Cover Page for Protocol, Statistical Plan and ICF

Official Title:	Defining and treating a new pediatric asthma endotype: depression-related asthma mediated by the cholinergic pathway
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Complete Research Protocol (HRP-503)

Table of Contents

PROTOCOL TITLE:

Include the full protocol title.

Defining and treating a new pediatric asthma endotype: depression-related asthma mediated by the cholinergic pathway

PRINCIPAL INVESTIGATOR:

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VERSION:

Include the version date or number.

Version 8/7/2018

GRANT APPLICABILITY:

Indicate whether this protocol is funded by a grant (e.g. NIH, foundation grant). For a grant with multiple aims, indicate which aims are covered by this research proposal.

NOTE: This question does not apply to studies funded by a sponsor contract.

Include a copy of the grant proposal with your submission.

Response: This protocol is funded by a University at Buffalo CTSA Pilot Grant, under award Number UL1TR001412.

RESEARCH REPOSITORY:

Indicate where the research files will be kept, including when the study has been closed. The repository should include, at minimum, copies of IRB correspondence (approval, determination letters) as well as signed consent documents. This documentation should be maintained for 3 years after the study has been closed.

Response:

Location: UBMD Pediatrics Division of Allergy/Immunology

Room 5454; 1001 Main Street, Buffalo NY 14203

1.0 Objectives

1.1 Describe the purpose, specific aims, or objectives of this research.

Specific Aim 1: To compare the degree of cholinergically-mediated bronchoconstriction in depressed children with asthma vs nondepressed children with asthma.

Response: Based upon studies of depressed asthmatic children showing increased parasympathetic/cholinergic reactivity in response to laboratory based emotional stimuli, along with a recent study showing that depressed asthmatic adults have decreased bronchodilatory response to beta-agonists, we hypothesize that asthmatic children with higher depressive indices will have more bronchodilatory response on spirometry following treatment with a short-acting inhaled anticholinergic, and less additional bronchodilation with an inhaled beta-agonist, compared to children with lower depressive indices.

Specific Aim 2: To define the inflammatory profile of depressed children with asthma, in contrast with non-depressed children with asthma.

Child asthmatics are mainly "atopic" asthmatics, with disease driven by Th2-mediated inflammation. Markers of inflammation in these patients include peripheral blood eosinophilia, sputum eosinophilia, and elevated exhaled nitric oxide. Fractional exhaled nitric oxide (FeNO) has been shown to correlate with eosinophilic inflammation, specifically with bronchoalveolar lavage eosinophils, peripheral blood eosinophils, and serum eosinophil cationic protein (Strunk et al, 2003; Silkoff et al, 2005). We hypothesize that depressed pediatric asthmatics during an episode of bronchoconstriction will show less evidence of airway inflammation as measured by FeNO and peripheral blood eosinophilia, compared to non-depressed child asthmatics during time of bronchoconstriction.

Specific Aim 3: To determine the atopic status of depressed children with asthma.

It has been estimated that 78-88% of child asthmatics are atopic (Kattan et al, 1997; Nelson et al, 1999), with positive skin prick testing to environmental allergens and/or elevated total serum IgE. Using these objective measures, we will test the hypothesis that lower rates of atopic sensitization in depressed asthmatics with cholinergically-mediated bronchoconstriction. In addition, we hypothesize that patient-identified asthma triggers will be different in the depressed asthmatic group, with increased identification of emotions and cold weather as triggers, and less identification of allergens as triggers.

1.2 State the hypotheses to be tested, if applicable.

NOTE: A hypothesis is a specific, testable prediction about what you expect to happen in your study that corresponds with your above listed objectives.

Response: We hypothesize that episodes of bronchoconstriction that occur in asthmatics with comorbid depression have an underlying cholinergic mechanism. Therefore, increased scores for depressive symptoms using standardized child depression scores will correlate with increased responsiveness (reversibility) of pulmonary function parameters with administration of inhaled ipratropium (an anticholinergic).

We next predict that with excess cholinergic activation as a cause of bronchoconstriction in depressed pediatric asthmatics, there will be less atopic sensitization and Th2-mediated inflammation driving the airway disease in this subset of asthmatics.

2.0 Scientific Endpoints

2.1 Describe the scientific endpoint(s), the main result or occurrence under study.

NOTE: Scientific endpoints are outcomes defined before the study begins to determine whether the objectives of the study have been met and to draw conclusions from the data. Include primary and secondary endpoints. Some example endpoints are: reduction of symptoms, improvement in quality of life, or survival. Your response should ***not*** *be a date.*

Response: Scientific endpoints include a continuous variable of change in Forced Expiratory Volume in 1 Second (FEV1), Forced Vital Capacity (FVC) and FEV1/FVC ratio following ipratropium; a continuous variable of Fractional Exhaled Nitric Oxide (FeNO); a continuous variable of serum IgE, and continuous variable of peripheral blood eosinophils, and positive vs negative skin testing to any environmental allergens.

3.0 Background

3.1 Provide the scientific or scholarly background, rationale, and significance of the research based on the existing literature and how it will contribute to existing knowledge. Describe any gaps in current knowledge. Include relevant preliminary findings or prior research by the investigator.

Response: Asthma is the most prevalent chronic disease of childhood, currently affecting 8.3% of children (NHIS, 2013). Disproportionately the burden of asthma falls on underserved populations. Black race, Puerto Rican Hispanic ethnicity, low socioeconomic status, and inner city residence are all associated with increased prevalence of asthma, but even more importantly, are also associated with increased morbidity and mortality of childhood asthma (Akinbami and Schoendorf, 2002). In Western New York, the highest rates of asthma-related emergency department visits and hospitalizations in children age 0-17 years are found in the zip codes of urban Buffalo and urban Niagara Falls. Subjects for this proposed study will be recruited from this high-risk asthma population, through the emergency department, primary care clinics, and Allergy and Pulmonology subspecialty clinics of)UBMD Pediatrics and Oishei Children's Hospital.Adults and children with asthma have higher levels of depressive symptoms than controls and persons with most other medical illnesses (Zielinski and Brown, 2003). Rates of current depressive disorders in outpatients with asthma have been estimated to 14-25%, with 31-47% of asthmatics estimated to have had depression at some point in their lifetime (Brown et al, 2000; Nejtek et al, 2001; Afari et al, 2001). Depression is associated with unfavorable asthma outcomes, including medication nonadherence, increased frequency of emergency room visits, hospitalizations, unscheduled visits for asthma (Eisner et al., 2005), and even asthma-related death (Mancuso et al., 2001). Morrison et al found that about 30% of children with asthma had scores on the Children's Depression Rating Scale-Revised consistent with major depressive disorder (MDD), and depressive symptom severity in these children was associated with a greater number of hospitalizations (Morrison et al., 2002). In a study of pediatric asthmatics residing in inner-city Buffalo, recruited through the WCHOB emergency room, 26% of children were in the clinical range for MDD and depression severity was associated with increased disease activity (Waxmonsky et al, 2006).

Mediators of the relationship between child depression and asthma activity have been proposed. One way in which stress and depression contribute to pediatric asthma morbidity is by causing compromised adherence to asthma controller therapy. (Bender et al. 1998) However there is also evidence that stress and depression have direct psychobiologic impacts on

asthma morbidity and mortality. Compared with nondepressed children, depressed children demonstrate increased impairment in pulmonary function when exposed to emotional stressors. Depression has been shown to cause an imbalance in parasympathetic activation versus sympathetic activation, (specifically the predominance of parasympathetic over sympathetic activation) (Reite et al, 1978) and this has formed the basis of a proposed parasympathetic/cholinergic mechanism for the airway constriction seen in depressed asthmatic children (Miller and Wood, 2003).

Basal airway smooth muscle contraction ("tone") is under autonomic nervous regulation, with cholinergic activity as the predominant driver of bronchoconstriction. Asthmatics have higher basal smooth muscle tone in the airways. In addition to airway smooth muscles, cholinergic activity is also believed to regulate other cell types within the lungs, including inflammatory cells and mucus-secreting goblet cells. While short-acting anticholinergics are in general poorer bronchodilators than beta-agonists, a very recent study of depressed adult asthmatics demonstrated poorer bronchodilatory effect of beta-agonists compared to non-depressed asthmatics (Han et al, 2016). This study suggests that depressed asthmatics are not receiving full benefit from at least one conventional asthma therapy. Our study has a potential for significant impact in the field of asthma research by determining the response of depressed asthmatics to anticholinergic bronchodilators, and guiding development of therapy for this subset of asthmatics in the future.

