S13-00448: Uncontrolled Lower Respiratory Symptoms in the WTC Survivor Program
NCT02024204

Principal Investigator: Joan Reibman, MD

Co-Investigators: *Angeliki Kazeros, MD*
Caralee Caplan-Shaw, MD
Kenneth Berger, MD
Milan Amin, MD
Nomi Levy-Carrick, MD
Bertram Bleck, PhD
Mengling Liu, PhD
Karen Carapetyan, MA
Samantha Kalish, BA
John Egan, MD
Catherine Wilkinson,BA

Purpose of the Study

Exposure to the dust and fumes of the World Trade Center (WTC) disaster resulted in adverse health including upper and lower respiratory symptoms in responders and community members. The WTC Environmental Health Center (WTC EHC), initiated in 2005, was the first and remains the only treatment program that targets community members, now called "Survivors," including local residents, local workers and clean-up workers with WTC dust and fume exposures { }. Lower respiratory symptoms (LRS) that include cough, wheeze, dyspnea, and chest tightness are prevalent in patients in the WTC EHC. Most patients with these symptoms in the "Responder" and "Survivor" programs are diagnosed with asthma and this diagnosis has guided therapy. Although spirometry is often normal, diagnosis has been supported by studies showing bronchial hyperresponsiveness (BHR) in some { }{ }, and distal or small airways disease measured with impulse oscillometry (IOS) { } { }. As a result, the WTC EHC program has used a treatment algorithm based on guidelines for asthma from the National Institutes of Health [1]. These guidelines focus on the use of "controller" therapy, which includes inhaled corticosteroids (ICS) and long acting bronchodilators (LABA) for persistent symptoms. Despite this approach, **eleven years after the destruction of the WTC towers, many patients in the WTC EHC report incomplete clinical response with continued lower respiratory symptoms.** In fact, patients with continued uncontrolled lower respiratory symptoms (LRS) remain on treatment with long-term high dose ICS often with additional LABA use, rendering them at risk for adverse health effects of long term ICS treatment. The persistence of symptoms, despite therapeutic interventions, necessitates a reevaluation and a search for causes of persistent symptoms. Possibilities include incomplete adherence with medical regimens, continuing airways disease (BHR or small airways disease) with persistent lung inflammation, or the presence of co-morbid conditions. **Our overall hypothesis is that WTC EHC patients with uncontrolled LRS despite aggressive medical therapy have increased rates of abnormal airway physiology, airway inflammation and co-morbid conditions. Identifying mechanisms for uncontrolled LRS is imperative to guide therapy with the important potential to reduce secondary adverse health outcomes.** We will test this hypothesis using a prospective study with the following aims:

Specific Aim 1. To conduct a clinical study with aggressive treatment for lower respiratory symptoms in the WTC EHC in order to identify a group of patients with controlled lower respiratory symptoms (CLRS) and a group of patients with persistent uncontrolled lower respiratory symptoms (ULRS).

SA1.a To test whether a three month treatment with combined high dose inhaled corticosteroids (ICS) and long acting bronchodilators (LABA) results in improved lower respiratory symptoms in patients overall.

Specific Aim 2. To test the hypothesis that discrete measures of lung physiology are associated with the status of ULRS and CLRS in patients in the WTC EHC.

SA2.a To test whether bronchial hyperresponsiveness (BHR) is associated with the status of ULRS and CLRS by comparing rates of BHR in patients with ULRS and CLRS.

SA2.b To test whether measurements of airflow and lung volume (FEV_1, FVC, FEV_1/FVC, RV/TLC) and of small airway dysfunction (impulse oscillometry) are associated with ULRS and CLRS status.

Specific Aim 3. To test the hypothesis that inflammatory markers associated with airway disease are increased in patients with ULRS compared to CLRS in the WTC EHC.

SA3.a Compare levels of an exhaled marker of inflammation (Fractional exhaled nitric oxide; FeNO) in patients with ULRS and CLRS.

SA3.b Compare levels of circulating biomarkers associated with a Th2 inflammatory response (total and allergen-specific IgE, circulating eosinophils, C-reactive protein, serum periostin) in patients with ULRS and CLRS.

Specific Aim 4. To test the hypothesis that increased rates of co-morbid conditions are associated ULRS compared to CLRS in the WTC EHC.

SA4.a Compare quantitative measures of PTSD, anxiety or depression in patients with ULRS and CLRS.

SA4.b Compare rates of chronic rhinosinusitis symptoms and probable paradoxical vocal cord motion (PVCM) in patients with ULRS and CLRS.

SA4.c Compare rates of gastroesophageal reflux symptoms in patients with ULRS and CLRS.

Background

Exposure to WTC dust/fumes/gas in the "Survivor" population

The attacks on the WTC on 9/11/01 generated a toxic plume of dust, fumes, and vapors that exposed nearly 250,000 people on the day of the event, and thousands more during participation in cleanup and resumption of work and residence in the area during the aftermath. Those potentially exposed include the members of the fire department of New York (FDNY) and the non-FDNY rescue and recovery workers. Importantly, over 300,000 community members including those in the daily work force (local workers), students, and local residents (residents) [2, 3]. Many of these community members were exposed to the acute events of 9/11 and were caught in the massive dust clouds created as the WTC buildings collapsed (dust cloud). Others returned to work (local workers) or homes (residents) in the following week, or participated in the clean up of the surrounding buildings (clean-up workers). These individuals were exposed for months to the more chronic fumes and gasses from the fires that burned through December 2001 and the resuspended dust from recovery activities, uncleaned streets and buildings, or cleaning efforts. **Thus community members, or "Survivors" had significant potential for both acute and chronic exposures to WTC dust gasses and fumes.**

Indoor and outdoor bulk samples of WTC dust collected after the disaster had an extremely alkaline pH and were composed primarily of pulverized building and construction materials, with some contamination with lead, asbestos, glass fibers, and polycyclic aromatic hydrocarbons [4]. Approximately 90% of the particles were > 10 microns in diameter [5]. Although the inhalable small particulate fraction of the dust (< 2.5 microns, $PM_{2.5}$) was only small percentage of the mass (10%), the quantity of particulate matter released was so massive that $PM_{2.5}$ levels in the surrounding air were extremely high [6]. The massive quantity of large particles had potential to overcome normal respiratory protective mechanisms and indeed, analysis of bronchoalveolar lavage provided evidence that these large fibers lodged in human lungs

and caused eosinophilic inflammation [7]. Additional studies of induced sputum and biopsies years after the event showed continued presence of particles and continued inflammatory cells [8, 9]. **The particles from the WTC dust have potential to cause acute and persistent airway inflammation and can reach large and small airways.**

WTC-related lower respiratory symptoms (LRS) in local community members.

