Assessing Inflammatory and Behavioral Pathways Linking PTSD to Increased Asthma Morbidity in WTC Workers
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Mount Sinai	Protocol Title:	Assessing Inflammatory and Behavioral Pathways Linking PTSD to Increased Asthma Morbidity in WTC Workers
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MSSM Protocol Template HRP-503a

Instructions:

1. *Prepare a document with the following sections. Note that, depending on the nature of your research, certain sections below may not be applicable. Indicate N/A as appropriate, explaining where possible.*
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Brief Summary of Research (250-400 words):

Asthma and post-traumatic stress disorder (PTSD) are the most common conditions in World Trade Center (WTC) rescue and recovery workers. A large number of WTC workers continue to report poor asthma control and impaired quality of life. Thus, asthma is a major cause of morbidity in this population. Several studies show a strong relationship between PTSD and increased asthma morbidity. PTSD is associated with systemic inflammation (increased levels of interleukin [IL]-1α, IL-2, IL-6, and tumor necrosis factor-alpha [TNF-α]). Some of these pro-inflammatory cytokines have been linked to more severe asthma phenotypes, potentially explaining the relationship between PTSD and worse asthma outcomes. However, biological pathways are likely only part of the drivers of asthma morbidity. Several observations suggest that PTSD has a stronger association with subjective (asthma symptoms, use of rescue medication, and quality of life) than objective (pulmonary function) markers of asthma morbidity, suggesting over-perception of symptoms. Additionally, theory and empirical evidence suggest that inaccurate perception of asthma symptoms and maladaptive illness and medication beliefs in patients with PTSD may lead to lower adherence to asthma self-management behaviors (SMB), a key determinant of asthma outcomes. With adherence to controller medications being low among asthma patients in general, behavioral mechanisms may also contribute to the association between PTSD and increased asthma morbidity in WTC workers. Our goal is to examine the interaction of biology and behavior in WTC workers with asthma and PTSD and use this information to design and pilot test an intervention to improve their care.

1) Objectives:

Research Question:

Our goal is to examine the interaction of biology and behavior in WTC workers with

asthma and PTSD and use this information to design and pilot test an intervention to improve their care. The Specific Aims are to:

1. Assess the relationship of PTSD with systemic and airway inflammatory patterns in WTC workers with asthma and evaluate the association with asthma control

H1a: PTSD will be associated with increased systemic levels of IL-1b, TNF-α and IL-6. H1b: WTC workers with asthma and PTSD will have an increased expression of sputum neutrophilia and IL-6 levels. H1c: Increased sputum neutrophilia and higher IL-6 levels will be associated with poorer disease control among WTC workers with asthma.

2. Examine the longitudinal association between PTSD and symptom perception in WTC workers with asthma

H2a: WTC rescue and recovery workers with PTSD will be more likely to over-perceive asthma symptoms in naturalistic settings compared to participants without PTSD. H2b: Associations between subjective (Asthma Control Questionnaire, use of rescue medications, and Asthma Quality of Life Questionnaire scores) and objective (forced expiratory volume in 1 second [FEV_1]) measures of asthma control will be weaker among WTC workers with PTSD than those without PTSD.

3. Assess the relationship between PTSD and adherence to asthma SMB (medication adherence, trigger avoidance, and inhaler technique) in WTC workers and identify the pathways linking them

H3a: PTSD is associated with lower adherence to SMB among WTC workers with asthma. H3b: Asthma (identity, timeline, and cause), medication beliefs (necessity and concerns about controller medications), and over-perception of symptoms will mediate, in part, the influence of PTSD on SMB.

4. Develop and pilot test an integrated intervention for asthma and PTSD by adapting the Relaxation Response Resiliency Program (3RP), a mind-body program, with counseling to promote asthma SMB, and education to correct over-perception of asthma symptoms

H4: The intervention will be acceptable to WTC workers, change beliefs about asthma, correct symptom over-perception, improve asthma medication adherence and quality of life and reduce symptoms of PTSD. We are currently seeking approval for the observational portion of the study only. We will request IRB approval for the interventional (pilot) phase at a later date, in advance of commencing the pilot.

2) Background

SIGINIFICANCE: Importance of the Problem: Multiple studies have shown a high prevalence of asthma in WTC rescue and recovery workers, local residents, and passersby.[3-6,28-31] Using data from the National Health Interview Survey (NHIS), we found that WTC workers have twice the risk of asthma compared to the general United States (US) population.[31,32] Data from the WTCHP shows a 28% cumulative incidence of asthma 9 years after September 11, 2001 among WTC workers.[1] These studies show that asthma is the most prevalent respiratory condition among WTC rescue and

recovery workers.

WTC workers with asthma include individuals with prior history of the disease and new cases of irritant-induced asthma.[4] Many workers with preexistent asthma developed worsening symptoms after WTC-related exposures (WTC-exacerbated asthma). Other workers developed new asthma symptoms without latency during or after WTC exposure and were diagnosed with irritant-induced asthma.[33] Multiple cases of new onset asthma among WTC workers have been reported in the years following exposure to the WTC site; characterization of these cases has been more difficult. Despite this potential heterogeneity, these conditions are frequently grouped in clinical practice as WTC-related asthma and managed similarly.

Studies found substantial burden of asthma morbidity in WTC workers and exposed community members, with reports of poorly-controlled in 34% and very poorly-controlled symptoms in 35% of exposed individuals.[5] Increased risk of emergency department (ED) visits and hospitalizations as well as poor quality of life in WTC workers with asthma have been reported, showing a major impact on health.[5]

Scientific Premise of Project: PTSD is Associated with Increased Asthma Morbidity in WTC Workers: Prevalence of psychological symptoms in WTC-exposed populations is high;[1,3,34-37] with PTSD reported as the most common (~30%) mental health condition.[1,2] Studies have also found high rates (25-35%) of PTSD comorbidity in WTC workers with asthma.[3,38,39] Mental health conditions and PTSD in particular, have been associated with increased asthma morbidity.[5,6] We found that WTC workers with PTSD had worse asthma control, increased healthcare use, and poorer quality of life (see preliminary data). Similarly, a study of WTC workers indicated that severity of PTSD symptoms predicted new onset and worsening of asthma.[40] Data from studies in the general population have also shown that PTSD is associated with higher asthma morbidity.[16,19,41-43] In summary, studies have documented a high level of overlap between asthma and PTSD in WTC workers and other exposed populations and have documented that PTSD is a major contributor to increased asthma morbidity. However, the underlying mechanisms explaining this relationship remain unknown.

Potential Biological Pathways Linking PTSD and Asthma Morbidity: The impact of PTSD extends to multiple organ systems as a consequence of changes in the hypothalamic-pituitary axis, the autonomic nervous system, and the immune system.[44-52] These PTSD-associated systemic alterations may impact asthma morbidity. PTSD is associated with a basal low-grade systemic inflammation, in particular, increased plasma levels of pro-inflammatory cytokines such as interleukin (IL)-1α, IL-2, IL-6, tumor necrosis factor-alpha (TNF-α and decreased IL-4, IL-5 ("Th2-cytokines").[7-10] Airway inflammation, a central feature of asthma, may be modulated by enhanced systemic inflammation as that observed in PTSD.[8,12-15] Major asthma endotypes, which describe asthma subtypes based on inflammatory mechanisms, include allergic, intrinsic (non-atopic), and noneosinophilic asthma.[53,54] Allergic asthma is characterized by airway eosinophilia driven by T_H2-dominant inflammation. Noneosinophilic asthma is characterized by airway neutrophilia has been associated with refractory disease,

severe exacerbations, and increased risk of intubation.[55-58] Key cytokines driving neutrophilic asthma include IL-1β, IL-6 and IL-17, which are elevated in patients with PTSD.[51] IL-6 directs and stabilized T-cells towards a Th17 subset,[59-62] which can then recruit and activate of neutrophils.[63-66] Therefore, systemic inflammatory changes associated with PTSD, may worsen asthma outcomes by driving a neutrophilic asthma phenotype. Identification of the biological pathways underlying worse asthma in patients with comorbid PTSD has important implications for disease management including indications for inhaled corticosteroids (ICS) and new biological drugs and may offer new alternative targets for therapy.[67,68]

Symptom Perception in Asthma Patients with Comorbid PTSD: Effective asthma SMB requires the patient to recognize and respond (use of rescue medication, contact physician, etc.) to their symptoms.[69,70] Self-monitoring of symptoms is also key for assessing response to treatment and thus, developing effective self-regulatory mechanisms (i.e., ICS linked to improved symptoms; see theoretical framework). Unfortunately, the symptoms that asthma patients experience do not always align with objective measures of their airway obstruction.[71-81] Experiments have identified 3 asthma symptom perception phenotypes that have important clinical implications: symptom under-perceivers, normal perceivers, and over-perceivers.[78,82-84] Prior studies have shown a strong relationship between misperception of symptoms and increased asthma morbidity.[77,85-88]

While PTSD is associated with increased objective and subjective asthma morbidity markers, the associations with subjective measures are stronger.[16,18] We found that PTSD had strong associations with disease control measures and quality of life in WTC workers with asthma.[17] However, the association with FEV_1 was weaker (see preliminary data). Other studies had similar findings.[16-20] These data strongly suggest that over-perception of symptoms may be prevalent among WTC workers with PTSD and may contribute to increased asthma morbidity and complicate SMB.