Currently, the main controller therapies for asthmatic patients are inhaled corticosteroids (ICS). While ICS have broad anti-inflammatory properties, and are very effective in many patients, it is becoming increasingly evident that certain subsets of asthmatic patients do not receive benefit from ICS; these patients need to have alternative therapies identified based on the underlying pathophysiology of their asthma. Patients with non-eosinophilic sputum profiles or neutrophilic inflammation do not gain the same benefit from inhaled corticosteroids (ICS) as those with eosinophilic inflammation, and hence may be candidates for anticholinergic therapy (Berry et al, 2007; Pavord et al, 1999). Anticholinergics are being investigated as adjunctive asthma therapy or as alternative asthma therapy for patients not well-controlled with traditional asthma medications. A small study has suggested that a short acting anticholinergic produced a better bronchodilatory response in non-allergic asthmatic compared to allergic asthmatics (Partridge et al, 1981). Phase II and III trials with tiotropium (a long-acting anticholinergic), as add-on therapy, have demonstrated improvements in lung function and a reduction in exacerbation risk in patients with poorly-controlled asthma despite the use

of ICS, or ICS plus a long-acting beta-agonist (LABA) (Kerstjens et al, 2012). As tiotropium specifically was beneficial for adults with severe asthma who had poor response to ICS, this suggests that the airway disease in these asthmatics is mediated by mechanisms alternative to the eosinophilic inflammation that is typically seen in asthmatics with good response to inhaled steroids. Indeed, earlier studies with tiotropium identified asthmatics lacking eosinophilic inflammation as good candidates for tiotropium therapy (Iwamoto, 2008).

Clinical trials for asthma controller therapies, including the trials of the long-acting anticholinergic, tiotropium, do not evaluate depression or anxiety as a possible comorbid state in study subjects. Therefore, there is no insight into whether depressed asthmatics were overrepresented in the tiotropium responder group. If depressed asthmatics, as we hypothesize, have airway disease that is not driven by atopy, and lack high levels of eosinophilic inflammation in their airways, they are likely to be less responsive to ICS, and may be an important subset of asthmatics for which a response to long-acting anticholinergics like tiotropium can be anticipated.

3.2 Include complete citations or references.

Response:

Afari N, Schmaling KB, Barnhart S, Buchwald D. Psychiatric comorbidity and functional status in adult patients with asthma. J Clin Psychology Medical Settings 2001; 8:245-252.

Akinbami LJ, Schoendorf KC. Trends in childhood asthma: prevalence, health care utilization, and mortality. Pediatrics 2002; 110(2):315-22.

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Berry M, Morgan A, Shaw DE, Parker D, Green R, Brightling C et al. Pathological features and inhaled corticosteroid response of eosinophilic and non-eosinophilic asthma. Thorax 2007; 62:1043–1049.

Brown ES, Khan DA, Nejtek VA, Thomas NR, Mahadi SF. Depressive symptoms and functioning in asthma patients. Primary Care Psychiatry 2000; 6:155-161.

Gao YH, Zhao HS, Zhang FR et al. The relationship between depression and asthma: a meta-analysis of prospective studies. PLoS One 2015;10:e0132424

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Iwamoto H, Yokoyama A, Shiota N, Shoda H, Haruta Y, Hattori N, Kohno N. Tiotropium bromide is effective for severe asthma with noneosinophilic phenotype. European Respiratory Journal. 2008; 31(6):1379-1380.

Kattan M, Mitchell H, Eggleston P, Gergen P, Crain E, Redline S et al. Characteristics of inner-city children with asthma: The National Cooperative Inner-City Asthma Study. Pediatr Pulmonol 1997; 24:253–262.

Kerstjens HA, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, Sigmund R, Seibold W, Moroni-Zentgraf P, Bateman ED. Tiotropium in asthma poorly controlled with standard combination therapy. New England Journal of Medicine. 2012; 367(13):1198-1207.

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Mancuso CA, Rincon M, Mcculloch CE, Charlson ME. Self-efficacy, depressive symptoms, and patients' expectations predict outcomes in asthma. Medical Care 2001; 39:1326-1338.

Miller BD, Wood BL. Emotions and family factors in childhood asthma: Psychobiologic mechanisms and pathways of effect. In: Brown ES, editor. Social and psychological factors and psychosomatic syndromes. 24th. Basel: Karger; 2003. p. 131-160.

Miller BD, Wood BL, Lim J, Ballow M, Hsu C. Depressed children with asthma evidence increased airway resistance: "vagal bias" as a mechanism? J Allergy Clin Immunol 2009 Jul;124(1):66-73.

Morrison KM, Goli A, Van Wagoner J, Brown ES, Khan DA. Depressive symptoms in inner-city children with asthma. Prim Care Companion J Clin Psychiatry 2002; 4:174-177.

Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, Pendergraft TB. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol 2004; 113(1):59-65.

(NHIS) National Health Institute Survey, 2013. http://www.cdc.gov/asthma/nhis/2013/table4-1.htm Accessed February 15, 2016.

Nejtek VA, Brown ES, Khan DA, Moore JJ, van Wagner J, Perantie DC. Prevalence of mood disorders and relationship to asthma severity in patients at an inner-city asthma clinic. Ann Allergy Asthma Immunol 2001; 87:129-133.

Nelson HS, Szefler SJ, Jacobs J, Huss K, Shapiro G, Sternberg AL. The relationships among environmental allergen sensitization, allergen exposure, pulmonary function, and bronchial hyperresponsiveness in the childhood asthma management program. J Allergy Clin Immunol 1999;104:775-785.

Omari-Asor L, Stewart R, Artero S, Ritchie K. 5-HTTLPR genotype, asthma, diabetes and late-life depression in an older French population. Int J Geriatric Psychiatry 2015; 30:1017-1022.

Partridge MR, Saunders KB. Site of action of ipratropium bromide and clinical and physiological determinants of response in patients with asthma. Thorax 1981; 36:530–533.

Pavord ID, Brightling CE, Woltmann G, Wardlaw AJ. Non-eosinophilic corticosteroid unresponsive asthma. Lancet 1999; 353:2213–2214.

Reite M, Short R, Kaufman IC, Stynes AJ, Pauley JD. Heart rate and body temperature in separated monkey infants. Biol Psychiatry 1978; 13:91-105.

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Silkoff PE, Lent AM, Busacker AA, et al. Exhaled nitric oxide identifies the persistent eosinophilic phenotype in severe refractory asthma. J Allergy Clin Immunol 2005; 116:1249-1255.

Strunk RC, Szefler SJ, Phillips BR, et al, Childhood Asthma Research and Education Network of the National Heart, Lung, and Blood Institute. Relationship of exhaled nitric oxide to clinical and inflammatory markers of persistent asthma in children. J Allergy Clin Immunol 2003; 112:883-892.

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Wood BL, Cheah PA, Lim J, Ritz T, Miller BD, Stern T, Ballow M. Reliability and Validity of the Asthma Trigger Inventory Applied to a Pediatric Population. J Ped Psychology 2007; 32(5):552–560.

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4.0 Study Design

4.1 Describe and explain the study design (e.g. case-control, cross-sectional, ethnographic, experimental, interventional, longitudinal, observational).

Response: This is a cross-sectional study designed to compare depressed and non-depressed asthmatics in their response to anticholinergics and the presence of atopic inflammation.

After informed consent and screening baseline spirometry described in Section 8.1, patients with decreased lung volumes for age/height/race (FEV1 <=80% predicted or FEV1/FVC <=85%) or significantly decreased compared to personal best lung volumes (FEV1 or FEV1/FVC >12% below the subject's personal best spirometry results for those with old spirometry results available) will continue to the study intervention. They will receive 2 puffs of ipratropium HFA (42mcg ipratropium total dose) administered through a disposable spacer device. They will have spirometry repeated 30 minutes after ipratropium is given.