Respiratory symptoms consisting of persistent and often unremitting cough, shortness of breath and wheeze were described soon after the WTC destruction initially in firefighters (FDNY) who had a existing medical program enabling pre and post-event comparisons [10, 11 , 12-15]. Similar findings were described in non-FDNY rescue workers [16]. Spirometry measurements remained within normal limits in the FDNY, albeit with a rapid decline in lung function [11, 13]. Persistent bronchial hyperreactivity (BHR) was also noted for a small number [13]. Information for community members has been more difficult to obtain because of the absence of organized advocacy groups (unions etc.). In the first detailed study of local residents, we described persistent new-onset lower respiratory symptoms (LRS; cough, dyspnea, wheeze, chest tightness) in previously asymptomatic residents [17-20]. In this door-to-door field study completed within 2 years following 9/11, screening spirometry was normal for the group, with nearly, 50% showing BHR in a sampled subgroup. These findings of lung symptoms were supported by subsequent studies from the New York City (NYC) Department of Health and Mental Hygiene (DOHMH) World Trade Center Registry (WTCHR) [2, 3, 21, 22]. In collaboration with the WTCHR, we later showed that both chronic and acute exposures to the events of 9/11 were independently associated with LRS among local workers and residents [23]. Moreover, we showed that WTC exposures and LRS were associated with reduced, although normal, spirometry measurements and abnormal impulse oscillometry (IOS) suggestive of distal airway involvement [24]. A separate analysis of BHR in a sampled population in the WTC EHC performed over 6 years after 9/11 similarly showed a 50% rate of BHR in symptomatic patients with LRS [25]. **These studies support the presence of WTC-related LRS in the community, and suggest the presence of BHR and distal airway involvement.**

Treatment program in the WTC Environmental Health Center.

The World Trade Center Environmental Health Center (WTC EHC) is a treatment program that evolved out of our initial studies and was developed in collaboration with community members to target local residents, local workers and clean-up workers [26]. Initially started as an unfunded community partnership, a more formal program was initiated in 2005 with funding from the American Red Cross; funding from the City of New York became available in 2006, and in 2008, federal funding was provided. To date, patients enter the program only if they have a possible WTC-related symptom. This is not a screening program for the asymptomatic person. Patients undergo a standardized initial evaluation with an administered questionnaire, physical examination by a physician who often specializes in pulmonary medicine, pre and post bronchodilator spirometry and IOS measurements, routine blood tests and a chest X-ray (CXR). In addition, patients are screened for symptoms consistent with posttraumatic stress disorder (PTSD), depression and anxiety. **Of the > 6,000 enrollees to date, most present with persistent LRS with nasal/sinus symptoms and symptoms consistent with gastroesophageal reflux (GER).** Despite initially seeking care for physical symptoms, rates of positive scores for PTSD, anxiety, or depression are high, exceeding those described in other exposed populations [27]. The need for services in the WTC EHC rapidly overwhelmed capacity, necessitating treatment of patients based on clinical symptoms and information from other exposed populations. Our treatment approaches are in accordance with national and international guidelines and are as follows:

Respiratory management. Patients with an abnormal CXR, sarcoidosis, or other interstitial lung disease undergo individualized studies and treatment including high resolution computerized tomography (HRCT) and diagnostic procedures (biopsy etc.). Patients with LRS and an obstructive pattern of spirometry with bronchodilator reversibility (an uncommon finding) are treated for asthma [1]. Patients with reduced vital capacity on spirometry undergo further lung function testing and HRCT. Some patients have undergone biopsy [9]. Many patients with LRS, normal spirometry and a normal CXR have IOS measurements, which are

often consistent with small or distal airway dysfunction [28]. The diagnosis of asthma is a clinical diagnosis based on a constellation of clinical findings and lung function measurements [1, 29], and thus we have treated patients with LRS and a normal CXR with normal, obstructive, or a reduced VC as if they had asthma according to asthma treatment guidelines [1]. Treatment of persistent symptoms is initiated with an anti-inflammatory controller agent, predominantly ICS with long acting bronchodilators (LABA) added as a step-up medication for uncontrolled symptoms [1]. **Since only a limited number of patients have undergone methacholine challenge, we define these patients in this proposal as having LRS rather than providing a diagnosis of "asthma."**

Management of co-morbid symptoms. Co-morbid conditions (gastroesophageal reflux; GER, chronic rhinosinusitis, PTSD/depression/anxiety) are also attended to with a treatment algorithm. GER symptoms are treated with a proton pump inhibitor, and if persistent, patients are referred to a gastroenterologist. Chronic rhinosinusitis is treated with nasal steroids, saline washes and if persistent, these individuals undergo sinus CT scans and are referred to a specialist. Patients who score positive for PTSD/depression/anxiety are referred to our mental health program, where they undergo further diagnostic evaluation and are provided with appropriate therapy.

Continued LRS in the WTC EHC

To understand the course of illness in the WTC, we recently examined longitudinal lung function and symptoms. Examination of longitudinal spirometry measurements in the WTC EHC suggests that many spirometric parameters improved over time [30]. However, our review of the presence of persistent LRS (present > 2 x/week in the preceding month) in the first patients who returned for a standardized monitoring examination (n = 1300), shows that LRS symptoms continue: 56% had persistent cough, 32% had wheeze and 50% had any LRS other than cough (Table 1;unpublished data). Thus, the WTC EHC now includes a cohort of patients with persistent LRS symptoms, many of whom remain on substantial doses of ICS. The continued use of high dose ICS puts these patients at risk for corticosteroid associated complications [31]. **The continued nature of the LRS despite treatment with high dose medications necessitates a re-evaluation of the disease process in this population.**

Lung physiology in WTC-exposed patients without other lung disease

Most studies of WTC-exposed populations report normal spirometry, with some symptomatic patients showing a restrictive spirometry pattern (reduced VC), and few showing classic airway obstruction or interstitial disease [12, 13, 16, 17]. Our initial study of local residents, completed within 2 years post-9/11 showed BHR in nearly 50% of a sampled group [17]. More recently, nearly 50% of a subset of patients with normal spirometry in the WTC EHC (n = 100) had BHR using stringent criteria [25] and nearly 70% had BHR using IOS as criteria [32]. Many patients in the WTC EHC, including those with a reduced VC, also have elevated IOS measurements, suggesting the presence of distal or small airway involvement [24, 28, 33]. Air trapping, consistent with distal airway disease, has also been shown in HRCT studies of responders [34]. **In the absence of abnormal parenchymal lung disease on imaging, these studies support a diagnosis of airways disease consistent with "asthma," but suggest that additional disease mechanisms, including the involvement of small airways, need to be considered.**

Inflammation and WTC-related LRS in WTC-exposed patients

Asthma is a heterogeneous disease with multiple clinical and biologic phenotypes [3536, 37]. Differences in inflammatory pathways may influence the severity of asthma and the response to treatment [38]. Some of these inflammatory pathways are refractory to corticosteroids, and thus using ICS in these patients may expose them to unnecessary risk. The importance of classifying these phenotypes has recently been reinforced in pharmaceutical studies of the anti IL-13 monoclonal antibody, in which high levels of periostin, a down-stream IL-13 target, predict response [39]. There are few descriptions of lung inflammation in patients with WTC-related LRS [40]. We recently described peripheral eosinophilia in some, but not all, symptomatic WTC EHC patients [41]. For our proposed studies, we will follow the current recommendations of the NIH for measurements of biomarkers [42] and focus on complete blood counts for circulating

eosinophils, fractional exhaled nitric oxide (FeNO), total and allergen-specific IgE and include novel measurements of serum periostin [39, 43]. **Through these studies, we will characterize the inflammatory pattern in WTC-related lung disease to help target therapy.**

Co-morbid conditions and LRS in WTC-exposed patients

It is well accepted that LRS may be caused and complicated by co-morbid conditions [44]. We will focus on conditions that have been described in the WTC or irritant-exposed populations with potential to modify asthma:

- *Upper airway disease and Paradoxical vocal cord motion (PVCM).* Nasal, sinus and bronchial diseases often coexist and upper respiratory symptoms, are a risk for asthma [45, 4647-49]. PVCM can produce symptoms that mimic asthma [50, 51] and can exist in isolation or co-exist with asthma; work-related or irritant-induced vocal cord dysfunction has also been described [52, 53]. Irritant induced vocal cord dysfunction has been described in WTC-exposed populations [54]. PVCM can complicate treatment decisions and lead to overuse of medications and despite its importance, PVCM can be difficult to diagnose [55]. The presence of isolated or concurrent PVCM in the WTC EHC may account for persistent respiratory symptoms despite high dose ICS/LABA therapy. Thus we propose a standardized evaluation of patients to assess for presence of continued upper respiratory tract symptoms.
- *PTSD/Anxiety/Depression*. High rates of post traumatic stress (PTSD), anxiety and depression are well-described in WTC-exposed populations [21, 56] including ours [27]. A strong association between PTSD and chronic medical illnesses has been suggested by several studies [57-65]. Thus the presence of PTSD and anxiety may aggravate the symptoms of asthma and make the disease more difficult to treat.
- *GER*. Asthma is associated with symptomatic and asymptomatic gastroesophageal reflux (GER) [66] and symptoms of asthma may overlap with those of GER [67]. Proposed mechanisms include the potential for microaspiration, as well as reflex-mediated effects of acid on the upper airway. However, in studies that included ambulatory esophageal pH-monitoring studies, we recently showed that treatment of asymptomatic GER did not influence asthma control [68, 69] that asymptomatic GER may not be a frequent cause of poor asthma control. In addition, proton-pump inhibitors failed to improve methacholine reactivity [68]. Because of the prevalence of symptoms consistent with GER our population [26], we will assess whether GER symptoms are a risk for ULRS.

New concepts in uncontrolled or "difficult to treat" asthma.

To understand the refractory nature of these LRS, we use the World Health Organization's (WHO) approach to severe asthma in which these patients were characterized as "difficult-to-treat" asthma or "severe therapy-resistant" [70, 71]. Possible reasons for uncontrolled asthma include:

- poor adherence with recommended medication regimens,
- treatment-resistant lung physiology and inflammation,
- the presence of co-morbid conditions, or environmental factors that aggravate symptoms [71-74].

We will confirm adherence and re-evaluate lung function to further characterize the underlying disease physiology including novel measurements of distal airway disease and BHR, lung inflammation to characterize disease process, and targeted co-morbid conditions.

INNOVATION

This study will fill an important knowledge gap for understanding and potential treatment of persistent LRS resulting from an environmental exposure. The measurements of distal lung function and inflammatory markers will provide novel information that will inform studies of asthma-like lower respiratory symptoms in these populations. The findings can be used to help guide therapy for this population including guidance for a subsequent reduction in the use of corticosteroids. Characterization of the underlying physiology, inflammatory response and co-morbid conditions in these patients has the

potential to provide information that can be used for other populations with airway disease, including those exposed to other environmental insults.

Study Design

Characteristics of the Research Population

Number of Subjects

Screening 300 subjects to enroll 200 subjects.

Patients will be recruited from the WTC EHC population using block stratification *a priori* to obtain a representative sampling of the monitoring population (i.e. 5 patients with recent monitoring visits, 5 patients with monitoring visits > 1 year previously). The sampling will not be stratified by race/ethnicity, age, and exposure but these variables will be adjusted in statistical analyses. We anticipate that we will telephone 300 patients for our final enrollment of 200 patients for the study.

Gender of Subjects

We intend to enroll both women and men in the approximate distribution of our clinic – 48% women, 52% men.

Age of Subjects

We will enroll patients from our adult clinic which includes patients ≥ 18 years of age (NIH definition of children is < 21) and will include patients up to age 75. Above age 75, there are few normal values for lung function testing.

Racial and Ethnic Origin

We will enroll subjects with the race/ethnic distribution of the data from our monitoring results in the WTC EHC clinic, which is approximately 40% Hispanic, 20% Black. 6% Asian.

Inclusion Criteria

Age ≥ 18 years and <75

Meet criteria for WTC EHC enrollment

Onset of LRS after 9/11/01

Persistent LRS at chart review of WTC EHC Monitoring visit

Pre-bd FEV1 within normal limits at chart review of WTC EHC Monitoring Visit

≤ 5 p-y tobacco

Not current smoker

Asthma Control Test Score ≤ 19 at chart review of WTC EHC Monitoring Visit

Normal CXR

Exclusion Criteria

Age < 18 years and Age ≥75
LRS or asthma history pre 9/11/01
No persistent LRS
pre-bd FEV1 below the lower limit of normal (NHANES)
> 5 p-y tobacco
Current smoker
Asthma Control Test Score ≥20

Abnormal CXR or parenchymal changes on HRCT

Uncontrolled major chronic illness (DM, CHR, cancer,mental health)

History of significant non-WTC occupational or environmental exposure
Allergy to study drug

Pregnancy, lactation or plans to become pregnant
Chronic oral corticosteroids

High risk of fatal or near-fatal asthma within previous 2 years
Other lung disease (IPF, sarcoid etc.)

Vulnerable Subjects

N/A

Methods & Procedures

Methods & Procedures

SA1.a To test whether a three month treatment with combined high dose inhaled corticosteroids (ICS) and long acting bronchodilators (LABA) results in improved LRS.

Trial Scheme. Subject recruitment and a trial scheme visit schedule is shown in Fig 1.

Database Pre-screening. Pre-screening will be used for initial subject recruitment. Dr. Reibman is a member of the WTC EHC Data Center, and will work in collaboration with the WTC EHC Data Center (collaboration letter included). Only patients who have agreed to be re-contacted will be included. Information on symptom frequency will be obtained from data from the standardized "monitoring" visit. Patients with persistent LRS will be invited for an Initial Visit (V1).

Definition of persistent LRS. We define "persistent LRS" based on definitions for the NIH asthma guidelines as LRS that occurs> 2x/week in the month preceding the monitoring visit. LRS will include: wheeze, shortness of breath at rest or with mild exertion, or chest tightness. These criteria for inclusion will be confirmed during V1 with a repeat questionnaire.

Fig. 1. Trial visit scheme.

Sampling strategy for screening and enrollment in V1. Patients will be recruited from the WTC EHC population using block stratification *a priori* to obtain a representative sampling of the monitoring population (i.e. 5 patients with recent monitoring visits, 5 patients with monitoring visits > 1 year previously). The sampling will not be stratified by race/ethnicity, age, and exposure but these variables will be adjusted in statistical analyses. We anticipate that we will telephone 300 patients for our final enrollment of 200 patients for the study.

