of the individual subjects treatment by the investigator will be limited to medical emergencies or urgent clinical situations in which knowledge of the subjects study treatment is necessary for clinical management.
   - If a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the DSMB will be notified within 24 hours of the unblinding event.
   - The investigator will consider whether the clinical event that prompted unbinding will be considered an SAE according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report.
   - The reason and the date of the unblinding will be documented clearly in the subjects study file.

Unmasking:

Routine unblinding will occur at the end of the participants V5b visit. The treatment assignment will only be provided to the participant and not the staff at the clinical center. Sealed envelopes with treatment assignment are provided to the clinic to provide the participants.

Treatment termination:

Participants may be withdrawn from the treatment if they have a serious adverse event or are intolerant of the treatment per study physician decision. All participants will be asked to return for study visits, until completion of the study.

We will review participants prior history and lung function testing to screen for eligibility, but all procedures will be performed as described in this protocol

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) ☐ ***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)

Mitoquinol and placebo will be supplied by MitoQ Ltd, (based in Auckland, New Zealand).
Name and Product. MitoQ™ (Mitoquinol mesylate) capsules
Active ingredient: Mitoquinol mesylate, inactive ingredients microcrystalline cellulose, tapioca, silica dioxide
Product will be supplied as 20 mg capsules and matching placebo.

Methacholine will be purchased as Provocholine® (methapharm) containing 100 mg in 20 ml vials

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

MitoQ" Product will be supplied as 20 mg capsules and matching placebo.

Methacholine will be reconstituted according to the FDA approved package insert. Dosing of methacholine for this study will be: 0.03125 mg/mL, 0.0625 mg/mL, 0.1250 mg/mL, 0.25 mg/mL, 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 4 mg/mL. Solutions will be prepared using Provocholine® 100mg in 20mL Diluent will be 0.9% Normal Saline.

Storage and stability – for both intact and mixed products.

MitoQ
Capsules are stored at room temperature and have been found to be stable for 23 months.

Methacholine: Store the powder at 59° to 86°F (15° to 30°C). Refrigerate the reconstituted solutions 36° to 46°F (2° to 8°C) for not more than 2 weeks.

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

Oral 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.

MitoQ
The Phase 1 pharmacokinetic study conducted in New Zealand and the two Phase 2 studies have demonstrated that MitoQ® is well tolerated at oral doses up to 80 mg bid for seven days and doses up to 80 mg/day for 12 months. Gastrointestinal complaints have been the most common adverse events seen in the two Phase II clinical studies and gastrointestinal events were dose limiting in the preclinical chronic dog toxicity studies. Per prior study in patients with Parkinson's Disease, the incidence of nausea was as follows:

- Placebo - 17.1%
- MitoQ 40 mg per day - 31.2%

The incidence of vomiting was as follows:

- Placebo - 4.9%
- MitoQ 40 mg per day 14.6%.

Co-administration with food reduces the bioavailability of mitoquinone. MitoQ® should be taken with a glass of water after an overnight fast, at least one hour prior to eating.

Methacholine

Methacholine can cause headache, throat irritation, lightheadedness, itching, and in rare cases, breathing difficulties when inhaled.

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.

MitoQ is available in the U.S. as an over the counter supplement, the recommended dose of the supplement is 20 mg per day, whereas we will be using a dose of 40 mg per day in this study.
We have an IND in place for this study (IND 132184).

Methacholine
Methacholine is approved by the FDA for the indication and at the doses we will be using in this study.

2. for the route of administration specified? If no, provide justification for route and describe the method to accomplish.

Yes

3. for the intended action?

See above

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.*

Our goal is to enroll 40 (approximately 20 locally) obese adults with poorly controlled asthma despite use of asthma controller drugs. We will include those with elevated oxidative stress, which we will measure as nasal lavage 8-isoprostane ≥ 13.0 pg/ml.

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.*

We anticipate we will need to enroll up to 50 participants in order to randomize 20 participants here. The total number of participants that will need to be enrolled will be 100, in order to randomize 40 participants for this trial at two centers.