Because some participants may not achieve maximum reversibility of their bronchoconstriction using ipratropium, all participants will receive 2 puffs of albuterol HFA after their second spirometry, which is the standard clinical practice to reverse airway obstruction of asthma, and spirometry will again be checked 15 minutes after albuterol.

During the study visit, participants will undergo standardized assessments with validated instruments to assess depressive/anxiety symptoms, asthma triggers, and asthma control.

Components of the assessment include:

1) Children's Depression Inventory will be used to classify depressed versus nondepressed subjects (CDI; a 27-item self-report for depression in children. Scale is validated in children 7-17 years. A parent's version of the CDI is a complementary tool to assess parent's perception of child's depressive symptoms). If a score on the depression inventory is suggestive of major depressive disorder (MDD), the guardian will be informed of this score, and

offered evaluation by the clinical child psychiatrist on our research team, who will make appropriate referrals if indicated.

2) Asthma Control Test (ACT) will be administered to children ages 12+ and the Childhood Asthma Control Test (cACT) will be administered to children ages 7-11. (Nathan et al, 2004; Liu et al, 2007) The ACT and cACT tools represent a continuum of asthma control assessment tools across childhood age ranges. In both tools, a score of >19 signifies controlled disease and scores of ≤19 signifies uncontrolled asthma.

3) Asthma Trigger Inventory (ATI) will be used to assess perceived asthma triggers for subjects (ATI contains 32 items comprising six trigger-type subscales: (a) emotions (e.g., angry, feeling alone, home stress, tense, depressed, worried, unhappy, arguments, excited, weak), (b) animal allergens, (c) pollen, (d) physical activity, (e) air pollution/irritants, and (f) infections. Patients rate on a 5-point scale (0=never, 1=rarely, 2=sometimes, 3=most of the time, 4=always) how often a particular trigger is related to their asthma symptoms (Wood et al, 2007).

4) Skin prick testing will be used to assess atopic sensitization. Children will undergo skin prick testing to seasonal (tree, grass, weed pollens) and perennial (mites, roach, animal dander, mold) allergens. Allergens eliciting a skin wheal of 3mm greater than the saline control will indicate positive sensitization.

5) Fractional exhaled nitric oxide (FeNO) will be used to assess lung inflammation. Subjects exhale into a FeNO analyzer for 60 seconds, and an exhaled nitric oxide reading measured in parts-per-million is obtained; this test can successfully be performed in individuals ages 5 and up.

6) Subjects will have peripheral blood draw in Kaleida lab adjacent to study clinic. 5ml of blood will be drawn, and CBC with differential and serum IgE will be measured. For those children who do not meet safety qualifications for skin prick testing, an additional 2ml of blood will be drawn for environmental allergy IgEs ("Region 1 Respiratory Panel").

5.0 Local Number of Subjects

5.1 Indicate the total number of subjects that will be enrolled or records that will be reviewed locally.

Response: 50 subjects

5.2 If applicable, indicate how many subjects you expect to screen to reach your target sample (i.e. your screen failure rate).

Response: 100-200 subjects (expect 50-75% screen failure rate)

5.3 Justify the feasibility of recruiting the proposed number of eligible subjects within the anticipated recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?

Response: In the UBMD Pediatric Allergy clinic, 752 unique patients with asthma diagnosis, age 7-17 years were seen in the last year. Because we would need to have 13-26% of these patients screened for our study to enroll 6.5% of these patients, we are also recruiting through flyers in the Kaleida primary care pediatric clinics and in the Oishei Children's Hospital emergency department, to make our recruitment feasible within the study period of 1 year.

6.0 Inclusion and Exclusion Criteria

*6.1 Describe the criteria that define who will be **included** in your final study sample.*

NOTE: This may be done in bullet point fashion.

Response: Inclusion criterion:

1. Patients with an established diagnosis of asthma between the ages of 7-17 years, *and:*

2. Decreased lung volumes for age/height/race (FEV1 ≤80% predicted or FEV1/FVC ≤85%) on day of study visit assessed by portable spirometry.

*6.2 Describe the criteria that define who will be **excluded** from your final study sample.*

NOTE: This may be done in bullet point fashion.

Response: Exclusion criterion:

1. Patients/parents who do not give written informed consent.

2. Patients who are unable to perform pulmonary function testing.

3. Patients who, on the day of study enrollment, require pulmonary function tests pre/post-albuterol bronchodilator, as part of their routine clinical care. These patients can be enrolled in the study at future visits when they are not receiving albuterol with pulmonary function testing.

4. Severely developmentally delayed patients, or those who suffer from other severe cognitive impairment not allowing them to perform spirometry or participate in study instruments.

5. Patients who are pregnant or nursing.

6. Patients that carry a diagnosis of significant cardiopulmonary disease other than asthma, including cystic fibrosis, alpha-1-antitrypsin deficiency, interstitial lung disease, tracheo-/broncheomalacia, or cyanotic congenital cardiac defect.

7. Patients with glaucoma, myasthenia gravis, or bladder neck obstruction (anticholinergics can worsen these conditions).

8. Patients currently taking another anticholinergic medication

9. Non-English speaking caregivers who cannot complete study instruments.

10. Patients otherwise eligible for study who have normal lung volumes for age/height/race (FEV1 >80% predicted and FEV1/FVC >85%, or <12% below the subject's personal best spirometry results for those with old spirometry results available) upon screening spirometry.

6.3 Indicate specifically whether you will include any of the following special populations in your study using the checkboxes below.

NOTE: Members of special populations may not be targeted for enrollment in your study unless you indicate this in your inclusion criteria.

Response:

☐ Adults unable to consent

☑ Individuals who are not yet adults (infants, children, teenagers)

☐ Pregnant women

☐ Prisoners

6.4 Indicate whether you will include non-English speaking individuals in your study. ***Provide justification if you will exclude non-English speaking individuals.***

In order to meet one of the primary ethical principles of equitable selection of subjects, non-English speaking individuals may ***not*** *be routinely excluded from research as a matter of convenience.*

In cases where the research is of therapeutic intent or is designed to investigate areas that would necessarily require certain populations who may not speak English, the researcher is required to make efforts to recruit and include non-English speaking individuals. However, there are studies in which it would be reasonable to limit subjects to those who speak English. Some examples include pilot studies, small unfunded studies with validated instruments not available in other languages, studies with

numerous questionnaires, and some non-therapeutic studies which offer no direct benefit.

Response: This pilot study will be limited to subjects with English-speaking parents/guardians and English-speaking children. Children and/or parents or legal guardians who cannot speak or read English will be encountered infrequently, and would represent diverse language groups. Of the 3 instruments used in this study (ACT, CDI, ATI), the ATI is only available in English and the CDI is only available in English and Spanish. The inability to use all 3 instruments on non-English speaking participants would make our results uninterpretable for those subjects.

7.0 Vulnerable Populations

If the research involves special populations that are considered vulnerable, ***describe the safeguards included to protect their rights and welfare.***

NOTE: You should refer to the appropriate checklists, referenced below, to ensure you have provided adequate detail regarding safeguards and protections. You do not, however, need to provide these checklists to the IRB.

7.1 For research that involves ***pregnant women,*** *safeguards include:*
NOTE CHECKLIST: Pregnant Women (HRP-412)

Response:

☑ **N/A**: This research does not involve pregnant women.

7.2 For research that involves ***neonates of uncertain viability or non-viable neonates,*** *safeguards include:*
NOTE CHECKLISTS: Non-Viable Neonates (HRP-413), or Neonates of Uncertain Viability (HRP-414)

Response:

☑ **N/A:** This research does not involve non-viable neonates or neonates of uncertain viability.

7.3 For research that involves ***prisoners****, safeguards include:*
NOTE CHECKLIST: Prisoners (HRP-415)

Response:

☑ **N/A:** This research does not involve prisoners.

7.4 For research that involves ***persons who have not attained the legal age for consent to treatments or procedures involved in the research ("children"),*** *safeguards include:*
NOTE CHECKLIST: Children (HRP-416)

Response:

☐ **N/A:** This research does not involve persons who have not attained the legal age for consent to treatments or procedures ("children").