Inclusion/Exclusion criteria. Detailed inclusion/exclusion criteria for subject identification for potential

enrollment include:

- Onset of LRS after 9/11/01
- Presence of LRS > 2x/week in the month preceding the monitoring visit at chart review of the WTC EHC Monitoring visit ~~and confirmed in V1~~
- Absence of abnormal CXR or other lung disease
- ACT score ≤ 19 at monitoring visit

Detailed exclusion criteria for potential enrollment include:

- Presence of abnormal CXR
- Presence of other lung disease (e.g. ILD, sarcoidosis)
- Current or ≥ 5 p-y tobacco use
- ACT score≥ 20 at monitoring visit

A study scheme and procedure chart is shown:

	Screening	V1 (enrollment)	V2	V3	V4
Time (weeks)		1	4	8	12
Consent		X			
Inclusion/exclusion	X	X			
Study review	X	X			
ACT		X	X	x	X
Physical Exam		X			
FeNO		X			X
Spirometry (pre/post bd)		X			X
IOS (pre/post bd)		X			X
Adherence counseling		X	X	X	
Daily diary review		X	X	X	
Medication distribution		X	X	X	
Classification confirmation		X			X
Co-morbidMedical Questionnaire (GSAS,SSS)			X		
Vocal Handicap Index					X
Respiratory questionnaire (ASUI)		X			X
MentalHealth Questionnaires(SF12V2, PHQ,PCL)		x			x
MMRC Dyspnea Scale		X			X
VCD assessment					X
MCT				X	
Pregnancy test		X		X	
Blood		X			
AE screen			X	X	X
Leicester Cough Questionnaire				X	
Urine Sample for Cotinine				X	
6 minute walk test				x	

Telephone screening visit (SV)

Patients with persistent LRS will be identified from the WTC EHC data base and will be contacted by telephone or in person. Study will be described and interest in study will also be determined.

Enrollment visit (V1)

Control status will be assessed with the Asthma Control Test (ACT), a symptom-based validated instrument [76, 77]. Questionnaires to assess detailed specific respiratory symptom frequency, current environmental exposures, and severity and co-morbid conditions of PTSD/depression/anxiety will be administered. The Modified Medical Research Council (MMRC) dyspnea scale will be completed to assess degree of dyspnea. Baseline FeNO (fractionated exhaled Nitric Oxide) and pre and post bronchodilator (bd; 360 mcg albuterol) spirometry and IOS will be obtained.

Patients will treated in the following manner based on assessment at V1:

- Patients who have uncontrolled LRS (ACT < 20) at time of this visit will be provided with study Advair for a total of 3 months.

- Patients who have uncontrolled LRS at V1, but do not fit criteria for Step 3,4 or 5 asthma therapy according to NIH EPR III asthma guidelines will be deferred from the study until they have been seen by their physician and tried on ICS therapy.
- Patients who had symptoms at monitoring visit but are now controlled at V1 will be asked to continue their current treatment (or no treatment) and will continue with the study. They will not be provided with any medications.

Study medication will be provided as open label high dose ICS/LABA diskus (fluticasone /salmeterol; 500/50 mcg; 1 inhalation twice daily, or MDI 230/21, 2 puffs bid) for a 1 month period. Inhaler training and adherence counseling will be performed. Patients will be instructed to maintain a daily diary.

Adherence visit (V2) Patients will return for a monthly visit. At this visit the study will be reviewed, inhaler technique reviewed, and adherence counseling administered. Notation of the counter denoting actuation of the ICS/LABA diskus will be made to assess adherence. Daily diary will be reviewed. Patients will be queried for any adverse effects. Questionnaires to assess co-morbid conditions of chronic rhinosinusitis, and gastroesophageal reflux (GER) will be administered as well as the ACT to assess for control status

Adherence visit (V3) This visit will be similar to V2, however, a methacholine challenge test with lung volumes and oscillometry will also be performed on all patients. Patients will complete the Leicester Cough Questionnaire at Visit 3. Urine will be obtained for cotinine measurements. as well as the ACT to assess for control status

Classification visit (V4): After 3 months, patients will return for their Classification. At this visit, medication use will be reviewed by noting the medication actuations, and ACT and disease-specific questionnaires for asthma control (ASUI) will be completed [78, 79]. Screening instruments for post-traumatic stress disorder (PTSD), depression and anxiety will be completed. Blood will be obtained for total and allergen specific IgE, peripheral eosinophil measurements, and measurements of serum periostin and C-reactive protein. FeNO, pre and post BD spirometry and IOS will be performed. Patients will complete a 6 minute walk test. Patients will also undergo laryngoscopy and vocal cord assessment If patients are unable to complete the vocal cord assessment on the same day as V4, they will be asked to return for a separate visit within two weeks of the end of study (Day 76-90) and will be compensated $100 for this additional time and effort.

Control Classification. Patients will be classified as ULRS or CLRS based on the ACT score obtained at V4.

Specific Aim 2. To test the hypothesis that discrete measures of lung physiology are associated with patients in the WTC EHC with URLS compared to CLRS.

Preliminary data pertinent for SA2.

Lung function in WTC EHC. We previously described characteristics of an initial group of participants (n = 1898) in the Bellevue WTC EHC [26]. Although diverse in gender, ethnicity, socioeconomic status, and types and degree of WTC exposure, the symptoms and clinical syndromes in this population are similar to those of responder cohorts with dyspnea on exertion (67%), cough (46%), wheeze and chest tightness (25%) the most frequent symptoms. Few (31%) of participants had any abnormality on spirometry, with the most common abnormality being a low forced vital capacity (FVC); a much smaller group had reduced forced expiratory volume in 1 second (FEV_1) consistent with classic obstruction. In collaboration with the NYC DOH, we also described lung function in persistently symptomatic enrollees in the DOH WTC Health Registry [23, 80], suggesting that symptoms are related to acute and chronic WTC exposures. Moreover, we demonstrated increased rates of abnormal IOS measurements, consistent with distal or small airway disease [80]. We also found abnormal IOS measurements in members of the WTC EHC with normal spirometry, and an association with symptom severity [28]. Most recently, we suggested that IOS measurements during MCT can provide additional information about BHR and symptoms [32].

Longitudinal improvement in spirometry but not IOS. Examination of longitudinal spirometry measurements in the WTC EHC suggests that many spirometric parameters improved over time [30]. A mixed

effects model showed a small but significant improvement in FEV_1 and FVC even in patients with a normal spirometry pattern at the time of enrollment, with greatest change in non-smokers. The increased access to health care services including free medication was one plausible explanation for the observation. Recently, we evaluated longitudinal measurements in IOS parameters [81]. Surprisingly we failed to document an improvement in IOS measurements. **These data raise the provocative question whether despite improvement in larger airways, patients have continued distal airway abnormalities that account for persistent LRS.**

SA2.a To test whether bronchial hyperresponsiveness (BHR) is associated with the status of ULRS and CLRS by comparing rates of BHR in patients with ULRS and CLRS.

Bronchial hyperresponsiveness (BHR). BHR is often used as a diagnostic tool and is consistent with, but not diagnostic of, asthma [29]. Use of ICS may reduce BHR, but may not normalize the response [82-84]. BHR and airway inflammation can therefore remain positive even in those with well-controlled asthma [85] and measures of BHR can be used to optimize treatment and control [86]. Routine BHR testing was never part of the WTC EHC or WTC Worker program and thus pre-treatment studies are not available for these populations. The possibility exists that patients with ULRS may have persistent BHR despite therapy. We will therefore compare rates of BHR in patients with ULRS and CLRS. All patients will undergo BHR during V3, when they have received 2 months of study therapy, to encourage patient return and to streamline the number of visits. For consistency, patients will be asked to withhold morning medications. They will then undergo a methacholine challenge test (MCT) as per ATS recommendations [87] and recent review [29]. Increasing doses of methacholine will be administered with a 2 minute tidal breathing protocol up to a maximum dose of 16mg/ml. The calculated provocative concentration that results in a 20% fall in FEV_1 (PC_{20}) will be used to determine the degree of BHR. We will use the tidal breathing technique as it is more accurate and sensitive than one using deep inspiration [29].