Our hypotheses for over-perception of symptoms among WTC workers with PTSD is based on Janssens's cognitive-affective model of symptom perception.[89] A central factor in this model is negative affect common among patients with PTSD.[90-93] Janssens's model[89] proposes that negative affect will be linked with over-perception of symptoms via an associative learning mechanism. Because asthma exacerbations cause a negative affective state,[94] an association between such a state and asthma symptoms develops in patients with PTSD. As a consequence, subsequent negative emotional states due to PTSD may results in the report of severe asthma symptoms in the presence of mild or no airway obstruction. The effect of negative affect is most pronounced on the affective component (i.e., unpleasantness dimension) of dyspnea. Thus, PTSD patients may perceive more asthma symptoms due to perceptions of unpleasant sensations of dyspnea.

PTSD is also characterized by a disruption in the ability to regulate emotions,[91,96-98] which can lead to exaggerated emotional reactions to asthma-symptoms, in turn leading to symptom magnification. One relevant cognitive vulnerability factor common to PTSD and asthma is anxiety sensitivity, the tendency to catastrophically misinterpret the bodily

sensations associated with anxious arousal (e.g., shortness of breath or chest pounding) as threatening.[99,100] Anxiety sensitivity is more common among patients with asthma, strongly implicated in the experience of dyspnea, and associated with poor asthma control,[101-105] and greater behavioral avoidance.[106] Recent work by Dr. Gonzalez (Consultant) indicates that anxiety sensitivity, physical concerns in particular, plays a significant role in understanding the PTSD-asthma symptom link in WTC workers (see preliminary data).

Assessing Asthma Symptom Perception: Symptom perception is typically measured in laboratories by self-reported respiratory symptoms while inducing airway constriction with histamine or methacholine.[78,82,107] However, this approach produces biased data because it generates anxiety and primes patients for certain reactions.[82,84,107,108] In contrast, measurements in naturalistic settings (e.g., their home), as we propose to do, is a validated method[87,109] that reduces the emotional threat of the test environment and omits pharmacological techniques and devices that may generate anxiety.[77]

PTSD May Negatively Impact Asthma SMB: Asthma self-management encompasses several complex behaviors such as adherence to controller medications, adequate inhaler technique, use of action plans, allergen avoidance, and avoiding tobacco exposure that are critical for adequate disease control. Adherence to controller medications in particular, is a factor that heavily influences the outcomes of asthmatics.[110-112] Studies conducted in the general population and our preliminary data from WTC workers shown that only ~50% of patients with asthma adhere to controller therapy or other SMB.[25-27,113-117]

Mental health conditions are associated with low adherence to chronic disease SMB.[118-120] PTSD, in particular, has been strongly associated with low treatment adherence in multiple chronic diseases.[21,23,24,121] With smoking being an important part of asthma self-management, it is of special concern that higher rates of smoking have been reported among WTC workers with PTSD.[122,123] Thus, low adherence to SMB may mediate, in part, the association between PTSD and increased asthma morbidity. However, there is limited data regarding the relationship between PTSD and asthma SMB in the general population or among WTC workers, in particular.

Theoretical Framework: Pathways Mediating the Influence of PTSD on SMB: We will use the Self-regulation Model (SRM) to guide our exploration of the relationship between PTSD and asthma SMB via illness beliefs, emotional representations and symptoms perception (Figure 1 and 5).[124-127] According to the SRM, people with chronic illness, like asthma, compare their somatic sensations (i.e., symptoms) to their "normal" self, and interpret deviations from "normal" in relation to their mental model of their illness, which in turn guides their SMB. Appraisal of the efficacy of their actions (i.e., improved asthma control) serves as a feedback loop to reinforce or modify SMB. The SRM posits five domains of cognitive representations of illness: identity (disease labels), cause (etiology and triggers), timeline (chronicity), consequences (perceived impact), and control (extent to which an illness can be controlled). For example, if asthma patients accurately perceive their respiratory symptoms (identity) and believe asthma is persistent (timeline) they will engage in SMB. The SRM also predicts that patients will be

adherent if they learn, via feedback loops, that their asthma medications can prevent symptoms (controllability). Emotional responses to asthma (i.e., worry, upset, or anxious) also influence SMB.[128-134] The framework of the SRM is highly useful for identifying the modifiable beliefs and emotional mechanisms which underlie behaviors worth targeting for self-management support interventions.[127]

We expect that PTSD may impact asthma SMB in several ways. WTC workers with PTSD may magnify asthma symptoms (identity) when they are actually experiencing negative emotions. Over-perception of symptoms could be a major barrier for internalizing positive feedback loops about medication effectiveness, leading to low adherence. WTC workers with PTSD and asthma may also misinterpret the causes of their asthma symptoms and thus, avoid situations that trigger the physical sensations they fear. Paradoxically, decreasing the frequency of PTSD symptoms via avoidance of perceived (not actual) asthma triggers may contribute to illness representations that focus more on this maladaptive avoidance, and less on SMB. Some patients view asthma as a chronic (timeline) inflammatory condition (cause), which requires adherence to daily ICS. Data from non-WTC asthma populations shows that patients with PTSD are more likely to view asthma as an acute, episodic disease.[135] This 'acute' representation of asthma has been associated to low medication adherence.[128] Patients with PTSD also tend to feel out of control (due to unexpected symptoms and catastrophic thoughts) and have lower self-efficacy, which has been linked to low ICS adherence.[136-138]

According to the SRM, emotional responses also influence SMB. As discussed above, patients with PTSD have emotional regulation difficulties; thus, strong negative emotional reactions to asthma may deplete WTC workers' self-regulatory resources managing emotions to the detriment of asthma SMB.[139] SRM has also shown that medication beliefs strongly predict ICS adherence.[130,140] Negative affect in workers with PTSD may extend to patients' beliefs about ICS (e.g., side effects, dependence, etc.) negatively influencing adherence.[133,141] Moreover, patients with PTSD may avoid asthma medications and awareness of symptoms because these factors may serve as trauma cues or reminders of 9/11, triggering memories of their WTC traumatic experiences. Thus, this copying style (avoidance) may lead to low medication adherence.[22,142]

Absence of Interventions Integrating PTSD and Asthma Management: Despite the strong link between asthma and PTSD in WTC workers, there are no interventions aimed at managing both conditions. Dr. Gonzalez is conducting a randomized clinical trial (RCT) to evaluate an integrative mind-body treatment, the 3RP, to improve the management of PTSD and lower respiratory symptoms in WTC workers (see preliminary data).[143-145] The 3RP is an 8-session group-based program that seeks to promote the physiological, emotional, cognitive and behavioral effects of the relaxation response.[146] The 3RP program focuses on 3 major areas to decrease stress and build resiliency: 1) eliciting the relaxation response via sustained mental focus with an attitude of open receptive awareness; 2) promoting stress awareness and decreasing reactivity, which involves identification of the 5 components of one's stress response (thoughts, emotions, physical reactions, behaviors, and relationship changes) and learning skills (e.g., cognitive restructuring) to change these components; and 3) increasing use of adaptive

strategies by focusing on skills to promote positive growth and self-efficacy in response to stress. However, this intervention was not specifically developed for WTC workers with asthma and thus, does not address misperception of symptoms or disease SMB.

3) Setting of the Human Research

The study sites will include New York City (the Mount Sinai Hospital [MSH]) and Queens (Queens College – Northwell Health).

The research at Mount Sinai will take place in the Center for Advanced Medicine Building at 17 East 102nd St., New York, NY 10029. The research at Queens College will take place at the Northwell Health Queens World Trade Center Health Program located at 97-77 Queens Boulevard, Rego Park, NY 11374.

4) Resources Available to Conduct the Human Research

The study cohort will consist of a sample of 400 WTC workers with asthma enrolled in the MSH or Queens World Trade Center Health Programs. There will be 300 subjects enrolled at MSH and 100 at Queens. Dr. Wisnivesky will be responsible for overseeing data collection activities and quality of data collected. For the observational cohort study (Aims 1-3), we selected validated tools and electronic measures that are known to be highly valid and reliable. Data will be collected using electronic forms with built in logic patterns to minimize data entry errors. Dr. Wisnivesky will train research assistants in survey administration techniques and appropriate maneuvers for assessing lung function; Drs. Katz and Gonzalez will train social workers or psychology graduate students in administration of the psychiatric interviews. We will randomly select 10% of audiotaped recordings of psychiatric interviews for Dr. Katz or Gonzalez to rate for accuracy and to provide feedback to the graduate students. We will also conduct random checks of 10% of all collected data to assess for data entry errors, ranges of input values, missing data, and overall data quality. Similar methods will be used to monitor data collected as part of the pilot RCT (Aim 4). Study team members will meet monthly to review progress in recruitment goals, review preliminary results, and identify and resolve emerging problems.

Research staff will include:

Name	Title	Dept./Institution/Company
Juan Wisnivesky, MD, MPH	PI	Medicine/ISMMS
Laura Crowley, MD	Co-I	Preventive Health/ISMMS
Paula Busse, MD	Co-I	Clinical Immunology/ISMMS
Rachel Yehuda, MD	Co-I	Psychiatry/ISMMS
Craig L. Katz, MD	Co-I	Psychiatry/ISMMS

Non-Key Personnel involved in study will be managed by the PI. Requisite certifications and records for these individuals will be included in the Regulatory Binder and Financial Conflicts of Interest will be reported on Sinai Central.