*7.5 For research that involves **cognitively impaired adults**, safeguards include: NOTE CHECKLIST: Cognitively Impaired Adults (HRP-417)*

Response:

☑ **N/A:** This research does not involve cognitively impaired adults.

*7.6 Consider if other specifically targeted populations such as students, employees of a specific firm, or educationally or economically disadvantaged persons are vulnerable. **Provide information regarding their safeguards and protections, including safeguards to eliminate coercion or undue influence.***

Response:

N/A

8.0 Eligibility Screening

*8.1 Describe **screening procedures** for determining subjects' eligibility. Screening refers to determining if prospective participants meet inclusion and exclusion criteria.*

Include all relevant screening documents with your submission (e.g. screening protocol, script, questionnaire).

Response:

Informed consent will be obtained. In a private room in the UBMD Allergy clinic, study investigators will screen interested subjects for eligibility criteria using questions 1-9 on the "Pediatric Cholinergic Study Data Sheet", and if patient is not screened out by history of exclusion criteria 1-9, they will have baseline spirometry performed by study investigator, to assess FEV1, FVC, FEV1/FVC ratio. Patients with normal lung volumes for age/height/race (FEV1 >80% predicted and FEV1/FVC >85%) will screen out of the study.

Patients with decreased lung volumes for age/height/race (FEV1 <=80% predicted or FEV1/FVC <=85%) will be eligible to continue to the study intervention.

☐ **N/A:** There is no screening as part of this protocol.

9.0 Recruitment Methods

☐ **N/A:** This is a records review only, and subjects will not be recruited. NOTE: If you select this option, please make sure that all records review procedures and inclusion/exclusion screening are adequately described in other sections.

9.1 Describe when, where, and how potential subjects will be recruited.

NOTE: Recruitment refers to how you are identifying potential participants and introducing them to the study. Include specific methods you will use (e.g. searching charts for specific ICD code numbers, Research Participant Groups, posted advertisements, etc.).

Response: Potential subjects will be recruited through flyers posted in waiting areas of OCH ED and Hodge and Towne Garden clinics, or through a mailed letter explaining study which will be mailed to potential subjects who are already patients of UBMD Pediatrics Allergy/Immunology or Pulmonology clinics. Subjects from the Allergy/Immunology and Pulmonology clinics will be identified through chart query for ICD-9 diagnosis code 493.*/ ICD-10 code J45.*, and age 7-17 years. Interested prospective subjects will call the UBMD Pediatrics Allergy office to state they are interested in the trial, and may either make a study appointment, or ask to speak to the PI or study nurse to hear more information about the study. We will also use the i2b2 database through UB's Institute for Healthcare Informatics (IHI) to recruit participants from the UBMD medical data base.

9.2 Describe how you will protect the privacy interests of prospective subjects during the recruitment process.

NOTE: Privacy refers to an individual's right to control access to him or herself.

Response: Potential subjects will either respond to a posted flyer or letter to home. The list of potential subjects identified through chart query (based on age and ICD-9/-10 code) will be shredded once study information letters are sent out to those on the list. Interested prospective subjects will call the office to state they are interested in the trial, and may either make a study appointment, or ask to speak to the PI or study nurse to hear more information about the study. The PI or study nurse will explain the personal information that would be shared if they agree to be in the study. If they agree, they will be scheduled for an in person study visit, and they will hear fully about the study and undergo informed consent in a private clinic room with closed door, and interact with the study enroller and study nurse, who will administer questionnaires, FeNO, skin testing and spirometry. The privacy of patients recruited using the i2b2 data will be protected by following the UB IRB-approved procedure. A letter will be sent to the eligible patient's physician (see attached). After one week, if the physician doesn't contact the research team to refuse, a recruitment letter will be sent to participants via mail (see attached). If we don't hear from the patients within two weeks, one follow-up call will be made (see attached phone script). If at any point the physician or the patient declines, the patient will be removed from the contact list.

9.3 Identify any materials that will be used to recruit subjects.

NOTE: Examples include scripts for telephone calls, in person announcements / presentations, email invitations.

For advertisements, include the final copy of printed advertisements with your submission. When advertisements are taped for broadcast, attach the final audio/video tape. NOTE: You may submit the wording of the advertisement prior to taping to ensure there will be no IRB-required revisions, provided the IRB also reviews and approves the final version.

Response: A study informational flyer with tear-off tabs will be posted in waiting areas of OCH ED and Hodge and Towne Garden Pediatric clinics. A mailed letter explaining study will be mailed to potential subjects who are already patients of UBMD Pediatrics Allergy/Immunology and Pulmonology clinics.

10.0 Procedures Involved

*10.1 Provide a description of **all research procedures or activities** being performed and when they are performed once a subject is screened and determined to be eligible. Provide as much detail as possible.*

NOTE: This should serve as a blueprint for your study and include enough detail so that another investigator could pick up your protocol and replicate the research. For studies that have multiple or complex visits or procedures, consider the addition of a schedule of events table in in your response.

Response: The entire research procedure will occur in a single study visit. After informed consent and screening baseline spirometry described in Section 8.1, patients with decreased lung volumes for age/height/race (FEV1 <=80% predicted or FEV1/FVC <=85%) will continue to the study intervention. They will receive 2 puffs of ipratropium HFA (42mcg ipratropium total dose) administered through a disposable spacer device. They will have spirometry repeated 30 minutes after ipratropium is given.

Because some participants may not achieve maximum reversibility of their bronchoconstriction using ipratropium, all participants will receive 2 puffs of albuterol HFA after their second spirometry, which is the standard clinical practice to reverse airway obstruction of asthma, and spirometry will again be checked 15 minutes after albuterol.

Participants will undergo standardized assessments with validated instruments to assess depressive/anxiety symptoms, asthma triggers, and asthma control.

Components of the assessment include:

1) Children's Depression Inventory will be used to classify depressed versus nondepressed subjects (CDI; a 27-item self-report for depression in children. Scale is validated in children 7-17 years. A parent's version of

the CDI (Parental CDI) is a complementary tool to assess parent's perception of child's depressive symptoms) which the parent will complete at the same time the child is completing the CDI. If a score on the depression inventory is suggestive of major depressive disorder (MDD), the guardian will be informed of this score, and offered evaluation by the clinical child psychiatrist on our research team, who will make appropriate referrals if indicatedMcG.

2) Asthma Control Test (ACT) will be administered to children ages 12+ and the Childhood Asthma Control Test (cACT) will be administered to children ages 7-11. (Nathan et al, 2004; Liu et al, 2007) The ACT and cACT tools represent a continuum of asthma control assessment tools across childhood age ranges. In both tools, a score of >19 signifies controlled disease and scores of ≤19 signifies uncontrolled asthma.

3) Asthma Trigger Inventory (ATI) will be used to assess perceived asthma triggers for subjects (ATI contains 32 items comprising six trigger-type subscales: (a) emotions (e.g., angry, feeling alone, home stress, tense, depressed, worried, unhappy, arguments, excited, weak), (b) animal allergens, (c) pollen, (d) physical activity, (e) air pollution/irritants, and (f) infections. Patients rate on a 5-point scale (0=never, 1=rarely, 2=sometimes, 3=most of the time, 4=always) how often a particular trigger is related to their asthma symptoms (Wood et al, 2007).

4) Skin prick testing will be used to assess atopic sensitization. Children will undergo skin prick testing to seasonal (tree, grass, weed pollens) and perennial (mites, roach, animal dander, mold) allergens. Allergens eliciting a skin wheal of 3mm greater than the saline control will indicate positive sensitization.

5) Fractional exhaled nitric oxide (FeNO) will be used to assess lung inflammation. Subjects exhale into a FeNO analyzer for 60 seconds, and an exhaled nitric oxide reading measured in parts-per-million is obtained; this test can successfully be performed in individuals ages 5 and up.

6) Subjects will have peripheral blood draw by our study nurse, labeled only with a study ID, and the nurse will transfer this blood sample to the OCH Kaleida lab. 5ml of blood will be drawn, and CBC with differential and serum IgE will be measured. For those children who do not meet safety qualifications for skin prick testing, an additional 2ml of blood will be drawn for environmental allergy IgEs ("Region 1 Respiratory Panel").