SA2.b To test whether measurements of airflow and lung volume (FEV_1, FVC, FEV_1/FVC, RV/TLC) and of small airway dysfunction (IOS) are associated with ULRS and CLRS status.

Spirometry/Lung function. To determine whether spirometry measurements and bronchodilator (bd) response are associated with ULRS, patients will undergo pre and post-bd (360 mcg albuterol sulfate) spirometry at V1 and V4. For consistency, patients will be asked to withhold morning medications. Spirometry will be performed according to American Thoracic Society/European Respiratory Society standards (Vmax, CareFusion, Yorba Linda, CA) [88]. Data collected will include FVC, FEV_1 and FEV_1/FVC. Predicted values will be derived from National Health and Nutrition Education Survey (NHANES III) [89, 90]. Lung volumes will be assessed by plethysmography, and pulmonary diffusion will be measured using the single breath technique. Data collected will include functional residual capacity (FRC), total lung capacity (TLC), residual volume (RV) and the pulmonary diffusing capacity for carbon monoxide (D_LCO). The measured D_LCO will be adjusted for the presence of anemia based on the measured hemoglobin level. All tests will be conducted in accord with the American Thoracic Society/European Respiratory Society recommendations.

Distal or small airway function. IOS is a non-invasive tool that measures the relationship between pressure waves applied externally to the respiratory system and the resulting respiratory airflow. IOS can provide information about the distal airways. We previously demonstrated an association of LRS with measurements of distal airway dysfunction using IOS [28, 33, 80]. We will now test whether ULRS is associated with elevated measurements of distal airway function and compare IOS measurements obtained in V4 in patients with ULRS and CLRS. IOS maneuvers (Jaeger Impulse Oscillation System) will be performed in accordance with European Respiratory Society recommendations [91] and as described [80]. Maneuvers will be performed during tidal breathing with patients in the seated position, with a nose clip in place, supporting their cheeks with their hands. A minimum of three trials, each lasting 30 seconds, will be performed. Only data from trials with constant tidal volume and coherence >0.70 at 5Hz and 0.85 at 10Hz will be analyzed [33, 92]. Reproducibility between trials (variability <10%) will be required. IOS data will include resistance measured at an oscillating frequency of 5 Hz (R_5) and 20 Hz, which can identify an

increased resistance in the system even when spirometry is normal. Frequency dependence of resistance (FDR) calculated as the difference between resistance at 5 Hz and 20 Hz (R_{5-20}) provides a measure of non-uniformity of airflow distribution, which may reflect regional functional abnormalities in the distal airways [93-95].Analyses of IOS data will be adjusted for covariates including BMI as previously described [28, 80].

Specific Aim 3. To test the hypothesis that inflammatory markers associated with airway disease are increased in patients with ULRS compared to CLRS in the WTC EHC

Preliminary data pertinent for SA3.

Elevated circulating eosinophils in WTC EHC patients with wheeze.

We recently reported elevated levels of peripheral eosinophils in a cohort of WTC EHC patients [96]. Patients who met inclusion criteria (n = 1508) had a mean age of 47 years with diverse race/ethnicity. A larger percentage of those with wheeze had elevated peripheral eosinophils compared to those without wheeze (21 vs. 13%, p<0.0001). Individuals with elevated peripheral eosinophils were more likely to have airflow obstruction on spirometry (34% vs. 14%, p = 0.0003). We also recently found elevated peripheral eosinophils in phenotypic subgroups of asthmatics supporting our ability to identify heterogeneity in asthma [97].

Elevated levels of FeNO in WTC EHC patients.

We obtained fractional exhaled nitric oxide (FeNO) measurements on individuals from our WTC clinic who presented with lower respiratory symptoms (n = 100), patients with asthma but without WTC exposure (n = 23), and a control group without asthma (n = 11) for a pilot study. Mean FeNO was elevated in individuals with WTC-related asthma compared to controls (31 ppb *vs.* 20 vppb p=0.001. These data show our ability to measure FeNO and suggest that levels are increased in patients with WTC-related asthma.

Elevated CRP is associated with reduced lung function. We evaluated peripheral C-reactive protein (CRP) as a measure of systemic inflammation in a sequentially enrolled cohort of WTC EHC patients (n = 208). Exposure categories (local workers, clean-up workers, residents) were associated with normal and elevated CRP levels (p = 0.01). Smokers had a larger portion of elevated CRP than non-smokers ($p < 0.05$), and body mass index (BMI) was significantly higher among the high CRP group ($p < 0.001$). FEV_1 and FVC were lower among the high CRP group ($p < 0.02$, $p < 0.04$). Multiple regression analysis confirmed that log(CRP) values were inversely correlated with % predicted FEV_1(p = 0.009) and positively correlated with IOS measurements ($logR_5$; p = 0.02) and $logA_X$; p = 0.005) after adjustment for logBMI. These data suggest a role for systemic inflammation in patients in the WTC EHC.

SA3.a Compare levels of FeNO in patients with ULRS and CLRS.

FeNO. Measurement of FeNO is simple, safe and reproducible, and higher FeNO levels are associated with eosinophilic inflammation and responsiveness to corticosteroids [42]. We will measure FeNO at V1 and again at V4 with the handheld NIOX MINO (Aerocrine; Stockholm, Sweden). Subjects will avoid eating or drinking at least 1 hour before testing, and measurements will be taken before spirometry. FeNO results will be reported for an exhalation flow rate of 50 mL/s, and measurements will be expressed in part per billion (ppb). Our initial analysis will compare FeNO levels between ULRS and CLRS at V4.

SA3.b Compare levels of circulating biomarkers associated with a Th2 inflammatory response in patients with ULRS and CLRS.

Atopic status. Atopic status is an important phenotype for asthma with implications for treatment [98]. The general rates of allergen sensitization in WTC-exposed populations are unknown. Consistent with recent recommendations for asthma biomarkers, we will characterize atopic status of ULRS and CLRS using quantitative serologic measures of total IgE and individual allergen-specific IgE antibodies for allergens significant for the Northeastern United States obtained from a commercial laboratory (Pharmacia ImmunoCAP assay; Quest Diagnostics; Teterboro, NJ). An allergen-specific IgE level $\geq$ 0.35 kilo-international units (kIU)/L will be considered positive. Atopy will be defined as the presence of at least one

elevated allergen-specific IgE. Comparisons between total IgE level, atopy and presence of indoor or outdoor allergens will be made between ULRS and CLRS.

Eosinophils. Analysis of blood and sputum eosinophils can provide useful information to characterize a study population for observational studies [42]. Our preliminary data suggest elevated circulating eosinophils in WTC EHC patients with wheeze reflecting a Th2, IL-13 inflammatory pathway. We will perform automated complete blood cell counts on all patients during V4. Data will be compared as complete eosinophil counts as well as dichotomized to high and low % eosinophils in ULRS *vs.* CLRS.

Periostin.Periostin is a matricellular protein expressed by mesenchymal cells and airway epithelial cells [43, 99, 100]. Elevated epithelial and serum levels of periostin are associated with treatment success with an anti-IL-13 monoclonal antibody [39]. We will measure serum periostin in blood obtained during V4. For quantitative determination of human periostin (OSF-2) between ULRS and CLRS, we will use a commercially available ELISA kit (Adipobioscience, Santa Clara CA) with a range of 31 – 2,000 ng/mL.

Future inflammatory markers. Blood samples obtained at V4 will also be saved as serum/plasma for future evaluation of potential inflammatory markers in the CTSI biorepository.

Specific Aim 4. To test the hypothesis that increased rates of co-morbid conditions are associated ULRS compared to CLRS.

Preliminary data for SA3.

Coexistence of PTSD symptoms and persistent respiratory symptoms. Since the inception of the WTC EHC, our clinical screening has included evaluation for PTSD, depression and anxiety using the PTSD Checklist and the Hopkins symptom checklist. The PTSD Checklist (PCL) is a 17 item self report score based on DSM-IV symptoms of PTSD and has been validated for screening, diagnosis and monitoring of treatment of PTSD in military, civilian, and event specific contexts [101]. The Hopkins symptom checklist-25 is a widely employed assessment tool for depression and anxiety symptoms [102]. Although insufficient to make formal psychiatric diagnoses; these elevated symptom scores can be used to asses for probable PTSD, depression and anxiety. In our analysis of our initial patients enrolled for physical symptoms, (n = 1825), we described high rates of probable PTSD, anxiety and depression. Elevated mental health scores were associated with LRS but not with lung function.

SA4.a Compare rates of PTSD, anxiety or depression in ULRS and CLRS.

PTSD/depression/anxiety. ULRS symptoms could be complicated by co-existent mental health conditions. We will administer validated tools to assess PTSD symptoms, depression and anxiety at V1 and V4 using the Patient Health Questionnaire (PHQ). We will also use theSF12v2, a validated instrument that contains 12 questions that cover social activity limitations, mood and practical and existential concerns. Because these illness are often co-related, we will assess for the association of ULRS with elevated scores for PTSD, anxiety/panic and depression individually using the Wilcoxon rank test and with logistic regression models. The logistic regression model can estimate the effects the psychiatric comorbidity scores jointly and evaluate the significance adjusting the presence of others.

SA4.b Compare rates of rhinosinusitis and paradoxical vocal cord motion (PVCM) in patients with ULRS and CLRS.

Rhinosinusitis symptoms. Sinusitis and rhinitis often co-exist with uncontrolled asthma. Diagnosis of chronic rhinosinusitis is difficult, and guidelines recommend symptom-based criteria [108, 109]. Although imaging is also recommended by some, computerized tomography is expensive and results in a radiation dose. Validated instruments to screen for chronic rhinosinusitis have recently been developed. We will use a 5-item questionnaire at V4 to assess the presence of chronic rhinosinusitis disease [110]. This instrument is highly sensitive and specific for diagnosing chronic sinonasal disease with a cutpoint of 1 (experiencing each symptom an average of one to four times per month).

Nasal endoscopy and analysis for PVCM. Nasal endoscopy and analysis for PVCM will be performed during V4 in all patients at the New York University Langone Medical Center (NYULMC) Voice Center, located adjacent to Bellevue Hospital. Patients will be escorted to the NYULMC Voice Center where they will undergo evaluation by an otolaryngologist. Flexible nasal endoscopy will be performed and scored as: discharge (0 = absent, 1 = clear, 2 = purulent), mucosal inflammation/scarring (0 = absent, 1 = mild, 2 = severe) and the presence of polyps (0 = absent, 1 = middle meatus, 2 = beyond middle meatus) [110]. In addition, examination and evaluation for findings associated with GER will be performed during laryngoscopy.

Paradoxical vocal cord motion (PVCM) refers to inappropriate adduction of the vocal folds during respiration and is often misdiagnosed as refractory asthma [111] and PVCM may mimic asthma or co-exist with asthma [71]. The NYULMC Voice Center is equipped to evaluate patients with WTC asthma for PVCM as an isolated condition, or as a co-morbid condition that might cause symptoms despite adequate asthma therapy [112, 113]**.** Laryngoscopy with videolaryngostroboscopy to exclude other more subtle neurological abnormalities is currently the most widely accepted standard for the diagnosis of PVCM [112]. However, because PVCM occurs episodically, failure to visualize the abnormal vocal fold motion on a single exam cannot exclude the disorder. In clinical practice, the diagnosis is frequently established based on a constellation of historical details (laryngospasm, voice pattern abnormalities) and laryngoscopic findings. Our evaluation will include a history and physical exam and administration of the Voice Handicap Index 10 [114]. Videolaryngostroboscopy with provocation will be performed at V4. All patients will be assessed at baseline for PCVM. If subjects demonstrate PCVM exam findings, the patient will be labeled as "definite PCVM" and the scope will be removed. If PCVM features are not noted at baseline, a provocation test may be performed. Patients may be exposed to challenges that are designed to bring out symptoms. These challenges include different scents, including perfume or cleaning products. In addition, an exercise challenge may be performed. The patient may be asked to exercise by walking in a hallway or up and down stairs in order to try to mimic symptoms. A final assessment will be performed by videolaryngostroboscopy to determine presence of PCVM and the scope will be removed. Each patient will be given a designation of "no PVCM," "probable PVCM" or "definite PVCM," based on the comprehensive evaluation and rates compared between ULRS and CLRS.

SA4.c Compare rates of GER symptoms in patients with ULRS and CLRS.

GER. We have a high rate of GER symptoms in our population, and these symptoms can affect LRS. We will use a validated questionnaire to gauge the presence or absence of symptoms due to GER via the Gastroesophageal Reflux Disease Symptom Assessment Scale (GSAS), which measures both the number and the severity of symptoms. [115]We will evaluate the rates of GER symptoms between URLS and CLRS.

Data Analysis and Data Monitoring

Sample size estimation

Our primary outcome will be the rate of LRS and CLRS after the 3 month adherence period (SA1). We base our sample size and recruitment on our initial analysis of the WTC EHC monitoring in which 88% of patients who had ever received ICS or ICS/LABA had an ACT score of $\leq$ 19. We assume however, that many of these patients were either no longer using medication at the time of the assessment, were on minimal dose, or were non-adherent. Thus we predict by V4 that we will have a 60% rate of ULRS and a total of 200 patients would yield 120 patients who will fit criteria as ULRS and 80 as CLRS. To take into account potential screen failures and dropouts, we will approach 300 patients initially to obtain the total sample size of 200. We will include drop-outs in our intention to treat analysis as these patients can be considered for baseline analysis.

For categorical endpoints, such as BHR, PTSD and PVDM, the sample sizes of 120 in ULRS group and 80 in CLRS group will achieve 80% power to detect an odds ratio of 2.08 at significance level of 0.05, assuming that the rate of disease is 30% in the CLRS group. A logistic regression of the ULRS *vs*. CLRS on a continuous,

normally distributed variable (such as depression score or log-FeNo) with a sample size of 200 observations will achieve 80% power at a 0.05 significance level to detect an OR of 1.498 for 1- standard deviation (SD) difference in the continuous covariate.