Qualifications of Key Personnel:

Dr. Wisnivesky is a Professor of Medicine and Chief of the Division of General Internal Medicine of the Mount Sinai Health System. He is a clinical researcher with expertise in asthma and COPD epidemiology, chronic disease self-management, and lung cancer. Dr. Wisnivesky has considerable experience conducting large observational cohort studies including and ongoing study of WTC workers with asthma. He was also involved in the Data Coordinating Center of the WTC program and participated in Steering Committee meetings, oversaw data management processes, and led or collaborated in several manuscripts summarizing the long-term health conditions among WTC workers. He is PI of a U01 grant to conduct a project evaluating WTC workers, has been PI of a phase I-II NIH-funded randomized controlled trial evaluating a novel herbal medicine for asthma, and MPI of two grants to assess self-management behaviors among COPD patients. He received a K award from the federal Agency for Healthcare Research and Quality to identify determinants of medication adherence and outcomes among inner-city asthmatics. He has also been involved in several inpatient, outpatient and physician studies assessing the treatment and outcomes of inner-city asthmatics.

Dr. Crowley is an Assistant Professor in the Department of Preventive Medicine at the Icahn School of Medicine at Mount Sinai. She has worked as a clinician in the WTCHP since 2006 and serves as the Deputy Director of the Data Coordination Center since 2008. In her role as Deputy Director, she oversees the revision of clinical examination components, data capturing protocols, and is involved in organizing multiple operational and scientific activities. She is also a practicing clinician in the WTC Treatment Program. Dr. Crowley has published several manuscripts reporting on the health of WTC responders and has collaborated with Dr. Wisnivesky on prior projects.

Dr. Busse's research has focused upon the study of chronic airway inflammation in asthma. Her K08 funding centered upon the role of TNF-α in airway mucus metaplasia in mouse models of asthma. As an internist and a T. Franklin Williams Scholar, her research expanded to the study of asthma in older patients. Her laboratory developed and characterized a murine model of allergic asthma using aged mice. To expand these studies into human disease, she has evaluated airway inflammatory markers in older vs. younger patients with asthma, supported by an NIH R21 grant on which Dr. Wisnivesky

was a Co-Investigator. She has published extensively in the area of asthma epidemiology, inflammation, and allergic markers.

Dr. Yehuda is the director of the Mental Health Patient Care Center and founder and director of the PTSD program of Medicine at James J. Peters VA Medical Center (JJP VAMC). She oversees a research laboratory dedicated to neuroendocrine and genetic/epigenetic assays with a particular focus on PTSD, and she has broad experience conducting research with the range of biological measures used in this study. Her research has produced about 300 peer-reviewed publications.

Dr. Katz is an Associate Professor of Psychiatry at the Icahn School of Medicine at Mount Sinai. He co-developed and directed the WTC Worker/Volunteer Mental Health Screening and Treatment Program, a collaboration between Disaster Psychiatry Outreach and the Icahn School of Medicine at Mount Sinai that was partnered with a federally funded medical screening and treatment program for 9/11. By 2007, the program had become successful enough to be incorporated into the National Institute of Occupational Safety and Health's funding of what eventually became known as the WTC Medical Monitoring and Treatment Program. He has considerable expertise evaluating the mental health impact of disasters including the WTC terrorist attacks. He has collaborated with Dr. Wisnivesky in the ongoing cohort study of WTC workers with asthma.

a) Recruitment Methods

Source of potential subjects:

The study cohort will consist of a sample of 400 WTC workers with asthma enrolled in the MSH or Queens WTCHPs. We will invite participants in our prior WTC-asthma cohort (HSM#12-00422; consent included language authorizing contact for future studies) as well as recruit new study subjects.

Recruitment of potential subjects:

Potential participants with a diagnosis of asthma will be identified from the WTCHP database and our prior WTC cohort study (HSM#12-00422; consent included language authorizing contact for future studies). The research team will send out a letter from the study's PI, Dr. Wisnivesky, or an investigator who is a practicing physician at the WTCHP sites. Participants will have 1 week to respond to the letter. If the research team does not hear back from the participant after 1 week, then we will call the participant to offer participation in the study. WTC workers who agree to

participate will be contacted by a research assistant (RA) who will explain the study and schedule an in-person assessment.

b) Inclusion and Exclusion Criteria

Inclusion Criteria: Participants will be ≥18 years of age, have a diagnosis of asthma made by a health care provider, and speak English or Spanish. Exclusion Criteria: WTC workers will be excluded if they have chronic obstructive lung disease (COPD) or other chronic respiratory illness. Additionally, individuals with a history of heavy smoking (≥15 pack-years) will be excluded because of the possibility of undiagnosed COPD. Current smokers with be included in the study if their cumulative smoking history does not exceed this threshold.

c) Number of Subjects

A total of 400 patients will be enrolled over a 3-year period and followed for 1 year. At the ISMMS site, we will recruit 300 patients. At the Queens College site we will recruit 100 patients.

d) Study Timelines

The study will take place from September 1, 2016 to August 31, 2021. Participants will be followed for 12 months with in-person interviews at baseline, 1 month, 6 months and 12 months.

Table 5. Study Timeline

TASK	Yr 1		Yr 2		Yr 3		Yr 4		Yr 5	
Study Preparation										
Baseline interviews										
Follow-up interviews										
Data Analysis										
Pilot RCT										
Dissemination										

e) Study Endpoints

N/A

f) Procedures Involved in the Human Research

For the observational phase of the study, sources of data will be the interviewer-administered surveys, the WTCHP database, spirometry, airway and peripheral blood samples, the AM2 device, electronic

adherence monitors, and the electronic medical record (EMR). Interviews will be conducted in English or Spanish in person (as required for several measures) at baseline, 1, 6, and 12 months (See Table below).

Summary of Measures and Timing of Data Collection

Variables	Instrument(s) or Measure(s)	Source	Timing of Collection (Month)			
OUTCOMES			**0**	**1**	**6**	**12**
Inflammatory Markers						
Sputum Cell Differential	Sputum induction/cytospins	Sputum		✓		
Sputum Cytokines	Multiplex assays of sputum supernatant	Sputum		✓		
Systemic Cytokines	Multiplex assays	Plasma	✓	✓	✓	✓
Symptoms Perception						
Symptom Perception	AM2 electronic devices		✓		✓	✓
Self-management						
Objective Adherence	Smartinhaler, Smart disk		✓		✓	✓
Self-reported Adherence	Medication Adherence Report Scale	Horne[160]	✓		✓	✓
Other Behaviors	Inhaler technique, trigger avoidance, etc.	Van Beerendonk[190]	✓		✓	✓
Asthma Morbidity						
Airway Obstruction	Forced expiratory volume at 1 second/PEF	Spirometry/AM2	✓	✓	✓	✓
Asthma Control	Asthma Control Questionnarie	Juniper[197]	✓	✓	✓	✓
Use of Beta-$_2$ Agonists	Doser electronic devices		✓		✓	✓
Resource Utilization	Emergency Department use, Hospitalizations	EHR/self-report	✓	✓	✓	✓
Quality of Life	Asthma Quality of Life Questionnaire	Juniper[210]	✓	✓	✓	✓
PREDICTORS						
PTSD	SCID, PTSD Checklist	First[200]	✓		✓	✓
Asthma Health Beliefs	Asthma-Illness Perception Questionnaire	Weinman[211]	✓	✓	✓	✓
Asthma Medication Beliefs	Beliefs about Medications Questionnaire	Horne[130]	✓	✓	✓	✓
Anxiety Sensitivity	Anxiety Sensitivity Index 3	Taylor[209]				
Asthma History	Age of onset, intubations, asthma regimen, etc.		✓			
Medication Regimen	Chart review and self-report		✓	✓	✓	✓
Comorbidities	Charlson Index	Charlson[212]	✓			
Depression	SCID/PHQ-9	Spitzer[204]	✓		✓	✓
WTC exposures	Exposures at the WTC site, protection	WTCHP survey	✓			
Sociodemographics	Age, sex, race/ethnicity, language, health literacy	NHIS, NVS[213]	✓			

PEF: peak expiratory flow, NAS: National Asthma Study, NAEPP, EHR: electronic health record, PTSD: posttraumatic stress disorder, SCID: Structured Clinical Interview, PHQ-9: Patient Health Questionnaire, NIHS: National Health Interview Survey, NVS: New Vital Sign

Outcome Measures (Appendix A and Table 3): A. Systemic and Airway Inflammatory Markers: Peripheral Pro-inflammatory Cytokines: To measure peripheral cytokine, blood will be collected at baseline, 1-, 6, and 12-months, in the morning (8-9 AM, prior to eating) to decrease potential confounding factors of diurnal variation and diet,[7] using methods employed by members of our research team.[176] Samples will be processed with 30 minutes of collection by centrifugation and separation of plasma into aliquoted samples stored at -80°C. Plasma cytokine levels will be analyzed using a multiplex assay (Milliplex Human Th17 Magnetic Bead, Eotaxin and IL-8, Billerica, MA, USA) as in our prior studies.[177] Briefly, samples, standards, and controls will be added to the appropriate wells. The premixed magnetic beads will be added to each well and incubated on a plate shaker for 18 hours at 4°C. After washing, detection antibody will be added and incubated on a plate shaker for 1 hour, followed by Strepaviden-

Phycoerythrin for 30 minutes. The plate will be run on the Luminex 200 system (Luminex Corp., Austen, TX) and data will be analyzed using the MILLIPLEX Analyst Software (EMD Millipore Corp., Billerica, MA).