10.2 Describe what data will be collected.

NOTE: For studies with multiple data collection points or long-term follow up, consider the addition of a schedule or table in your response.

Response: Subjects with scores above CDI clinical cutoff for depression will be compared to the response of those below the cutoff for depression in the following areas:

a. The response (% change in volume) of lung volumes to anticholinergic (ipratropium)

b. The response (% change in volume) of lung volumes to beta agonist (albuterol)

c. Airway inflammation as measured by the FeNO

d. Peripheral blood eosinophilia (eos/uL) as a measure of Th2-mediated inflammation

e. Total serum IgE as a measure of atopy

f. Atopic sensitization to perennial and seasonal allergens as measured by skin prick test

g. Current asthma control per ACT tool

h. Perceived asthma triggers per ATI tool

In addition, the CDI depressive symptom score will also be examined as a continuous variable versus the above measures.

10.3 List any instruments or measurement tools used to collect data (e.g. questionnaire, interview guide, validated instrument, data collection form).

Include copies of these documents with your submission.

Response:

1. Child Depression Inventory (CDI) and Parental CDI

2. Asthma Control Test

3. Asthma Trigger Inventory

4. Skin testing result sheet

5. Screening history questionnaire

10.4 Describe any source records that will be used to collect data about subjects (e.g. school records, electronic medical records).

Response: Electronic Medical Records from Kaleida Health and/or UBMD Pediatrics.

*10.5 Indicate whether or not **individual** subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings will be shared with subjects or others (e.g., the subject's primary care physician) and if so, describe how these will be shared.*

Response: Subjects/guardians will be informed at time of visit of their initial spirometry results, skin testing results, and if they experience responsiveness of their bronchoconstriction to ipratropium.

If a score on the depression inventory is suggestive of major depressive disorder (MDD), the caregiver will be informed of this score, and offered evaluation by the clinical child psychiatrist that is part of our research team, who will make appropriate referrals if he deems that it is indicated.

*10.6 Indicate whether or not **study** results will be shared with subjects or others, and if so, describe how these will be shared.*

Response: The study results will not be shared with others aside from at time of publication in peer-reviewed journal.

11.0 Study Timelines

11.1 Describe the anticipated duration needed to enroll all study subjects.

Response: one year is anticipated to enroll all study subjects

11.2 Describe the duration of an individual subject's participation in the study. Include length of study visits, and overall study follow-up time.

Response: Individual subjects will only participate in the study during a single visit day, lasting approximately 2 hours.

11.3 Describe the estimated duration for the investigators to complete this study (i.e. all data is collected and all analyses have been completed).

Response: 14 months (12 months for data collection and 2 months for final analysis.

12.0 Setting

12.1 Describe all facilities/sites where you will be conducting research procedures. Include a description of the security and privacy of the

facilities (e.g. locked facility, limited access, privacy barriers). Facility, department, and type of room are relevant. Do not abbreviate facility names.

NOTE: Examples of acceptable response may be: "A classroom setting in the Department of Psychology equipped with a computer with relevant survey administration software," "The angiogram suite at Buffalo General Medical Center, a fully accredited tertiary care institution within New York State with badge access," or, "Community Center meeting hall."

Response: The clinic settings of UBMD Pediatrics, in the Sweethome Road office, the Southwestern Boulevard office, and the Conventus building 4th floor subspecialty clinic at 1001 Main Street will be the settings for conducting this study. All of these clinic sites have private patient rooms where subjects will be consented, enrolled, and participate in study.

12.2 For research conducted outside of UB and its affiliates, describe:

- *Site-specific regulations or customs affecting the research*
- *Local scientific and ethical review structure*

NOTE: This question is referring to UB affiliated research taking place outside UB, i.e. research conducted in the community, school-based research, international research, etc. It is not referring to multi-site research. UB affiliated institutions include Kaleida Health, ECMC, and Roswell Park Cancer Institute.

Response:

☑ **N/A:** This study is not conducted outside of UB or its affiliates.

13.0 Community-Based Participatory Research

13.1 Describe involvement of the community in the design and conduct of the research.

NOTE: Community-Based Participatory Research (CBPR) is a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. CBPR begins with a research topic of importance to the community, has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities.

Response:

☑ **N/A:** This study does not utilize CBPR.

13.2 Describe the composition and involvement of a community advisory board.

Response:

☑ **N/A:** This study does not have a community advisory board.

14.0 Resources and Qualifications

*14.1 Describe the qualifications (e.g., education, training, experience, expertise, or certifications) of the Principal Investigator **and** staff to perform the research. When applicable describe their knowledge of the local study sites, culture, and society. Provide enough information to convince the IRB that you have qualified staff for the proposed research.*

NOTE: If you specify a person by name, a change to that person will require prior approval by the IRB. If you specify a person by role (e.g., coordinator, research assistant, co-investigator, or pharmacist), a change to that person will not usually require prior approval by the IRB, provided that the person meets the qualifications described to fulfill their roles.

Response:

Dr. Heather Lehman is board certified in Allergy/Immunology and is the Clinical Director of the UBMD Pediatrics Allergy/Immunology service (clinic sites of this service will be the study recruitment sites). She has trained multiple personnel on spirometry techniques.

Dr. Wood is a developmental and family psychologist who focuses on childhood physical and emotional illness as influenced by specifically modeled family and parent-child relational patterns.

Dr. Miller is a child psychiatrist whose research examines psychobiologic mechanisms (autonomic dysregulation) by which stress and depression impact asthma in children and adolescents.

Over the last 20 years Drs. Miller and Wood have collaborated in examining how caregiver depression, family stress, and negative parenting affects the child's asthma control, and pulmonary function. Drs. Miller and Wood are co-directors of the Center for Child and Family Asthma Studies (Women and Children's Hospital of Buffalo).

Rachel Reid is a clinical LPN who works in the UBMD Pediatric Allergy/Immunology clinic and the Severe Asthma Clinic. She is trained in performing spirometry, skin testing, phlebotomy, and FeNO measurement, and is able to administer medications.

Describe other resources available to conduct the research.

14.2 Describe the time and effort that the Principal Investigator and research staff will devote to conducting and completing the research.

NOTE: Examples include the percentage of Full Time Equivalents (FTE), hours per week. The question will elicit whether there are appropriate resources to conduct the research.

Response: Dr. Lehman will spend 0.1 FTE or 4 hours per week on this study. Rachel Reid is the study nurse and will spend 8 hours per week conducting this study.

14.3 Describe the availability of medical or psychological resources that subjects might need as a result of anticipated consequences of the human research, if applicable.

NOTE: One example includes: on-call availability of a counselor or psychologist for a study that screens subjects for depression.

Response: Because we will be assessing participant's emotional state in this study, if a score on the depression inventory is suggestive of major depressive disorder (MDD), the caregiver will be offered evaluation by the clinical child psychiatrist that is part of our research team, who will make appropriate referrals if he deems that it is indicated.

14.4 Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

Response: All subjects and families will be informed about the study in detail by the enroller, and given adequate time to review the study consent/assent forms and ask any questions they may have about the study. *Other Approvals*

14.5 Describe any approvals that will be obtained prior to commencing the research (e.g., school, external site, funding agency, laboratory, radiation safety, or biosafety).

Response: Approval was already obtained from National Center for Advancing Translational Sciences (NCATS), as required for CTSA pilot studies.

☐ **N/A:** This study does not require any other approvals.

15.0 Provisions to Protect the Privacy Interests of Subjects

15.1 Describe how you will protect subjects' privacy interests during the course of this research.

NOTE: Privacy refers to an individual's right to control access to him or herself. Privacy applies to the person. Confidentiality refers to how data collected about individuals for the research will be protected by the researcher from release. Confidentiality applies to the data.

Examples of appropriate responses include: "participant only meets with a study coordinator in a classroom setting where no one can overhear", or "the

participant is reminded that they are free to refuse to answer any questions that they do not feel comfortable answering."