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. participant reported physician diagnosis of asthma
2. participant reported on regular prescribed controller therapy for at least 3 months
3. positive methacholine challenge (as determined by spirometry PD_{20} or oscillometry $PD_{50} \leq 4.0$ mg/ml at visit 2)
4. age: ≥18 years
5. BMI ≥ 30 kg/m^2 (at visit 1)
6. poorly controlled asthma defined as one of the following:
    a. Asthma Control Test[5] Score ≤ 19 (at visit 1), or
    b. Participant reported use of rescue inhaler on average > 2 uses/week for preceding month, or
    c. Participant reported nocturnal asthma awakening on average 1 or more times / week in preceding month, or
    d. Participant reported ED/hospital visit or prednisone course for asthma in past six months
7. ability and willingness to provide informed consent

Exclusion criteria:

1. participant reported use of an investigational agent in the prior 30 days
2. participant reported physician diagnosis of chronic obstructive pulmonary disease
3. pregnancy and/or participant reported lactation
4. females of childbearing age who do not agree to practice an adequate birth control method for the duration of the study (abstinence, combination barrier and spermicide, or hormonal)
5. participant reported greater than 10 pack year smoking history
6. participant reported smoking conventional tobacco products (cigar, cigarette, & pipes) within the last 6 months
7. participant reported e-cigarette use more than 2x/week
8. participant unwilling to withhold e-cigarette use for the duration of the study
9. participant reported vaping more than 2x/week
10. participant unwilling to withhold vaping for the duration of the study
11. participant reported marijuana use (inhalation) more than 2x/week
12. participant unwilling to withhold marijuana use (inhalation) for the duration of the study
13. participant reported sinus surgery performed ≤ 4 weeks from visit 1
14. participant reported eye surgery within the prior 3 months
15. participant reported use of the antioxidants idebenone or co-enzyme Q10 within 8 weeks
16. participant reported tendency to develop severe nose bleeds
17. $FEV_1 < 60\%$ predicted or < 1.5 Liters at visit 1
18. participant reported treatment for asthma exacerbation in the previous 4 weeks
19. participant was not able to complete at least 50% of the days on the diary cards returned at visit 2
20. other significant disease that in the opinion of the investigator would interfere with the study

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, but will exclude pregnant women.

Minorities:

Although Vermont is predominantly Caucasian (96.4% Caucasian, 0.9% African American, 1.4% Hispanic), we have had great success reaching out to our local community health clinics and student populations to increase representation in our studies. Based on our previous recruitment for clinical studies, we anticipate that we will be able to recruit minorities in higher numbers than our overall population. We also anticipate that we will recruit a high proportion of minorities from North Carolina.

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 and teens younger than 18 years of age will not be recruited because of the likelihood that the phenotype of both asthma and obesity may be somewhat different in these individuals,

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

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 participanting in this study.
We will recruit participants through IRB approved flyers posted in the community.
We will inform patients of the study in the adult pulmonary clinic, and invite them to participate.
We will post advertisements on online platforms such as craigslist, Facebook, etc..
We will reach out to Primary Care Providers and ask them to refer their patients to us, if appropriate, using the IRB approved provider and patient research referral letters.
We will prescreen the Pulmonary Function Lab schedule, if we find a patient who may be eligible we will reach out to the referring provider (if they are not a Pulmonary provider) using the IRB approved provider and patient research referral letters. Referring providers will reply to our EPIC message or secure email indicating whether the patient is interested and if they have given permission for us to reach out to the participant. We will print this communication for study records and document on the consent process documentation.

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 will be reimbursed for travel at standard UVM rates if traveling ≥ 20 miles each way.
Participants will be reimbursed up to $75 per visit for mileage.
Participants will be paid for their time - $100 for visits 1, 2, 5a, & 5b
Participants will be paid $50 for visit 3 & 4.
If participants have a negative methacholine challenge at visit 2 they will receive only $50 compensation.
Participants can receive up to $500 total.
If a follow-up visit is required then participants will be compensated $50 per additional visit.

***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)*

☐ ***Not applicable***

Duke University will be a collaborating site, FWA00009025

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.

We will provide participants the option to consent remotely over the phone. We will e-mail or mail participants a copy of the consent form based on their verbal permission. We will schedule a full phone consent. If participants elect to participate they may manually sign the consent form and mail or e-mail it back to us. If participants have the ability to use an electronic signature they may.

***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.

All materials must be submitted electronically to the IRB via InfoEd. Proper security access is needed to make electronic submissions. Visit the InfoEd Resource Materials page for more information.