Sputum Inflammatory Markers: To limit participant burden, we will only perform sputum induction at the 1-month visit. However, we will have repeated measures of systemic cytokines, which will allow for longitudinal assessment of the association of PTSD-related inflammation and asthma control. During the baseline visit, we will collect data on ICS use and monitor adherence for 4 weeks. Using this information, we will be able to control for the potential effect of ICS and sputum inflammatory markers. Sputum will be collected on 175 participants (see power calculation) following standardized protocols.[178,179] Briefly, subjects will be pre-treated with 360 µg of albuterol followed by spirometry to ensure an FEV_1 ≥60% predicted. They will then undergo a 12-minute sputum induction with PEF monitoring for participant safety. Subjects will be excluded from sputum induction if: 1) their FEV_1 <60% predicted (for safety reasons), 2) they had a respiratory tract infection <4 weeks prior to sputum induction, or 3) an asthma exacerbation or oral corticosteroid use <4 weeks prior to sputum induction. We will weight sputum samples, add a dithiothreitol (DTT) containing Sputolysin Reagent (Calbiochem, San Diego, CA, USA; 1 ml to 1 gram of sample), and then will place samples in a 37°C shaker for 15 minutes. The sample will be washed with PBS and spun down; the supernatant will be stored at -80°C.

Sputum Cell Differential: Cytospins will be prepared and stained with Diff-Quick (Dade Diagnostics of PR, Aguada, PR) for differential cell counts. The sputum cell differential will be determined by counting ~500 white blood cells on cytospin slides, excluding samples with a cell viability <50% and >20% squamous cells.[178,180] Sputum eosinophilia will be defined as >2%;[181-183] sputum neutrophilia as ≥40%.[180] Sputum Cytokines: Sputum supernatant will be analyzed for a panel of cytokines using the multiplex assay as described above.

Asthma Symptom Perception: We will use the AM2 computerized peak flow monitor (ERT Corporation, Philadelphia, PA; Figure 2) to assess symptom perception by comparing actual and perceived PEF values for 4 weeks following the baseline, 6- and 12-months interviews.[77,109,184] Following a well validated protocol, RAs will train participants to enter the PEF estimate (step 1) and then perform the PEF effort (step 2). To help them estimate their PEF, the RA will attach a colored sticker to the AM2 showing the participant's s predicted PEF values (based on age, sex and height) that correspond to the go (green), caution (yellow), and danger (red) zones of asthma control (Figure 3).[172] After entering their estimated PEF, participants will perform 3 maximal effort blows, with 2 minute rests between each. The actual peak flow values of each blow will not appear on the device. The AM2's acoustic alarm will remind them to use it in the morning and evening.

The asthma risk grid (Figure 4) was developed to quantify symptom perception accuracy.[77,109,172,184,185] Each objective PEF is plotted against the corresponding subjective estimate of PEF to generate a percent of objective personal best. Patients' estimates are categorized in the *accurate*, *under-perception*, and *over-perception* zones, and must be at least 10% higher or lower than the actual PEF value (to ensure that estimates close to the accurate zone are not classified as inaccurate) to be considered in these zones, respectively. Each participant's symptom perception will be characterized as the percent of time they spend within each perception zone. The percentage of estimates in the over-perception one will be the main study measure. Home Peak Flow Meter (PFM) use: We will ask patients with their own PFMs not to use them while they are using the AM2. In our prior studies, <5% of participants used a PFM ≥1 time/week.

Figure 2: AM2 Peak Flow Meter

Figure 3. AM2 Sticker to Help Patients Estimate their PEF

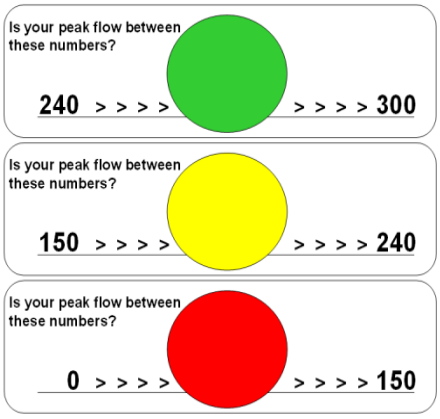
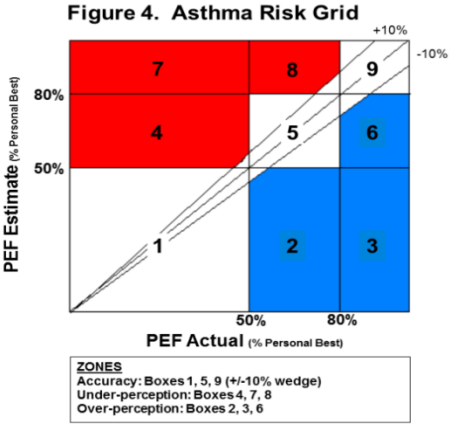


Figure 4. Asthma Risk Grid



C. Asthma SMB: will be based on NIH guidelines.[172] Asthma Controller Medication Adherence: Electronic Monitoring: We will objectively measure ICS adherence using the Smartinhalers (Nexus6, Franklin, OH) or Doser electronic device (Meditrack, MA) for metered dose inhalers and the Smartdisk (Nexus6, Franklin, OH) for dry powder inhalers for 4 weeks after each in interview. RAs will attach the monitoring device to the inhaler, and patients will return them by mail in a pre-stamped envelope (95% return rate among 317 participants in our prior studies). Adherence will be defined medication use on ≥70% of days prescribed, a commonly applied convention.[160,186] In secondary analyses, we will examine adherence as a continuous measure. Self-reported: The Medication Adherence Rating Scale (MARS) will be used to measure self-reported adherence.[160,187-189] We found the MARS to have good psychometric properties both in English and Spanish.[160] 2) Inhaler technique: We will assess inhaler technique on placebo devices using validated checklists.[190-192] 3) Action Plans: Use of action plans will be evaluated with questions from our prior research.[128,153] 4) Asthma Trigger Avoidance: We will use validated items from the National Asthma Survey[193] to document allergen exposure and actions taken to limit exposure. We will also assess tobacco smoking behaviors and second hand exposure to tobacco. 5) Routine Asthma Care: will be defined as ≥2 routine (non-urgent) annual visits for asthma.

Asthma Morbidity: Objective Measures: Spirometry: FEV_1 is a direct, reproducible, physiologic measure of asthma activity.[194] We will follow standard performance guidelines.[195,196] Electronic Peak Flow Monitoring: As described above we will collect detailed PEF data from AM2 devices for 4 weeks after each visit.

Subjective Measures: Asthma Symptoms: Asthma control will be assessed with the Asthma Control Questionnaire (ACQ).[197,198] It is available in English and Spanish and has excellent validity. Use of Beta2-agonists: Over-perception may be associated with increased use of quick relievers. Thus, we will use self-reports as well as Doser devices to objectively capture use of these medications for 4 weeks after each interview. Acute Resource Utilization: will include self-reported and electronic data on unscheduled office and ED visits and asthma-related hospitalizations. We will identify visits occurring at outside institutions by self-report and request external records. Although resource utilization can be considered a more objective measure it also is influenced by subjective perceptions concerning the need to seek help. Asthma quality of life: We will use the validated Mini Asthma Quality of Life Questionnaire (AQLQ); available in English and Spanish.[199]

Independent Variables (Table): PTSD: Structured Clinical Interview (SCID): The SCID is considered the gold-standard psychiatric interview.[200] The Bilingual version of the SCID will be used at the baseline, 6- and 12-month visits as the semi-structured psychiatric interview.[200-202] A psychology graduate student or social worker will administer the PTSD and the mood disorders modules. Dr. Katz and Gonzalez will provide supervision for all diagnostic issues. Quality Assurance: We will randomly select 10% of audiotaped recordings for Drs. Katz or Gonzalez to rate for accuracy and to provide feedback to interviewers. Patient Safety: If patients with active suicidal ideation are identified, the PIs will be notified to determine the need for an emergency psychiatric consult. Participants with PTSD will be given a list of counseling sites. Additionally, we will ask for patients' consent (signed HIPAA authorization) to alert their physicians about the SCID results after a lag of 4-6 weeks (to be able to assess the impact of PTSD on symptom perception and SMB). We will collect detailed data on medications for PTSD and/or depression by self-report and EMR review.

Other Mental Health Assessments: PTSD Checklist: PTSD symptom severity will be measured using the PTSD Checklist-Civilian Version,[203] a self-report questionnaire that assesses 17 symptoms based on diagnostic criteria for PTSD. Probable PTSD will be defined as a score ≥50 and endorsement of each of the 3 criteria required for a diagnosis of PTSD. 2) Patient Health Questionnaire (PHQ-9): The PHQ-9 has excellent validity, good sensitivity and specificity, it is sensitive to change over time, and has been used in the WTCHP.[34,204]

Illness and Medication Beliefs: Asthma Health Beliefs: We will assess asthma-related beliefs using the Brief-Illness Perceptions Questionnaire (B-IPQ).[205,206] This is an English and Spanish validated instrument that includes items for the 5 cognitive domains of the SRM. We will use items from the full IPQ assessing emotional representations of asthma. We will also include items measuring illness and medication beliefs specific about WTC-related asthma (e.g., "WTC asthma is more difficult to control") used in our WTC cohort study. Medications Beliefs: We will use the Beliefs about Medicines Questionnaire (BMQ),[129,130,207,208] an English and Spanish validated 10-item scale that measures beliefs about asthma controller medication in 2 subdomains: necessity and concerns (reliability: 0.80). Self-Efficacy: Self-efficacy regarding

asthma management and control will be assessed using items adapted from questionnaires used in our prior studies.[128,133]

Anxiety Sensitivity: We will use the Anxiety Sensitivity Index-3,[209] a validated scale to assess fear arousal-related anxiety sensations along 3 domains: somatic, social, and cognitive concerns.[209]

Covariates: Asthma History: Items about asthma history will include: age of onset and relation to 9/11, oral steroid use, history of intubation, and past ED visits and hospitalizations. We will obtain detailed information regarding onset of symptoms in relation to WTC-related exposure and whether symptoms or medication requirements worsened after WTC work among workers with preexisting asthma (WTC-exacerbated asthma).[4] Individuals with onset of asthma symptoms shortly after 9/11 exposures (no latency), will be categorized as having irritant-induced asthma. Patients with insidious onset of asthma symptoms within 1-2 years of exposure will be classified as having late onset asthma, possible irritant-induced;[4] those with asthma onset >2 years post exposure will be coded as having late onset asthma, probably not irritant-induced. At each visit, we will determine participants' asthma medications and their dosages by self-report and by querying the EMR. The concentration of total and allergen-specific (house dust mites, molds, cockroaches, cats, and mice) IgE will be used to assess sensitization to key indoor allergens in peripheral blood.[214-216] Information on home environmental exposures will be obtained from validated questionnaires.[217,218] We will also collect data on asthma symptoms in relation to current job and environmental triggers encountered in the current workplace.