Response: Potential subjects will either respond to a posted flyer or letter to home, Interested prospective subjects will call the UBMD Pediatrics Allergy office to state they are interested in the trial, and may either make a study appointment, or ask to speak to the PI or study nurse to hear more information about the study. If they agree, a study appointment is made in which they will hear about the study in a private room with closed door, and interact with that study enroller and study nurse, who will administer questionnaires, FeNO, skin testing and spirometry.

15.2 Indicate how the research team is permitted to access any sources of information about the subjects.

NOTE: Examples of appropriate responses include: school permission for review of records, consent of the subject, HIPAA waiver. This question ***does apply*** *to records reviews.*

Response: The research team will be permitted to access information about subjects in the Kaleida Health and UBMD EMRs, through consent of the subject and HIPAA waiver.

16.0 Data Management and Analysis

16.1 Describe the data analysis plan, including any statistical procedures. This section applies to both quantitative and qualitative analysis.

Response: For Primary Study End Point we will conduct Repeated Measures Analysis of Variance (RM-ANOVA) statistical procedures, with depression vs non-depression as independent variables and % predicted of FEV1, FVC, FEV1/FVC ratio, and % reversibility as dependent variables. For the Secondary Study End Point we will conduct liner regression analyses. We will correlate the continuous depression severity score (CDI) with % predicted of FEV1, FVC, FEV1/FVC ratio, and % reversibility. We will set 0.05 as the cut off p value for significance.

16.2 If applicable, provide a power analysis.

NOTE: This may not apply to certain types of studies, including chart/records reviews, survey studies, or observational studies. This question is asked to elicit whether the investigator has an adequate sample size to achieve the study objectives and justify a conclusion.

Response: There have been no studies testing the particular relationships between the specific variables hypothesized in the proposed study, so it is impossible to conduct a reliable and valid power analysis. One of the objectives of this pilot study is to obtain information on distribution, variance and effect sizes necessary to conduct an accurate power analysis, which will be necessary to properly design and justify sample size for an application for funding for the larger study.

16.3 Describe any procedures that will be used for quality control of collected data.

Response: The completed data collection forms and study instruments will be checked by the PI regularly for completeness and quality control; weekly for the first 4 weeks of the study and then monthly thereafter.

17.0 Confidentiality

A. Confidentiality of Study Data

*Describe the local procedures for maintenance of confidentiality of **study data and any records that will be reviewed for data collection**.*

*17.1 A. Where and how will all data and records be stored? Include information about: password protection, encryption, physical controls, authorization of access, and separation of identifiers and data, as applicable. Include physical (e.g. paper) **and** electronic files.*

Response: Information related to each subject will be treated with confidentiality to the extent provided by law. Each subject will be assigned with a single unique study identification number (study ID number). The medical record number, patient's date of birth, and their date of office visit will not appear on the actual data collection form or completed study instruments; instead, only the study ID number will appear on the data collection form/instruments, and a separate identifier form will be stored in a separate locked cabinet with the original signed consent forms. All paper data forms/consent forms and study log will be stored in locked cabinets in the PI's office, Room 5454 of the 1001 Main Street/Conventus Building. Data will be entered in a password-guarded spreadsheet on a password-guarded computer. Verbal or written communications among study team members will only include study identification numbers, if needed, for reference. When the results of the study are presented and/or published, only group data will be provided such that no individual study participant will be identifiable.

17.2 A. How long will the data be stored?

Response: 3 years following study completion.

17.3 A. Who will have access to the data?

Response: Only study investigators (all CITI-trained) will have access to the data.

17.4 A. Who is responsible for receipt or transmission of the data?

Response: Only study investigators (all CITI-trained) will be responsible for the receipt or transmission of the data.

17.5 A. How will the data be transported?

Response: Data forms will be transported only by study investigators, bringing them immediately to the PI's office/locked cabinet after subject enrollment.

B. Confidentiality of Study Specimens

*Describe the local procedures for maintenance of confidentiality of **study specimens**.*

☐ **N/A:** No specimens will be collected or analyzed in this research.
(Skip to Section 19.0)

17.6 B. Where and how will all specimens be stored? Include information about: physical controls, authorization of access, and labeling of specimens, as applicable.

Response: Samples will be labeled with a study ID number only, and ordered/resulted through a special study account set up with the Kaleida laboratory. No data will go into patient clinical charts.

17.7 B. How long will the specimens be stored?

Response: The blood samples will be processed immediately for CBC/diff and IgE. Excess blood will be discarded. No blood will be stored long-term.

17.8 B. Who will have access to the specimens?

Response: The study nurse will have access to the specimens, followed by the Kaleida laboratory staff, who will only have a study ID label on the specimens, with no identifiable patient information attached.

17.9 B. Who is responsible for receipt or transmission of the specimens?

Response: The study nurse is responsible for transmission of the specimens to the laboratory.

17.10 B. How will the specimens be transported?

Response: Specimens will be drawn by study nurse and transported directly to OCH Kaleida Core lab for processing.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

NOTE: Minimal risk studies may be required to monitor subject safety if the research procedures include procedures that present unique risks to subjects that require monitoring. Some examples include: exercising to exertion, or instruments that elicit suicidality or substance abuse behavior. In such cases, N/A is not an acceptable response.

18.1 Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

Response: All research personnel will be trained on all study procedures (protocol and consenting procedures) and the Principle Investigator will monitor and document the training and the conduct of the study on a regular basis, including weekly for the first 4 weeks of the study, and then monthly thereafter. The PI will also monitor recruitment, enrollment rates, and events and problems involving risks to subjects. The i2b2 data will be protected by only accessing identifiable contact information remotely on IHI's "virtual machine", so the identifiable data never leaves their secure encrypted server. All use of identifiable data is done behind the firewall on IHI's secure system. Although this study presents minimal risk to the subjects and serious events/problems (SEPs) are unlikely to occur, SEPs will be monitored and reported to the IRB. In addition to reporting serious adverse events, protocol deviations and data integrity issues will be reported to the IRB.

18.2 Describe what data are reviewed, including safety data, untoward events, and efficacy data.

Response: Case reports of safety concerns will be reviewed immediately by the PI.

18.3 Describe any safety endpoints.

Response: There are no safety endpoints in this study.

18.4 Describe how the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).

Response: Safety information will be collected during the study visit. If a safety concern arises, after addressing acute safety concerns, a case report will be generated in writing, for immediate review by the PI.

18.5 Describe the frequency of safety data collection.

Response: Data collection will only occur on the single timepoint of study recruitment.

18.6 Describe who will review the safety data.

Response: The PI will review the data.

18.7 Describe the frequency or periodicity of review of cumulative safety data.

Response: The cumulative data will be reviewed when the entire sample size has been recruited, or if continuing review is required by IRB prior to the time that we recruit our entire sample size. Throughout the study, however, the PI will monitor enrollment rates and safety case reports.

18.8 Describe the statistical tests for analyzing the safety data to determine whether harm is occurring.

Response: N/A

18.9 Describe any conditions that trigger an immediate suspension of the research.

Response: Any adverse events not immediately reversible with in office treatment will trigger research suspension and a report to the IRB.

19.0 Withdrawal of Subjects

☐ **N/A:** This study is not enrolling subjects. This section does not apply.

*19.1 Describe **anticipated** circumstances under which subjects may be withdrawn from the research without their consent.*

Response: If a subject is unable to adequately perform spirometry maneuvers or complete the study instruments/questionnaires, they will be withdrawn.

19.2 Describe any procedures for orderly termination.

NOTE: Examples may include return of study drug, exit interview with clinician. Include whether additional follow up is recommended for safety reasons for physical or emotional health.

Response: None. Each subject will only be involved for a single study visit, so this would be done in person with the study investigator at that visit.

19.3 Describe procedures that will be followed when subjects withdraw from the research, including retention of already collected data, and partial withdrawal from procedures with continued data collection, as applicable.

Response: Participants that ask to be withdrawn from the study before completing all instruments or spirometry tests at study visit will be withdrawn and no data will be collected after withdrawal. Data collected prior to timepoint of withdrawal from the study will be used in the data analysis.

20.0 Risks to Subjects

20.1 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related to their participation in the research. Consider physical, psychological, social, legal, and economic risks. Include a description of the probability, magnitude, duration, and reversibility of the risks.