Statistical analysis of the data. To compare variables between ULRS and CLRS groups, we will use the Chi-square test for categorical variables (e.g. the presence of BHR) and the nonparametric Wilcoxon rank test for continuous variables (e.g. depression score, CRP level). Logistic regression models will be used to evaluate the association between the disease status (ULRS vs. CLRS) and the variables under hypothesis adjusting for other demographic variables and confounders such as age, gender, BMI, and WTC exposures (obtained from initial questionnaires). Odds ratios (ORs) of ULRS in relation to risk variables will also be estimated and confidence interval and statistical significance will be reported. In exploring the shape of the effect of continuous variables, log transformation may be conducted to improve the fit of the model and the interpretation of results if a skewed distribution is present, or categories defined by quartiles of continuous variables will also be used in logistic regression. To identify joint effects of multiple important variables in the logistic regression models, we will use the likelihood ratio test and Akaike's Information Criterion (AIC) for model evaluation. The likelihood ratio test is a standard approach to compare nested models, and the AIC is used for comparing non-nested models.

Data Storage and Confidentiality

Data will be kept in a secure database in the NYU CTSI server. Any paper data will be maintained in a locked file in a locked room. Data will be available to the data manager, clinical coordinator coder and the PI for routine verification of case report forms and de-identified data will be available to study personnel.

Blood Sample Storage and Use

Samples will be kept according to CDC/NIOSH regulations for sponsored projects. Blood samples obtained as part of the standard protocol will be tested for markers of inflammation. These markers include, but are not limited to, proteins such as periostin, eotaxin C-reactive protein, and others that may be identified as important markers of inflammation.

For the duration of the study, and for a period of up to 3 years after the conclusion of the study, blood sample specimens obtained during Visit 4 will be stored in the NYU-CTSI BioRepository. Only members of the study team will have access to these samples and sample information. Samples will be labeled with the patient study identification (coded number) information only, not personal health information. The investigator will ensure that patient anonymity is maintained. Patient study identification information will be stored in password-protected computers.

Sample storage for future use

Additional blood samples that are obtained by patients who have given this optional consent will be stored in the NYU-CTSI BioRepository indefinitely and marked with the study patient indentification (coded number) information only. This label will not contain personal health information (PHI). Only members of the study team will have access to these samples and sample information. Future testing will aim to better understand asthma and inflammatory markers that may be associated with the disease.

Samples will only be shared with outside investigators through a signed Materials Transfer Agreement (MTA). Patient health information linked to the samples will only be shared after the outside investigators have received Insitutional Review Board approval for their studies. Results of testing on the blood samples will not be shared with patients. Subjects will be allowed to withdraw their samples at any time, at which point they will be destroyed and removed from any future analysis. Storage of samples for future use is not required for participation in the study.

Data Safety Monitoring Plan

All adverse events including unanticipated effects of the study drug, lung function studies or vocal cord assessments and protocol violations will be collected. Serious adverse events such as unanticipated urgent care visits other than for asthma exacerbations that the investigator thinks might be due to study intervention will also be collected.

Adverse events and serious adverse events will be reported on case report forms completed by the research staff and reported immediately to the Principle Investigator, Dr. Reibman,. The monitoring entity for this study, Dr. Reibman,and co-investigators Dr. Kazeros and Dr. Caplan-Shaw ,will review the data and the circumstances of the event to ensure that any required changes to the protocol or procedures are made and submitted to the IRB.

The monitoring entity (Dr. Reibman, Dr. Kazeros, Dr. Caplan-Shaw) will meet every 6 months to ensure protocol compliance and to review any adverse events. Documentation of these meetings and safety summaries will be maintained in the regulatory binder and reported to all regulatory bodies as required.

Throughout the study, Drs. Reibman, Kazeros and Caplan-Shaw will monitor the participants for adverse events. Events determined by the Principle Investigator to be unanticipated problems involving risk to subjects or others will be reported by the PI to the IRB within 5 working days as per NYUSOM IRB regulations. Other adverse events that the PI determines are not unanticipated problems involving risks to subjects or others will be reported by the PI to the IRB at the time of continuing review.

Any serious adverse events will result in a delay in the continuation of the study pending review of the Serious Adverse Event

If upon review, trends are reported from this protocol that indicate a risk to subjects or others, the protocol will be modified in accordance with the research plan and patient safety regulations to minimize any adverse events that are occurring in the study. Protocol changes will not be made prior to IRB approval unless necessary to eliminate apparent immediate hazards to the research subjects.

Data Monitoring

All research staff will be trained in Good Clinical Practice, IRB regulations and HIPAA regulations and will be responsible for data entry. Data will be collected following the consent process and will be entered in the secure NYU CTSI Redcap system within 3 days of each visit by the research staff. Data will be entered into the secure CTSI Redcap program by research staff. All primary source documents will be kept in a locked cabinet in a locked room. Protocol compliance and data verification will be performed by the investigators Reibman, Dr. Kazeros and Dr. Caplan-Shaw, every 6 months. Random audits will be performed on every 10th primary source document and every 10th database entry to ensure data accuracy and compliance with the protocol.

Risk/Benefit Assessment

Protection against Risk

The following are risks and discomforts that patients may experience during their participation in this research study. Study staff will be trained to report adverse events to the study doctor so that risks to patient health will be minimized.

We will ask you to withhold all your inhaled medications for 8 hours before the study. The withholding of your medications may allow your breathing to become worse. Should this occur, we will advise you to restart your medications and we reschedule your appointment.

Spirometry and oscillometry. Spirometry is a standard test performed on all patients with asthma or breathing difficulties. During the study, we will ask you to breathe hard. There is a risk that this could make your asthma worse. Should this occur, we will administer a bronchodilator (albuterol sulfate by metered dose inhaler) to treat the asthma. During the spirometry examination we will administer albuterol sulfate

by a metered dose inhaler or nebulizer (180 - 360 mg) and then perform the spirometry maneuvers again for a "post bronchodilator study". This is a standard procedure for patients with asthma. Albuterol sulfate is a bronchodilator used by almost all patients with asthma. Some people find that the inhalation of this medication makes them jittery and may make their heart beat faster. Should this occur, these symptoms will resolve on their own within a few hours. For the oscillometry testing we will ask you to breathe quickly. There are no known risks to this.

Exhaled Nitric Oxide. For the measurement of exhaled nitric oxide we will ask you to breathe slowly or to breathe regularly into a tube. There are no known risks to breathing into a tube unless you are allergic to latex. Please let us know if you are allergic to latex.

Inhaled fluticasone proprionate and salmeterol (Advair Diskus). This is a standard medication used for the treatment of asthma and you may even be taking this medication before the study. We are treating you with this medication because you have continuing symptoms and we are providing you with a short course (3 months) of treatment, which reduces the possibility of many of these side effects. This medication consists of two medications: an inhaled corticosteroid and a long-acting beta2-adrenergic agonist (LABA). The possible risks mentioned in the Physicians' Desk Reference include:

Localized infections: *Candida albicans* infection of the mouth and throat may occur. To prevent this we advise patients to rinse their mouth following inhalation.

Immunosuppression: Potential worsening of infections (e.g., existing tuberculosis, fungal, bacterial, viral, or parasitic infection; ocular herpes simplex) can occur with prolonged use. We use with caution in patients with these infections and will screen you for some of these questions by questionnaire before including you in the study. More serious or even fatal course of chickenpox or measles can occur in susceptible patients.

Hypercorticism and adrenal suppression: May occur with very high dosages or at the regular dosage in susceptible individuals.

Paradoxical bronchospasm (increase in asthma symptoms): We will discontinue Advair Discus and institute alternative therapy if paradoxical bronchospasm occurs.

Patients with cardiovascular or central nervous system disorders: We will screen you with an electrocardiogram before enrolling you in this study and will use with caution because of beta-adrenergic stimulation.

Metabolic effects: We will screen for many of these conditions in our initial evaluation but will be alert to eosinophilic conditions, hypokalemia, and hyperglycemia. We will screen for these coexisting conditions and use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis.

In addition, long-acting beta2-adrenergic agonists (LABAs), such as salmeterol, one of the active ingredients in ADVAIR DISKUS, can increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs but recommendations are now to prescribed LABA only with an inhaled corticosteroid, which is why we use the combination treatment.

According to current recommendations for use, we only prescribe ADVAIR DISKUS for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. We are including you in this study because your asthma or lower respiratory symptoms have not been controlled.

Methacholine Challenge. Methacholine Challenge will not be done in anyone with current asthma or breathing problems (such as asthma causing shortness of breath or chest discomfort or wheezing on the day of the test) or low lung function. We will also not do a methacholine challenge test if you already have a response to bronchodilator on your spirometry test. The methacholine challenge will only be done after a breathing test measures your lung function to be above 70%. Methacholine challenge will not be done in anyone with known allergy to methacholine. There may be other reasons you cannot take this test. The study doctor will discuss this with you. There are other medical conditions that are affected by methacholine. If you have such a condition, your study doctor must approve of you taking the test.

This test is not likely to cause serious symptoms. Some people have coughing or a tight sensation in their chest from breathing the methacholine, but it is usually mild. About 1 in 4 subjects having this test notice some cough or shortness of breath and about 1 in 10 notices some wheezing. However, reaction to methacholine can include severe bronchoconstriction (such as a severe asthma attack) and loss in breathing function. If you develop an asthma episode during any of this procedure, we will stop the procedure and provide you with albuterol to improve your breathing. This will be provided by a physician involved in the study and you will be checked until your breathing has returned to its baseline.

Blood test. Blood will be obtained by venipuncture. We will collect a blood sample that we will store and test for markers of inflammation as part of this research study. Blood will be drawn from a vein in the arm by usual venipuncture. The risks associated with a venipuncture procedure may include pain, bruising, swelling and/or infection where the needle is put in the vein. The total amount of blood to be drawn will be 30 ml (2 tablespoons).

Vocal Cord Assessment. The vocal cord assessment involves the placement of a small camera through the nose. This is typically done after numbing the nose with topical oxymetazoline (decongestant) and topical 4% lidocaine delivered via an atomizer. The risks are nasal bleeding and discomfort with the spray. Allergies are very rare, but are possible.

If you do experience a reaction to the medication, treatment will be administered until your condition returns to normal. The placement of the camera can result in minor discomfort in the nose for about 1-2 minutes (the typical length of the exam). Rarely (<1% of the time), there may be some minor bleeding from the nose after the exam is complete. This is usually limited and can be treated easily by the physician seeing you at the time. Patients may experience lower respiratory symptoms due to the presence of the laryngoscope and during the exercise challenge.

The vocal cord assessment will take place at the NYU Voice Center,located at 345 East 37th Street, Suite 306 New York, NY 10016. Patients will be accompanied by study staff member to the NYU Voice Center. If a patient is unable to walk to the NYU Voice Center from Bellevue Hospital for any reason, a taxi will be provided at no cost to the patient.

Protection Against Risks

Protection against risks from specific procedures are described above. Furthermore, personnel will be appropriately trained in the identification and reporting of adverse events to the study doctor to minimize any potential risks or discomfort. If adverse events are reported, study will be delayed until the study doctor may determine the safest course of action, which may include withdrawal of the subject under monitoring of WTC EHC physicians. If patients experience adverse mental health events, patients may be referred to WTC EHC mental health services.

Potential Benefits to the Subjects

There are potential benefits to the subjects. This research study may change the treatment that the patient would otherwise receive. Patients will be provided with a summary of results to bring to their health care

provider that will include the results of their breathing studies, methacholine challenge test, and vocal cord assessment. This may help the health care provider to guide his or her therapy.

Investigator's Qualifications & Experience
Please see attached documents.

Subject Identification, Recruitment and Consent/Assent

Method of Subject Identification and Recruitment

Pre-screening will be used for initial subject recruitment. Dr. Reibman is a member of the WTC EHC Data Center, and will work in collaboration with the WTC EHC Data Center (collaboration letter included). Only patients who have agreed to be re-contacted will be included. Information on symptom frequency will be obtained from data from the standardized "monitoring" visit. Patients with persistent LRS will be invited for an Initial Visit (V1). Patients will be recruited from the WTC EHC population using block stratification *a priori* to obtain a representative sampling of the monitoring population (i.e. 5 patients with recent monitoring visits, 5 patients with monitoring visits > 1 year previously). The sampling will not be stratified by race/ethnicity, age, and exposure but these variables will be adjusted in statistical analyses. We anticipate that we will telephone 300 patients for our final enrollment of 200 patients for the study.

Patients will be asked if they would like to participate in the study by telephone and by written invitation. In order to further protect the privacy of patients, those who cannot be reached by telephone will be contacted at a later time (voicemail will not be utilized). For those patients who will return to the WTC EHC for care, the WTC EHC physicians will also describe the study to the patient by the treating physician during an office visit. For those without appointments during the recruitment period, the study will be described via a telephone screening. This will include the purpose of the study, and the risks and benefits of entering into the study. We will also explain what information will be collected prospectively, including questionnaire data and the procedures that will be administered during the study such as spirometry,oscillometry and methacholine challenge. Any questions that the subject will have will be answered. If the patient decides to participate in the study, informed consent will be administered.

Process of Consent

If the patient decides to schedule a Visit 1, informed consent process will be administered. The informed consent will primarily be obtained by the clinical coordinator and will only be obtained by study staff listed on the protocol. The informed consent document will include information, in lay terms, about the patient's history of continued lower respiratory symptoms and use of inhaled corticosteroids, what it means, and what the purpose of the study is. The informed consent is attached. Informed consent will be obtained in CTSI behind closed doors to protect the patient's privacy. Signed informed consent will be kept in a file in locked cabinets. No other specific recruitment methods will be utilized. Patients will also have the right to withdraw from the study at any time point. If this is the case, they may contact the principal investigator, Dr. Reibman, 462 1st Avenue, Floor 7 Room 7N24, New Bellevue, New York, NY 10016.

Subject Capacity
Patients with decisional making capacity will be provided informed consent. Informed consent will be explained to patients and patients will be assessed to see if they understand the study purpose, risks,

benefits, etc. Vulnerable subjects, including children, cognitively impaired, pregnant women, and prisoners will be excluded from the study.

Subject/Representative Comprehension

Patients will be provided with adequate time to complete the informed consent process. If patients decide they need additional time to consider their participation in the study and discuss the consent document with family, etc. the visit will be rescheduled. Patients will be given opportunities to ask questions about the study and request additional information to make their decision.

Debriefing Procedures

None.

Consent Forms

Please see attached consent forms.

Documentation of Consent

Please see above.

Costs to the Subject

There is no cost to the subject for this study. All test and procedures preformed are covered by the study and will be at no expense to the participants.

Payment for Participation

Patients will receive fifty dollars for Visits 1 and 2 and one hundred dollars for Visits 3 and 4 to reimburse patients for their corresponding time and effort. Payment reflects the length of each visit. Patients who do not complete the visit or decide to withdraw their consent during the visit will still be reimbursed for their time without penalty. Reimbursements will be distributed as cash payments.