Medical Comorbidities: History of physician diagnosis of sinusitis, rhinitis, GERD, and OSA will be assessed using questions from the WTCHP survey.[219] Body mass index will be assessed using height and weight data collected during spirometry. We will use Charlson's Index to assess the workers' burden of comorbidities.[212] Smoking and Alcohol Use: will be measured with items from the National Health Interview Survey (NHIS).[220]

WTC-Related Exposures: We will use data collected as part of the WTCHP to characterize WTC exposures of study participants. Variables include time of arrival, exposure to the dust cloud, work location, total duration of exposure, and type of activities performed. Exposure will be categorized in four levels based on the total time a responder spent working at the WTC site, exposure to the cloud of debris, and work on the pile of debris.[1] We will also assess for psychological stressors including shift length, exposure to body parts, and fear for personal safety. Use of respiratory protection will be assessed with data collected as part of WTCHP survey.

Demographics and Cultural Factors: Basic demographics will include age, sex, race/ethnicity, education, income, and occupation.[220] Health literacy: The Newest Vital Sign is a 3-minute assessment validated in English and Spanish.[213] Access to Care: We will obtain information on insurance status and query subjects about whether they participate in the WTCHP and have a regular doctor.

g) Specimen Banking

Data specimens will be stored in an identifiable manner using indirect identifiers. The patient study identifiers will be linked to the blood sample. The file that links the study identifiers with

the patient is stored on a secure server that is encrypted and password-protected and encrypted.

The specimens with be stored in Dr. Paula Busse's laboratory in the Icahn Medical Institute at 1425 Madison Avenue [redacted]. The specimens will be stored in -80 degree freezer and locked securely to minimize the risk of a breach of confidentiality.

These specimens will not be released to any additional requestors until a formal request has been submitted to the IRB and Dr. Wisnivesky.

h) Data Management and Confidentiality

Data Management and Security: We will use standard IRB-approved and HIPAA compliant measures to maintain patient confidentiality, privacy, and data security. Data privacy and security procedures will include: a) training staff on data sensitivity and protocols for safeguarding confidentiality; b) storing and processing samples and sensitive hardcopy in a secured, centralized location; c) securing sensitive hardcopy in locked files when not in use; d) removing names, addresses, and other direct identifiers from samples, hardcopy and computer readable data after they are not necessary for participant tracking and then using codes for subsequent identification of subjects; e) destroying all identifiable linkages to data after data accuracy has been verified and final analyses have been completed; and f) using restricted logon identification and password protection computer protocols for all computerized entry, retrieval, and analysis.

All study data will be entered on a weekly basis into a computerized database. A computerized record system will be used to help the research assistants to track the follow-up interviews. To preserve participant confidentiality, study subjects will be assigned code numbers. Using these codes, none of the collection forms will contain the names or medical record number of the participants. There will be a master list matching the names of the participants to the code numbers. The list will be secured in a locked cabinet. All data will be stored on mainframe and terminals will be password protected and maintained in locked offices.

Data Analyses: We will obtain a HIPAA waiver to use de-identified data to compare non-respondents and those lost to follow-up to study participants by age, gender and ethnicity. Descriptive Analyses: We will use the chi-square test, t-test or Wilcoxon test to compare the baseline characteristics of WTC workers with and without PTSD. Then, we will examine the distribution of dependent variables and, as appropriate, consider transformations to reduce non-normality of continuous outcomes.

Aim 1. Assess the relationship of PTSD with systemic and airway inflammation in WTC workers and evaluate the association with asthma control: We will use the chi-square or Wilcoxon test to compare the distribution of airway inflammatory cells and systemic and sputum cytokine levels from WTC workers with and without PTSD. We will use a

generalized linear model to assess the association of PTSD with sputum eosinophilia or neutrophilia (logit link), or cytokine levels (identity link) after controlling for possible confounders such as age, sex, race/ethnicity, ICS dose (calculated after adjusting for adherence), asthma onset in relation to WTC exposure, BMI, comorbidities, and depression. We will calculate the false discovery rate from the p-values to control for testing of multiple cytokines.[223] Then, we will assess the unadjusted association of plasma and sputum cytokine levels as well as the associations of airway eosinophilia, neutrophilia, and cytokines levels with measures of asthma control using correlation coefficients or Wilcoxon test. The adjusted relationship of inflammatory markers (systemic and sputum) and asthma control measures over time will be assessed using generalized estimating equation (GEE) models (logit or identity link and autoregressive correlation structure for repeated measures over time). The model will include an interaction between inflammation markers (e.g., neutrophilia, etc.) and PTSD status to assess for potential effect modification (i.e., differential effect in subjects with vs. without PTSD). Finally, we will fit a fixed effects model (i.e. limited to within subject variability) to assess the longitudinal effect of changes in systemic cytokines levels on asthma morbidity makers.

We will use structural equation modeling (SEM; see details below) to test whether systemic inflammation, leading to airway neutrophilia and high IL-6 levels, mediates the association between PTSD and increased asthma morbidity. Following the MacArthur approach[224] for assessing mediation, main effects as well as interactions between PTSD and inflammatory markers will be included as predictors of asthma morbidity.[225,226] The analyses described above will establish if PTSD has a significant effect on the mediators (i.e., inflammatory markers), which is the first step of mediation. What is then needed is to also show that these factors are also associated with asthma morbidity measures while controlling for PTSD. Building a SEM including inflammatory markers, PTSD and an interaction variable of PTSD with the potential mediators, while controlling for other confounders, will provide a formal test of mediation.

Table 3. Power Calculations for Aim 1

Outcome	Proportion/ Mean among Participants without PTSD	Δ Proportion/ Mean for Participants with PTSD	Sample Size for 80% Power
Sputum Neutrophilia	0.25	0.30	106
	0.25	0.25	149
Sputum Eosinophilia	0.50	0.25	107
	0.50	0.57	157
IL-6, pgr/ml	4 (2)	2	67

Power Calculations: Assumptions about the expected retention rate (≥80%), the prevalence of PTSD (~30%) and the distribution of inflammatory markers were derived from our preliminary data and the literature.[1,7,8] Under these assumptions, with 175 participants undergoing sputum induction, the study will be powered to test Aim 1 hypotheses (Table 3).

Aim 2. Examine the longitudinal association between PTSD and symptom perception in WTC workers with asthma: We will calculate the proportion of blows that each participant over-estimate using AM2 data. A probit transformation will be applied to normalize the proportion of over-perceived guesses; differences in the distribution of the transformed variable at each time point in participants with and without PTSD will be assessed with a t-test.[227] We will use a GEE model to assess the association between PTSD and symptom perception over time.[228] We will then fit a fixed effects model (i.e., limited to within subject variability) to assess the longitudinal effect of changes in PTSD symptoms (PCL scores) on symptom perception. We will repeat these analyses adjusting for potential confounders as described above.

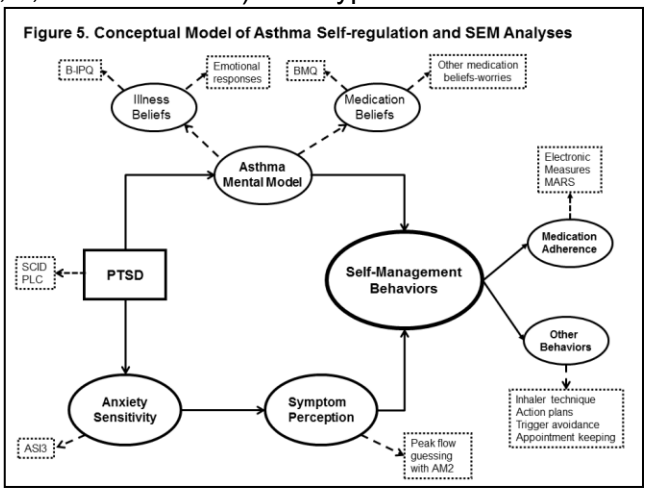
We will also assess the correlation between subjective (ACQ scores, use of beta2-agonists, AQLQ scores) and objective (FEV_1) measures of morbidity separately in asthmatics with and without PTSD and apply a Fisher's z' transformation to assess if the association varies between these groups. Then, we will fit a GEE model with ACQ scores (or use of beta2-agonists/AQLQ) as the dependent variable and as predictors, FEV_1, PTSD status, and an interaction between PTSD and FEV_1. In this model, the interaction term will test whether the association between objective and subjective measures varies according to the participant's PTSD status.

Power Calculations: We estimated rates of over-perception and asthma morbidity from our prior studies or the literature.[27,109,154,155,168,229] We adjusted the sample size for the expected correlation of measurements within a participant (interclass correlation coefficient ≥0.8).[230] These analyses showed that with 400 patients, the study will have >90% power to detect a 10% increase in the probability of over-perception in participants with PTSD. We also evaluated the power to identify whether the regression coefficients for the association between the ACQ/AQLQ scores and FEV_1 is different for patients with vs. without PTSD (equivalent to testing an interaction). These analyses showed that with 400 subjects (and 80% retention), the study will have an 82% power to detect a difference or 1 unit between the slopes of patients with and without PTSD.

Aim 3. Assess the relationship between PTSD and adherence to asthma SMB in WTC workers and identify the pathways linking them: Medication adherence analyses will be restricted to patients prescribed controller medications (>80% of the sample based on prior studies). Primary analyses will use electronic adherence measures; secondary analyses will use MARS scores and other SMB. The univariate association of adherence and PTSD will be assessed using a chi-square test. Multivariable analyses will use a GEE model (logit link function) to control for potential confounders as listed above. We will use similar approaches to assess the associations of potential mediators (over-perception of symptoms, anxiety sensitivity, and illness and medication beliefs, Figure 5) of the relationship between PTSD and medication adherence.

Latent Growth Curve Modeling (LGCM): We will employ LGCM approaches to test the mediation model presented in Figure 5.[231,232] The analysis will involve longitudinal assessment of asthma SMB across 3 time points (0, 6, and 12 months). We hypothesize that both time-varying covariates (e.g., illness and medication beliefs) and time-invariant covariates (e.g., age, sex, etc.) will predict asthma SMB assessed at these time points. We also hypothesize potential lagged effects of covariates at earlier time points. As a first step, we will identify the measurement model for the latent variables using confirmatory factor analysis. Specifically, we will create latent variables representing random effects intercepts and slopes for illness and medication beliefs (IB_{t0}, IB_{t6}, and IB_{t12}; where *t0* represents baseline illness beliefs scores), anxiety sensitivity and asthma SMB measures. Illness representations will be measured by 5 independent factors (i.e., identity, timeline, etc.), medication representations by 2 factors (i.e., necessity and concerns), and anxiety sensitivity by 3 factors. Emotional representations will be modeled as a single domain. This approach will allow us to test specific pathways. This model will also include the control variables listed above. We will estimate slope and intercept parameters using a Weighted Least Squares Mean-Variance adjusted (WLSMV) estimator, which provides robust estimates for complex models with modest sample sizes. We will test this measurement model for absolute fit using Chi-square and RMSEA statistics.[232,233]

Figure 5. Conceptual Model of Asthma Self-regulation and SEM Analyses



Next, an overall unconditional model will be fitted to identify the growth trajectory across time. To that end, we will fit a growth function for anxiety sensitivity, symptom perception, illness beliefs, and asthma SMB using linear, quadratic, and unstructured models. Relative model fit will be evaluated based on the: χ^2 index (>.05), the comparative fit index (>.97), the root mean squared error of approximation (RMSEA<.05), and the weighted root mean square residual when using WLSMV (WRMR<.90). The most parsimonious model with the best fit will be retained. Finally, we will fit the full structural model, including the hypothesized relationships. For example, PTSD will be included as a predictor of asthma SMB. To address the possible mediational effects of anxiety sensitivity, symptom perception, illness and medication beliefs on the relationship between PTSD and asthma SMB, we will fit models to estimate both direct and indirect effects, first separately, and then combined. Lagged effects of the time-varying predictors, as well as the effects of the latent growth variables themselves (intercept, slope, and their random effects) will be evaluated as potential mediators; we will also be able to assess models of complete vs. partial mediation.[128] Relative fit, as well as estimates of effect size will be calculated, along with Sobel tests and Monte Carlo CIs to evaluate the mediational hypotheses.[234]

Integrating Biological and Behavioral Pathways: Finally, we will employ LGCM to characterize the interrelation and relative contribution of biological and behavioral pathways linking PTSD and asthma morbidity (Figure 1).

Power Calculation: Power calculations for LGCM were based on published methods.[235] Effect size in this approach is defined as a null and alternative hypothesis value of the RMSEA index, which we hypothesize to be 0.05 (adequate fit) and 0.03 (good exact fit), respectively. Power in SEM can be conceptualized as a function of sample size and the number of parameters to be estimated in the model, relative to the information provided in the overall variance-covariance matrix of the observed variables. The estimated power is based on a proposed sample size of 360 (assuming that 80% of total sample will be on controller medications) with an 80% follow-up rate, yielding estimated power >0.80 for an average effect of 0.10 with an alpha of 0.05. Overall, despite the challenges of estimating *a priori* power for SEM approaches, especially those involving growth models, we believe the proposed study will be adequately powered to address this aim.

We will request a separate IRB approval prior to the intervention phase of the study that is outlined in Aim 4.

Aim 4. Develop and pilot test an integrated intervention for asthma and PTSD by adapting the 3RP, with counseling to promote asthma SMB, and education to correct over-perception of symptoms: **Overview:** Based on the results of Aim 3, we will script messages aimed to counter beliefs linked to low adherence and to support those that promote better asthma SMB; these messages will be incorporated into specific sessions of the 3RP (Appendix D). If Aim 2 shows symptom over-perception in participants with PTSD, we will also integrate strategies to train individuals to more accurately perceive symptoms by providing feedback.[87] We will conduct a proof-of-concept pilot RCT in a subset of 60 WTC workers with asthma and PTSD who have completed their 12-month study visit to test the enhanced 3RP for PTSD and asthma. We are currently seeking approval for the observational portion of the study only. We will request IRB approval for the interventional (pilot) phase at a later date, in advance of commencing the pilot.

Correcting Asthma Symptom Over-perception: As part of the intervention, participants will receive an AM2 device. Before each daily PEF measurement, they will be instructed to guess their PEF with no advantage for guessing too high vs. too low. After the maneuver, participants will be able to view, in the display of the AM2 device, their PEF values and will be instructed to compare their results with their pre-effort estimated values. Similar PEF feedback training strategies have been shown to be effective in children with asthma.[87] We will also explain to the consequences of over-perception (e.g., over-use of β-2 agonists) and links with asthma and medication beliefs, and SMB. This approach is consistent with adaptive perspective taking and cognitive restructuring, which are taught in the 3RP. In addition, we will provide psychoeducation on anxiety sensitivity (if linked to over-perception) using mindfulness skills and relaxation training, which are taught in the 3RP, and shown to be effective in patients with PTSD.[236,237]

Integrating Asthma SMB into 3RP: To guide design of the SMB support components of

the intervention, we will apply the SRM, which has been used to build coping strategies, knowledge, and skills in patients with low adherence to self-management tasks by addressing beliefs that influence SMB.[127] Illness and medication beliefs having the strongest associations with SMB will be addressed in the intervention. Cognitive restructuring and adaptive perspective taking methods will be incorporated into the 3RP sessions to address misconceptions about asthma in WTC workers with PTSD. For example, patients may feel that WTC-related asthma cannot be controlled or that arousal symptoms resulting from PTSD are specific to asthma. These views can be "reconstructed" by teaching patients about the effective management of asthma and how to differentiate PTSD and anxiety symptoms from asthma symptoms. In addition, according to the SRM, patients interpret symptoms in relation to their mental model of illness and these assessments in turn guide their SMB. Appraisal of the efficacy of their actions reinforces or modifies SMB. Thus, we will work on helping WTC workers develop accurate perceptual discrimination of symptoms arising from asthma, thereby creating a process in which they search for the appropriate signals to initiate and appraise the effects of self-management thus, generating effective self-regulatory feedback controls. We will also address avoidance behaviors – specifically, avoidance of asthma SMB because of their association with the WTC disaster (i.e., trauma-cues). Mindful awareness training included in the 3RP will focus specifically on reducing these avoidance behaviors.

Refinement of New Components: We will conduct qualitative interviews with ~10 participants who completed the 12-month interview to evaluate and refine the new 3RP components. During the audio-recorded sessions, we will share the educational messages and counselling strategies and ask participants to provide feedback.[238] Training and Fidelity: Masters-level clinicians will be trained to deliver the adapted 3RP intervention by Dr. Gonzalez. Dr. Gonzalez will provide weekly supervision and review audio-taped sessions for treatment fidelity. Pilot RCT Procedures: Dr. Gonzalez will adapt the 3RP procedural manual to incorporate new components. We will use data from the 12-month interview to identify WTC workers with asthma and PTSD for the pilot (N=60). Eligible WTC workers who agree to participate will be randomized 1:1 (using adaptive randomization to balance the number of participants in each arm with respect to age, sex and PTSD symptoms severity) to the intervention vs. an attention control group. Intervention Group: Participants randomized to the adapted 3RP condition will participate in the manualized 8-session group -based program (4-8 participants per group). They will also receive an unblinded AM2 device during the first 6 weeks of the intervention. Attention Control: Control patients will participate in an 8-session group-based program of similar time and therapist attention. The control intervention will consist of educational sessions covering general asthma knowledge (Asthma 1-2-3)[239] group-based support. They will receive blinded AM2 devices. Outcome Assessment: A telephone follow-up survey 4 weeks after the last session will be administered to assess the patient's illness and medication beliefs, anxiety sensitivity, their adherence to asthma SMB, and PTSD symptoms. Data Analysis: 1) Quantitative Assessment: Differences in illness (B-IPQ), medication beliefs (BMQ), anxiety sensitivity (ASI-3), adherence to asthma medications (MARS), and PTSD symptoms (PCL) will be assessed using a t-test

or Wilcoxon test, as appropriate. 2) Qualitative Feedback: The post-intervention interview will also include open-ended questions for: a) recollection of specific messages from the counseling, b) satisfaction and perceived usefulness, and c) ways of improving the messages and their delivery. Power: The study will have >80% power to identify a clinically meaningful differences in IPQ, BMQ, ASI, MARS, and PCL scores for 30 patients in each study arm (n=60).

i) Provisions to Monitor the Data to Ensure the Safety of subjects

Data Safety and Monitoring Plan

We have established a monitoring plan for the observational phase of the study (Aims 1-3).

Overview

A. Brief description of the purpose of the study: The goal of the proposed study is to examine the inflammatory and behavioral mechanisms underlying the association between PTSD and increased asthma morbidity among WTC rescue and recovery workers.
B. Adherence statement: The Data Safety Monitoring Plan (DSMP) outlined below for the proposed study will adhere to the protocol approved by the MSH and Queens College IRBs.
C. Data quality and management: Principal investigators will review all data collection forms on an annual basis for completeness and accuracy of the data as well as protocol compliance. A statement reflecting the results of the review will be sent to the NIOSH in the annual report.

Adverse Events

A. Adverse event grading
    1. Attribution scale: An adverse event is defined as both an expected side effect that is of a serious nature, or an unexpected side effect/event regardless of severity. All events will be graded as to their attribution (unrelated to protocol, or possibly, probably, or definitely related to protocol). Any event that is reported to either a principal investigator or their designated research associates by the subject or medical staff caring for the subject and which meets the criteria will be documented as such.
    2. Expected risks: As detailed in the consent form, the expected risks include:
        - Discomfort caused by personal questions asked in the survey.
        - Distress resulting from the questions related to PTSD or depressive symptoms.
        - Complications of the breathing test which may include dizziness or light-headedness due to deep respirations.

- Complications of blood draws which may include pain, discomfort, bruising, dizziness, and faint.
- Distress resulting from the sputum induction, which may feel like it's worsening their asthma.

These risks are considered to be minimal and are addressed in the protocol and consent form. In order to further safeguard the mental health of the study participants we will: (1) Any participant who becomes discomforted or distressed will be given the opportunity to speak with a clinical psychologist, social worker or qualified medical professional; (2) we will track the occurrence of these events and after two incident reports are filed for a participant, they will be flagged for a consultation with a counselor (clinical psychologist, social worker or qualified medical professional). Complications from the breathing test will be tracked. A clinician will be called in the event of breathing problems following spirometry, or dizziness or faint following phlebotomy. Albuterol inhaler will be given before the sputum collection to try to prevent worsening asthma, and respiratory status will be monitored throughout the procedure for signs of worsening or trouble breathing, at which point the test will be stopped and participants will be given more albuterol. A physician (PB) will oversee all sputum inductions and will therefore be present for any treatment needed. The albuterol inhaler can cause the participant to feel hand shaking, dizziness, fast heart beats, or feeling nauseous.

B. Plan for reporting both anticipated and unanticipated adverse events: All expected and unexpected serious adverse events will be reported according to protocols defined by the NIOSH. We will expedite reporting of serious adverse events to the MSH or Queens College IRBs, where applicable, when such events are unexpected (within 7 calendar days when life-threatening or fatal; within 15 calendar days for all other unexpected serious adverse events).

The research staff, including project managers and research coordinators, will be trained to identify and report all adverse events, regardless of severity, as well as problems of data security, to the PI. Weekly study conference calls will involve the PI, Queens College site PI, project manager, and research coordinators. One of the main purposes of the calls will be to ensure patient and study safety and ensure compliance with monitoring and reporting. Toward these objectives, every meeting will include: (1) a report of the number and nature of all adverse events occurring during the previous week (monitoring study safety); (2) a discussion of the adverse events and development of a plan or change in study protocol to prevent similar or related adverse events, where possible (minimizing research-associated risk); (3) initiation of the process of reporting adverse events and unanticipated problems to the IRB, if they have not yet been reported already (adverse event reporting); (4) identification of breaches of confidentiality of participant data or problems of data

security, and discussion and development of plans to prevent problems of data security (ensuring data security). The protocol will be modified as needed to ensure patient safety and data security.

Safety Review Plan and Monitoring

A. Safety reviews. During the observational study (considered low risk), a data safety monitoring board will not be employed. The PI will have overall responsibility for overseeing the safety of all study participants in this phase of the study. Locally, Dr. Wisnivesky will have primary responsibility for the safety of patients recruited at MSH. Dr. Markowitz (site PI) will have responsibility for patients recruited through the Queens site. During the pilot study (considered greater than minimal risk), a Data Safety Monitoring Board will oversee the safety of the study participants (see below).
B. Annual review. The PI will review this protocol on a continuing basis for subject safety and include results of the review in the annual progress reports submitted to the IRB and NIOSH.
C. Annual report. The annual report will include a list of adverse events.
D. Content of annual report. The annual report will address: (1) whether adverse event rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; and (3) whether all participants met entry criteria.

Data Safety and Monitoring Board (DSMB)

We will convene a DSMB to oversee participant safety for the pilot intervention proposed for Aim 4. (We will also submit a new IRB for this phase of the study.)

A. Brief description of the DSMB: The board members will meet prior to implementation of the pilot RCT of the intervention to review the study protocol and measures to ensure that adequate protections and the plan to monitor for adverse events are adequate. They will then meet every 6 months after implementation of the pilot to review data, including the following elements: recruitment rate, study withdrawal, reasons for withdrawal, adverse events, impact of intervention on beliefs and behaviors, asthma symptom perception and symptoms of PTSD.
B. Qualifications of DSMB members: The board will consist of a mental health expert, a pulmonologist, and a biostatistician. The board will not serve as co-investigators on the study. A DSMB chair will be identified and will convene the board yearly to review the study and accumulated data.
C. Role and Responsibilities of the DSMB: The DSMB is an independent group advisory to the PI and is required to provide recommendations about starting, continuing, and stopping the study. In addition, the DSMB is asked to make recommendations, as appropriate, to the PI about:
    - Efficacy of the study intervention

- Benefit/risk ratio of procedures and participant burden
- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Amendments to the study protocol and consent forms
- Participant safety
- Notification of and referral for abnormal findings

The DSMB will monitor patient safety, consider new scientific or therapeutic developments that could impact safety or trial ethics, and make recommendations to continue, terminate, or modify the trial based on interim analyses. The DSMB will specifically review: 1) hospitalization and mortality rates; 2) study disenrollment unrelated to death; 3) and any participant and healthcare provider concerns. The DSMB may recommend stopping the trial if there is clear evidence of harm or overwhelming benefit. Adverse events will include disruption of previously established regular care such that the participant's health is jeopardized or excessive burden created by the time required to participate in the study. The DSMB can recommend changes in study protocol or termination of the study if it concludes the study design causes disruptions in patient-provider continuity which jeopardized the health of the study subject or if the study imposes excessive burden on participants. Finally the DSMB, at the request of the sponsor, will review accrual and evaluate study progress towards meeting recruitment targets.

The DSMB will review safety and data information yearly. Should a temporary or permanent suspension of the study occur, in addition to the PPHS, we will report this to NIOSH.

j) Withdrawal of Subjects

Participants may choose to withdraw from the study at any time without any penalty. If participants decide to withdraw from the study, they need to contact the PI or research staff. If participants wish to withdraw their permission for use and disclosure of any of their protected health information for research, they must do so in writing to the PI at the address on the consent.

5) Risks to Subjects

The proposed study will use survey instruments and interventions that are similar to those used by us and other investigators previously. We do not anticipate any significant physical, psychological, or social risk to the study participants. Research subjects could become fatigued during the interview. To limit this risk we will provide multiple opportunities for breaks. Distress may also result from questions relating to depressive

symptoms. A clinical psychologist, social worker or qualified medical professional will be sought in PTSD or cases where participants become upset or wish to speak to someone further. The protocol to address patients with suicidal ideation is described below (see Protections Against Risks). The expected risks also include dizziness related to performing a pulmonary function test. Those who report dizziness will be promptly instructed to discontinue the test, and a qualified medical professional will be sought if symptoms persist. Subjects may experience pain, discomfort, bruising, dizziness or faint from blood draws. There is also a very small risk of infection at the needle insertion site. To reduce these risks, all blood draws will be performed by a trained phlebotomist. A physician will be called to evaluate any subject who appears faint. Additionally, participants will cough during sputum induction, which may feel like it's worsening their asthma. Albuterol inhaler will be given before the sputum collection to attenuate the risk of worsening asthma, and respiratory status will be monitored throughout the procedure for signs of worsening or trouble breathing, at which point the test will be stopped and participants will be given more albuterol. A physician (PB) will oversee all sputum inductions and will therefore be present for any treatment needed. The albuterol inhaler can cause the participant to feel hand shaking, dizziness, fast heart beats, feeling nauseous, or produce rash, and/or hives. All risks of participation will be explained to subjects and included in the written informed consent document.

We anticipate no adverse events arising from the intervention we propose to test for Aim 4, which consists of counseling to promote better asthma self-management behaviors (SMB), education to correct over-perception of asthma symptoms, and an adapted version of the Relaxation Response Resiliency Program to improve symptoms of PTSD. We will obtain physicians' consent to approach their patients, and notify them that we may randomize their patients to an intervention that involves asthma SMB and PTSD counseling. If physicians believe that it is unsafe for their patients to participate in asthma SMB and PTSD counseling, they may choose to decline patient participation.

6) Provisions for Research Related Injury

N/A

7) Potential Benefits to Subjects

Participants may enjoy the opportunity to talk about how their illness and or experiences impact their life or to simply express their opinions. Participant may also find satisfaction in contributing to a research effort intended to ultimately improve the health of WTC workers and other exposed populations. Individuals participating in the pilot study may benefit from the counseling related to asthma SMB and PTSD. They may also find satisfaction in contributing to a research effort intended to ultimately improve the health of people like them.

8) Provisions to Protect the Privacy Interests of Subjects

Confidentiality

A. Protection of subject privacy. To preserve patient confidentiality, study subjects will be assigned code numbers. Using these codes, none of the collection forms will contain the names or medical record number of the participants or other personal identifiers. There will be a master list at each institution matching the names of the participants to the code numbers. The list will be safely stored in secure network drives. Paper-based consent and HIPAA documents will be stored in locked cabinets within locked offices, separate from the master lists. All electronic data will be stored on mainframe servers, and terminals and Tablet PCs will be password protected and maintained in locked offices.

B. Database protection. Participant information will only be accessible to the PI, project manager, and research coordinators associated with the research. Data collected on Tablet personal computers (PC) will be uploaded on a daily basis to mainframe servers supported by the local institutions and encrypted using Bitlocker software. These data will lack personal identifiers other than a study identification code. Following the upload, the data on the Tablet PCs will be deleted. Encrypted data from the Queens WTCHP site will be transferred electronically to Mount Sinai, which will serve as the data coordinating center, on a weekly basis. The transferred data will be free of personal data that qualifies as PHI. All data received at the data coordinating center (Mount Sinai) will be entered into a computerized database and stored in encrypted files on a mainframe server that is backed up nightly by the Mount Sinai Hospital IT Department.

C. Confidentiality during adverse event reporting. Adverse event reports and annual summaries will not include subject-identifiable material. Each will include the coded identification number only.

9) Economic Impact on Subjects

N/A

10) Payment to Subjects

Patients will be paid up to $280 for their participation in the observational portion of the study. They will receive $50 for the baseline, six-month and twelve-month interviews after the completion of each interview. They will receive $90 for completion of the sputum test at the 1-month follow-up visit. They will receive $10 for returning the electronic monitoring devices (Peak Flow Monitor and the electronic medication monitoring device) each time they are used: after the baseline, 6-month, and 12-month interviews. The electronic monitoring devices following the baseline interview will be returned at the 1-month interview, in person. The electronic monitoring devices following the 6-month and 12-month interviews will be returned by mail using a pre-stamped envelope provided by the researchers. Subjects may also receive $10 for completing the follow-up phone call after the baseline interview.

If selected to participate in the pilot study, subjects may receive up to $160 for their participation in this pilot. Upon completing the pilot study baseline interview they will receive $70 for their time and effort. Upon completing the follow-up interview for the pilot study they will receive $20 for their time and effort. This will be given to them at the end of the study in cash unless otherwise requested. At their completion of the pilot study, they will receive $70 for your time and effort.

Research Interview	Payment
Observational Study	
Baseline Interview	$50
Follow-up Phone call after baseline	$10
1-month interview (including sputum test)	$90
Return of electronic monitoring devices (from baseline) in person	$10
6-month Interview	$50
Return of electronic monitoring devices (from 6-month interview) by mail	$10
12-month Interview	$50
Return of electronic monitoring devices (from 12-month interview) by mail	$10
Total (Observational Study)	$280
Pilot Study	
Pilot Baseline	$70
Follow-up Phone Interview	$20
End of Study	$70
Total (Pilot Study)	$160

11) Consent Process

Setting:
Consent will take place in a private room in the outpatient clinics of the Pulmonary or General Internal Medicine (IMA) Departments at Mount Sinai Hospital.

Process:
Only members of the research team who have been fully trained in the protocol will obtain the treating provider's permission to recruit potential patients.

Using the WTC STMP patient list, the PI and/or research assistant will approach the physician who provides care to the patient, and ask him/her if they agree for the PI or research assistant to call their patient over the telephone to explain them details about the study, screen them for eligibility, and offer them the oppourtunity to participate in the research study. An explanation and letter with details about the study will be given to treating phsycisians. In addition, a letter will be sent, from their primary care physician, to the patient by mail prior to calling them. In this letter, their primary care physician will give details about the studyin addition to the PI's office phone number, in case the subjects have any questions or concerns. The screening questions that would be asked over the phone are the following: 1) has any physician ever told you that you have asthma, any other lung disease; and 2) have you ever smoked cigarettes regularly. Patients who screen eligible will be offer participation in the study. If the subject agrees to participate, a date and time will be set in the IMA clinic for which a private room will be used to explain in detail the study and the consent.

Before including a patient in the study, the investigator or research assistant will verify that the given consent documents are written in the language that the subjects can understand them. Also the investigator or research assistant will verify that the subjects understand the objectives of the study, the type of information that will be collected, when and how it will be collected, and that participation in this study is voluntary. This will be done by asking the patient to describe to us what they understand the study entails and also to state the potential risks and benefits of the study.

Non-English Speaking Subjects

For subjects non- English speaking subjects who speak Spanish, the bilingual research assistant will be conducting the consent in Spanish. The bilingual research assistant will be using the approved PPHS consent form template in Spanish. The bilingual research assistant will ask the patient to describe to us what they understand the study entails and state the potential risks and benefits of the study in Spanish.

Waiver of Informed consent

The waiver of informed consent that is being requested is for a research report query from the WTC STMP database. This will allow the research staff to identify potentially eligible adults being seen in the Mount Sinai through the WTC STMP database. This will also permit the research staff to find out the time and date of the research subjects next appointment so he/she can be approached. This search is necessary, so the PI and/or RA can identify patients with asthma that are seen in the Mount Sinai Medical Center. This informed consent waiver is only for the identification of patient's with a physician diagnosis of asthma and

their scheduled appointment. This informed consent waiver is to identify patients with a diagnosis of asthma followed in the Mount Sinai Medical Center Internal Medicine or Pulmonary clinic and to know of their next appointment. This information is already known by the research subject and will not provide any additional information to him or her.

Additional information:

1. The research poses minimal risk of harm to the subjects.
2. The waiver of informed consent does not adversely affect the rights and welfare of the subjects.
3. This is a non-invasive survey-based study. Questions pertain to demographic characteristics and self-reported health behaviors only. No drugs or treatments are involved.
4. None of the findings will be directly pertinent to the individual research subjects.
5. The research is not FDA-regulated.
6. The research does not involve non-viable neonates.
7. The research is not conducted or funded by the Department of Defense (DOD).
8. The research involves no more than minimal risk to the subjects.
9. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Data/specimen banking is not contingent upon participation in the study. Each patient can choose to have 10 cc of venous blood or 20 cc of venous blood, with the additional 10 cc to keep for future research studies. There are no limits that are to be placed on the intended future use of the specimens. Participants will be provided with the option to opt out of data/specimen banking and also to store the blood samples anonymously.

12) Process to Document Consent in Writing

The team will adhere to "SOP-HRP-090 Informed Consent Process" and "SOP-HRP-091 Written Documentation of Informed Consent

Written informed consent will be obtained from each subject at entry into the study using the standard PPHS consent template. Informed consent is obtained by the following process:

- Subject review the study consent form.
- PI, site PIs or research delegates speak with the subject to review the consent, confirm subject's understanding, and answer any questions.
- Once the investigator is convinced that the subject verbally demonstrates understanding and agrees to the process, the consent is signed by the subject

and the research delegate. Individuals authorized to obtain written consent are the PI, site PIs, co-investigators, and assigned research delegates specifically designated by the principal investigators to work on this project.

13) Vulnerable Populations

Include	Exclude	Vulnerable Population Type
	X	Adults unable to consent
	X	Individuals who are not yet adults
	X	Wards of the State
	X	Pregnant Women
	X	Prisoners
X		economically or educationally disadvantaged persons
	X	Individuals with diminished mental capacity

14) Multi-Site Human Research (Coordinating Center)

Dr. Wisnivesky will be responsible for overseeing data collection activities and quality of data collected. For the observational cohort study (Aims 1-3), we selected validated tools and electronic measures that are known to be highly valid and reliable. Data will be collected using electronic forms with built in logic patterns to minimize data entry errors. Dr. Wisnivesky will train research assistants in survey administration techniques and appropriate maneuvers for assessing lung function; Drs. Katz and Gonzalez will train social workers or psychology graduate students in administration of the psychiatric interviews. We will randomly select 10% of audiotaped recordings of psychiatric interviews for Dr. Katz or Gonzalez to rate for accuracy and to provide feedback to the graduate students. We will also conduct random checks of 10% of all collected data to assess for data entry errors, ranges of input values, missing data, and overall data quality. Similar methods will be used to monitor data collected as part of the pilot RCT (Aim 4). Study team members will

meet monthly to review progress in recruitment goals, review preliminary results, and identify and resolve emerging problems.

15) Community-Based Participatory Research

N/A

16) Sharing of Results with Subjects

Results will not be communicated with study participants as part of the study is not to influence decision making.

17) External IRB Review History

N/A

18) Control of Drugs, Biologics, or Devices

Note: The IDS has its own forms that must be completed and a review process that must be followed before the IDS representative will sign off on Appendix B for submission to the PPHS.