NOTE: Breach of confidentiality is always a risk for identifiable subject data.

Response:

Ipratropium is an inhaled anticholinergic agent with low risk of anticholinergic side effects. We will be excluding patients with disease states or medications which can be worsened by anticholinergic therapy (see exclusions). As an anticholinergic drug, cases of precipitation or worsening of narrow-angle glaucoma, glaucoma, halo vision, conjunctival hyperemia, corneal edema, mydriasis, acute eye pain, dry throat, hypotension, palpitations, urinary retention, tachycardia, constipation, bronchospasm, including paradoxical bronchospasm have been reported with the use of ipratropium. We will only be giving a one-time dose of ipratropium in the study so significant or long-term side effects are not anticipated.

Spirometry is considered a safe procedure that can occasionally may make a subject cough or feel lightheaded, and rarely can cause transient bronchospasm which can be treated with bronchodilator.

Allergy skin testing is a routine clinical procedure in an allergy office. Local skin reactions are common at positive testing sites. These positive reactions will gradually disappear over about 30-60 minutes, and usually no treatment is necessary. Occasionally, local swelling will appear 4-6 hours after testing, and will gradually disappear over the next week or so. Skin testing will infrequently cause systemic allergic reactions. These reactions may consist of any or all of the following symptoms: itchy eyes, nose, or throat; stuffy nose; runny nose; tightness in the throat or chest; wheezing; lightheadedness; faintness; nausea and vomiting; hives; generalized itching; and shock, the latter under extreme circumstances.

Risks with a simple venous stick for a blood drawn include bleeding from the site, bruising or hematoma formation, temporary dizziness, and a low risk of infection being introduced at the blood draw site.

Risks from psychological screening include possible embarrassment or discomfort secondary to the identification of possible depressive symptoms of which the child and guardian were not aware of; however, scores from our testing would not be sufficient to make a clinical diagnosis of psychological illness. Risks will be minimized by administering the psychological questionnaires privately (child undergoes CDI separate from parent who undergoes Parental CDI).

There is a small but present risk of breach of confidentiality in the study. All efforts will be taken to minimize this risk by conducting research in a private room, using study IDs only for all questionnaires/study samples, and storing study identifier sheet and signed informed consents in a separate locked area away from the locked area where all study results are stored.

20.2 Describe procedures performed to lessen the probability or magnitude of risks, including procedures being performed to monitor subjects for safety.

Response: To lessen the risk of allergic reaction to skin testing, this will not be performed on subjects with active wheezing, upper respiratory infection, or need for albuterol for active asthma symptoms in the prior 24 hours. These subjects that are not eligible for skin testing will have an extra 2ml of blood drawn to look for environmental allergen IgEs through a blood test.

*20.3 If applicable, indicate **which procedures** may have risks to the subjects that are currently unforeseeable.*

Response: Allergy skin testing, phlebotomy, exhaled nitric oxide measurement, and spirometry are the procedures involved in the study, and while they are common procedures routinely used in clinical practice, could have a potentially unforeseeable risks.

20.4 If applicable, indicate which research procedures may have risks to an embryo or fetus should the subject be or become pregnant.

Response: Skin testing is not recommended during pregnancy because an allergic reaction during pregnancy can include uterine contractions as a symptom. This is therefore a risk on day of study. Spirometry should be performed with caution during third trimester of pregnancy because of the mechanical stress on the gravid abdomen during a spirometry breathing maneuver, but is not contraindicated during the first or second trimester.

20.5 If applicable, describe risks to others who are not subjects.

Response: N/A

21.0 Potential Benefits to Subjects

21.1 Describe the potential benefits that individual subjects may experience by taking part in the research. Include the probability, magnitude, and duration of the potential benefits. Indicate if there is no direct benefit.

*NOTE: Compensation **cannot** be stated as a benefit.*

Response: Subjects have the potential to benefit by determining if they have significant responsiveness of their asthma to ipratropium therapy. As anticholinergic therapy emerges as an option for asthmatics, information on their ipratropium-responsiveness will help to guide whether an anticholinergic agent should be considered in their asthma regimen.

They also have the potential benefit of finding out what they are allergic to by skin testing at study visit.

22.0 Compensation for Research-Related Injury

☐ **N/A:** The research procedures for this study do not present risk of research related injury (e.g. survey studies, records review studies). This section does not apply.

*22.1 **If the research procedures carry a risk of research related injury,** describe the available compensation to subjects in the event that such injury should occur.*

Response: none

22.2 Provide a copy of contract language, if any, relevant to compensation for research related injury.

*NOTE: If the contract is not yet approved at the time of this submission, submit the current version here. If the contract is later approved with **different language regarding research related injury**, you must modify your response here and submit an amendment to the IRB for review and approval.*

Response: N/A

23.0 Economic Burden to Subjects

23.1 Describe any costs that subjects may be responsible for because of participation in the research.

NOTE: Some examples include transportation or parking.

Response: Transportation to the study site and parking at the study site are the potential costs to subjects.

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

24.0 Compensation for Participation

25.1 Describe the amount and timing of any compensation to subjects, including monetary, course credit, or gift card compensation.

Response: We will reimburse families with a $10 gift card for going through the baseline spirometry only (if they screen out due to normal spirometry), or with a $100 gift card if they qualify for and complete the entire study (spirometry post-ipratropium/post-albuterol, exhaled nitric oxide, skin testing, blood draw and 3 study instruments). Gift cards will be provided at the time of study visit.

Subjects receiving the $100 gift card will be asked to complete and submit an IRS W-9 form, which will be held confidentially by the PI in locked cabinets in the PI's office, Room 5454 of the 1001 Main Street/Conventus Building.

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

☐ **N/A:** There is no compensation for participation. This section does not apply.

25.0 Consent Process

25.1 Indicate whether you will be obtaining consent.

NOTE: This does not refer to consent documentation, but rather whether you will be obtaining permission from subjects to participate in a research study. Consent documentation is addressed in Section 27.0.

☑ ***Yes*** *(If yes, Provide responses to each question in this Section)*
☐ ***No*** *(If no, Skip to Section 27.0)*

25.2 Describe where the consent process will take place. Include steps to maximize subjects' privacy.

Response: Consent will be obtained in a private room in the UBMD Pediatric outpatient clinics.

25.3 Describe how you will ensure that subjects are provided with a sufficient period of time to consider taking part in the research study.

NOTE: It is always a requirement that a prospective subject is given sufficient time to have their questions answered and consider their participation. See "SOP: Informed Consent Process for Research (HRP-090)" Sections 5.5 and 5.6.

Response: The parent/guardian can take as much time as they would like to review the informed consent at the time of enrollment, and if desired, could even postpone study involvement until a future date.

25.4 Describe any process to ensure ongoing consent, defined as a subject's willingness to continue participation for the duration of the research study.

Response: The enroller and nurse will communicate verbally with the subject/guardian throughout the study visit to ensure ongoing consent through the single study visit.

25.5 Indicate whether you will be following "SOP: Informed Consent Process for Research (HRP-090)." If not, or if there are any exceptions or additional details to what is covered in the SOP, describe:

- *The role of the individuals listed in the application who are involved in the consent process*
- *The time that will be devoted to the consent discussion*
- *Steps that will be taken to minimize the possibility of coercion or undue influence*
- *Steps that will be taken to ensure the subjects' understanding*

Response:

☑ We have reviewed and will be following "SOP: Informed Consent Process for Research (HRP-090)."

Non-English Speaking Subjects

☑ **N/A:** This study will not enroll Non-English speaking subjects. *(Skip to Section 26.8)*

25.6 Indicate which language(s) other than English are likely to be spoken/understood by your prospective study population or their legally authorized representatives.

NOTE: The response to this Section should correspond with your response to Section 6.4 of this protocol.

Response:

25.7 If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.

NOTE: Guidance is provided on "SOP: Informed Consent Process for Research (HRP-090)."

Response:

Cognitively Impaired Adults

☑ **N/A**: This study will not enroll cognitively impaired adults.
(Skip to Section 26.9)

25.8 Describe the process to determine whether an individual is capable of consent.

Response:

Adults Unable to Consent

☑ **N/A**: This study will not enroll adults unable to consent.
(*Skip to Section 26.13)*

When a person is not capable of consent due to cognitive impairment, a legally authorized representative should be used to provide consent (Sections 26.9 and 26.10) ***and, where possible, assent of the individual should also be solicited*** *(Sections 26.11 and 26.12).*

25.9 Describe how you will identify a Legally Authorized Representative (LAR). Indicate that you have reviewed the "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" for research in New York State.

NOTE: Examples of acceptable response includes: verifying the electronic medical record to determine if an LAR is recorded.

Response:

☐ We have reviewed and will be following "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

25.10 ***For research conducted outside of New York State****, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the research. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of*

"legally authorized representative" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

Response:

*25.11 Describe the process for **assent of the adults**:*

- *Indicate whether assent will be obtained from all, some, or none of the subjects. If some, indicate which adults will be required to assent and which will not.*

Response:

- *If assent will not be obtained from some or all subjects, provide an explanation of why not.*

Response:

*25.12 Describe whether **assent of the adult** subjects will be documented and the process to document assent.*

NOTE: The IRB allows the person obtaining assent to document assent on the consent document using the "Template Consent Document (HRP-502)" Signature Block for Assent of Adults who are Legally Unable to Consent.

Response:

Subjects who are not yet Adults (Infants, Children, and Teenagers)

☐ **N/A**: This study will not enroll subjects who are not yet adults. *(Skip to Section 27.0)*

*25.13 Describe the criteria that will be used to determine **whether a prospective subject has not attained the legal age for consent to treatments or procedures involved in the research** under the applicable law of the jurisdiction in which the research will be conducted **(e.g., individuals under the age of 18 years)**. For research conducted in NYS, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children."*

NOTE: Examples of acceptable responses include: verification via electronic medical record, driver's license or state-issued ID, screening questionnaire.

Response: It will be determined whether a prospective subject has not attained legal age of consent by verification via electronic medical record.

25.14 ***For research conducted outside of New York State****, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."*

Response: N/A

25.15 Describe whether parental permission will be obtained from:

Response:

☑ One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.

☐ Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

☐ Parent permission will not be obtained. A waiver of parent permission is being requested.

NOTE: The requirement for parent permission is a protocol-specific determination made by the IRB based on the risk level of the research. For guidance, review the "CHECKLIST: Children (HRP-416)."

25.16 Describe whether permission will be obtained from individuals ***other than parents****, and if so, who will be allowed to provide permission. Describe your procedure for determining an individual's authority to consent to the child's general medical care.*

Response: Legal guardians may provide consent. They must provide legal documentation of their status at the time of informed consent, or this documentation must be readily available in the electronic medical record.

*25.17 Indicate whether assent will be obtained from all, some, or none of the **children**. If assent will be obtained from some children, indicate which children will be required to assent.*

Response: Assent will be obtained for all children age 7 and greater.

25.18 When assent of children is obtained, describe how it will be documented.

Response: Children age 7-13 will have a separate Assent Document to review and sign, and children ages 14-17 will have a separate Assent Document to review and sign.

26.0 Waiver or Alteration of Consent Process

Consent will not be obtained, required information will not be disclosed, or the research involves deception.

☑ **N/A:** A waiver or alteration of consent is not being requested.

26.1 If the research involves a waiver or alteration of the consent process, please review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" to ensure that you have provided sufficient information for the IRB to make the determination that a waiver or alteration can be granted.

NOTE: For records review studies, the first set of criteria on the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" applies.

Response:

26.2 If the research involves a waiver of the consent process for planned emergency research, please review the "CHECKLIST: Waiver of Consent for Emergency Research (HRP-419)" to ensure you have provided sufficient information for the IRB to make these determinations. Provide any additional information necessary here:

Response:

27.0 Process to Document Consent

☐ **N/A:** A Waiver of Consent is being requested.
(Skip to Section 29.0)

27.1 Indicate whether you will be following "SOP: Written Documentation of Consent (HRP-091)." If not or if there are any exceptions, describe whether and how consent of the subject will be obtained including whether or not it will be documented in writing.

NOTE: If your research presents no more than minimal risk of harm to subjects and involves no procedures for which written documentation of consent is normally required outside of the research context, the IRB will generally waive the requirement to obtain written documentation of consent. This is sometimes referred to as 'verbal consent.' Review "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" to ensure that you have provided sufficient information.

If you will document consent in writing, attach a consent document with your submission. You may use "TEMPLATE CONSENT DOCUMENT (HRP-502)". If you will obtain consent, but not document consent in writing, attach the script of the information to be provided orally or in writing (i.e. consent script or Information Sheet).

Response:

☑ We will be following "SOP: Written Documentation of Consent" (HRP-091).

28.0 Multi-Site Research (Multisite/Multicenter Only)

☑ **N/A:** This study is not an investigator-initiated multi-site study. This section does not apply.

*28.1 If this is a multi-site study **where you are the lead investigator**, describe the processes to ensure communication among sites, such as:*

- *All sites have the most current version of the IRB documents, including the protocol, consent document, and HIPAA authorization.*
- *All required approvals have been obtained at each site (including approval by the site's IRB of record).*
- *All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.*
- *All engaged participating sites will safeguard data as required by local information security policies.*
- *All local site investigators conduct the study appropriately.*
- *All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.*

Response:

28.2 Describe the method for communicating to engaged participating sites:

- *Problems*

- *Interim results*
- *Study closure*

Response:

28.3 Indicate the total number of subjects that will be enrolled or records that will be reviewed across all sites.

Response:

28.4 If this is a multicenter study for which UB will serve as the IRB of record, and subjects will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) describe those methods.

Response:

29.0 Banking Data or Specimens for Future Use

☑ **N/A:** This study is not banking data or specimens for future use or research outside the scope of the present protocol. This section does not apply.

*29.1 If data or specimens will be banked (stored) for **future use, that is, use or research outside of the scope of the present protocol**, describe where the data/specimens will be stored, how long they will be stored, how the data/specimens will be accessed, and who will have access to the data/specimens.*

NOTE: Your response here must be consistent with your response at the "What happens if I say yes, I want to be in this research?" Section of the Template Consent Document (HRP-502).

Response:

29.2 List the data to be stored or associated with each specimen.

Response:

29.3 Describe the procedures to release banked data or specimens for future uses, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

Response:

30.0 Drugs or Devices

☐ **N/A:** This study does not involve drugs or devices. This section does not apply.

30.1 If the research involves drugs or devices, list and describe all drugs and devices used in the research, the purpose of their use, and their regulatory approval status.

Response:

Ipratropium (Atrovent) HFA Inhalational Device – will be used to assess responsiveness of subject asthma to cholinergic bronchodilator. FDA-approved for bronchoconstriction related to COPD. Used "off-label" for asthma. We requested clarification from the FDA whether IND was required for this study and it was determined that an IND is not required.

Albuterol HFA Inhalational Device – will be used to assess responsiveness of subject asthma to beta-adrenergic bronchodilator. FDA-approved for treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease

30.2 Describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.

Response: The ipratropium HFA, albuterol HFA and portable spirometer used in this study will be stored in a locked cabinet in the PI's office (Rm 5454 of 1001 Main Street) and removed only by study personnel during study recruitment sessions.

If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:

30.3 Identify the holder of the IND/IDE/Abbreviated IDE.

Response: N/A; FDA has determined that no IND is required for this study.

30.4 Explain procedures followed to comply with FDA sponsor requirements for the following:

	Applicable to:		
FDA Regulation	***IND Studies***	***IDE studies***	***Abbreviated IDE studies***
21 CFR 11	***X***	***X***	
21 CFR 54	***X***	***X***	
21 CFR 210	***X***		
21 CFR 211	***X***		
21 CFR 312	***X***		
21 CFR 812		***X***	***X***
21 CFR 820		***X***	

Response: N/A

31.0 Humanitarian Use Devices

☑ **N/A:** This study does not involve humanitarian use devices. This does not apply.

31.1 For Humanitarian Use Device (HUD) uses provide a description of the device, a summary of how you propose to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures.

Response:

31.2 For HUD uses provide a description of how the patient will be informed of the potential risks and benefits of the HUD and any procedures associated with its use.

Response: