Study Protocol

Obstructive Sleep Apnea in WTC responders: Role of nasal Pathology

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Title of Project: **Obstructive Sleep Apnea in WTC responders: Role of nasal Pathology**

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1. Purpose/Specific Aims

Following the World Trade Center (WTC) disaster, responders who worked in rescue, recovery and debris removal were initially exposed to greater than 100,000 µm/m^3 total particles[1]. 63% of these responders examined in 2004 reported at least one new or worsened upper airway respiratory symptom since 911, and in June 2007, 50% of responders continued to have symptoms of chronic rhino-sinusitis or upper airway disease (UAD). In addition, about 50% of those with UAD referred to our sleep center reported new onset snoring on their questionnaires immediately following their exposure and had unusually high prevalence of obstructive sleep apnea (OSA)[2]. Usual risk factors for OSA include a high body mass index (BMI) and increasing severity of OSA as determined by the apnea+hypopnea index (AHI) correlates with increasing BMI. Unique to the WTC population was the fact that there was no correlation between AHI and BMI and those with new onset snoring had a lower BMI compared to habitual snorers. This suggests that mechanisms other than obesity may be important in the pathogenesis of OSA in these subjects and given their chronic nasal symptoms, provides a unique opportunity to examine the relationship between nasal pathology and OSA. Our hypothesis is that the nasal symptoms reported by the subjects in the WTC medical monitoring and treatment program (WTCMMTP) now termed WTC Health Program (WTCHP) are an indicator of increased nasal resistance due to nasal inflammation resulting from exposure to the WTC dust. In particular reversible nasal resistance may play an important role. Alternatively inflammation of the posterior pharynx without influencing nasal resistance may predispose to OSA in this population. Continuous Positive Airway Pressure (CPAP) is the standard therapy for OSA but despite its efficacy has poor adherence. Subjects with high nasal resistance may experience additional pressure during expiration at the upper airway due to high nasal resistance. This may result in greater difficulty in tolerating this therapy than those who do not have high nasal resistance. Reduction of excess expiratory positive pressure by the modality known as Cflex™ during CPAP therapy ($CPAP_{Flex}$) has been suggested to improve comfort without compromising CPAP efficacy.

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SA3. Relate nasal resistance to CPAP adherence in patients with OSA and show that reduction of expiratory pressure using $CPAP_{Flex}$ will improve CPAP adherence. Patients with OSA will be randomized in a double blind cross over design to receive CPAP or $CPAP_{Flex}$ and adherence will be measured.
In patients with OSA, we will test:
Hypothesis 3a: Increased nasal resistance is associated with decreased adherence to CPAP.
Hypothesis 3b: Use of $CPAP_{Flex}$ will improve adherence with CPAP in subjects with high nasal resistance, but not in those with low nasal resistance.
Hypothesis 3c: The benefit of $CPAP_{Flex}$ on adherence will be greatest if it is offered at CPAP initiation rather than as a "rescue" therapy in subjects with high nasal resistance.

2. Background and Significance

From September 11, 2001 onward following the World Trade Center (WTC) disaster, an estimated 40,000 individuals were exposed to significant amounts of dust while working in rescue, recovery and debris removal[3]. These workers included traditional first responders, such as firefighters and police, and a diverse population of construction, utility, and public sector workers. A medical screening program was developed to evaluate the health status of workers and volunteers who spent time at the WTC site and thus sustained exposure in the aftermath of September 11th. Standardized questionnaires were adapted for use in this unique population. These questionnaires underpin our exploration of the relationship between the new symptoms following the exposure and the presence of diseases such as OSA. The WTC Worker and Volunteer Medical Screening Program (MSP) and the follow up World Trade Center Medical Monitoring and Treatment program (WTCMMP) now called the World trade Center Health program (WTCHP) have successfully recruited more than 27,000 responders to assess and treat health effects from these exposures[4]. About 1700 of these responders are followed at the Environmental and Occupational Health Sciences Institute (EOHSI) of Rutgers Biomedical Health Sciences in Piscataway, New Jersey, about 2100 in the NYU School of Medicine Clinical Center of Excellence (NYUSOM CCE) at Bellevue Hospital in New York City and about 22,000 are followed at Mt. Sinai School of Medicine (MSSM CCE).

The collapse of the WTC towers resulted in a massive plume of building debris and particulates. Sources of associated pollutants varied over the months after the disaster,[1,5] but included combustion products, evaporating gases, gaseous fine and supercoarse particles[1]. These were from dust, rubble and debris from breakdown of WTC buildings, gases, dust, soot and smoke formed as a result of fires at the WTC site and motor vehicle emissions from vehicles at the WTC site. The dust was highly alkaline and corrosive, capable of causing chemical irritation to the upper respiratory tract.[6] It contained high levels of calcium sulfate (gypsum) and calcium carbonate (calcite)[7]known causes of irritation to mucus membranes (eyes, nose throat and large airways) as well as cough and sneezing and are likely to be among the major irritants of WTC dust.

OSA is a chronic condition with recurrent episodes of partial or complete upper airway collapse during sleep. The main risk factors for OSA are obesity and male gender and it is highly prevalent in the general population, with estimates ranging from 5-10% to >25%[18,19]. Upper airway inflammation resulting in mucosal congestion could mimic these predisposing conditions and provide an alternate mechanism for development of compromised upper airway patency during sleep.

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The health benefits of diagnosis and treatment of OSA are well recognized: untreated OSA is associated with daytime sleepiness, increase in motor vehicle accidents, increased hypertension, stroke, impaired glucose metabolism, and increase in all-cause mortality[30,33]. CPAP is the primary treatment for OSA.[34] CPAP use normalizes sleep architecture, reduces daytime sleepiness, and reduces automobile accidents and decreases blood hypertension and cardiovascular events[35-38]. Despite its efficacy, 29-83% of patients are non-adherent to CPAP[39] and no specific factors (demographic, disease specific) that predict CPAP adherence have been identified. In addition to problems with the mask and claustrophobia, pressure intolerance and "difficulty exhaling" are frequently cited by patients as limiting acceptance of CPAP therapy[39]. Nasal symptoms and side effects are also common and may account for 30-50% of cases of CPAP intolerance[40]. Thus, in addition to its role in causing OSA,[30] elevated nasal resistance may impact on initial acceptance of CPAP[27,41]. Small studies[40] have shown that nasal resistance was significantly higher in OSA patients who did not tolerate CPAP and reduction of nasal resistance by surgery[42]has been shown to increase CPAP use. CPAP adherence in WTC responders with UAD is unknown but in general has anecdotally been thought to be poor. High nasal resistance can play a potential role in their poor adherence.

CPAP keeps the UA open and nasal resistance becomes the primary determinant of total UA resistance. Thus, during CPAP use, high nasal resistance may continue to cause a patient to experience discomfort while exhaling despite adequate relief of OSA and could contribute to intolerance of CPAP. In preliminary data we have shown that, as expected, increased nasal resistance results in higher expiratory pressure. By decreasing this excess pressure during the expiratory cycle, $CPAP_{Flex}$ (Philips Respironics) may improve CPAP adherence. Although prospective, randomized studies have demonstrated that $CPAP_{Flex}$ is not inferior to conventional fixed CPAP, increased adherence has not been uniformly demonstrated. Some studies have shown $CPAP_{Flex}$ reduces discomfort and improves adherence,[43] but larger randomized studies[44] have shown no difference in adherence between CPAP and $CPAP_{Flex}$. However none of these studies have attempted to target therapy to patients based on elevated nasal resistance as we propose to do.**In specific aim 3 of this proposal we will relate nasal resistance to CPAP adherence in patients with OSA and show that reduction of expiratory pressure using $CPAP_{Flex}$ will improve CPAP adherence.**

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3. Research Design and Methods

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Objective Assessment of nasal pathology:
Clinical Examination: An investigator (a study physician, a research assistant, or the research coordinator) will perform a visual inspection of the inside of the nose to identify redness, swelling, polyps or polypoid swelling, crusting, mucus, and or frank pus. An oral exam will also be done to evaluate characteristics of the mouth (including tongue position, tonsillar size, and uvula size and a score will be given for each Dr. Sunderram will train all study investigators to perform the visual exams.

Rhinomanometry: The study technician will perform rhinomanometry which is a measurement of airflow through the nose. We will assess nasal resistance using the 4-phase-rhinomanometer (RhinoLab GmbH, Rendsburg, Germany) following the detailed technical, practical methodology, and referenced normative data published in the literature.[54] Briefly, during the rhinomanometry procedure, a small tube is held in place using tape over one nostril and a mask is placed on the subject's nose. The subject will be asked to take a few breaths with his/her mouth closed. The procedure will be repeated with the other nostril. Initially, the subject will be seated during measurement and measurements will be performed twice, before and 10 minutes after decongestion with 0.05% Xylometazoline solution. The procedure will be repeated while the subject is lying down. We have previously collected data using active anterior rhinomanometry (RhinoStream, Rhinometrics A/S, Lynge, Denmark) and published supine and sitting nasal resistances in subjects in patients coming to NYU sleep laboratory[55]. For the present study, we will change to the newer technology to bring it into accord with the more recent standardization recommendations.

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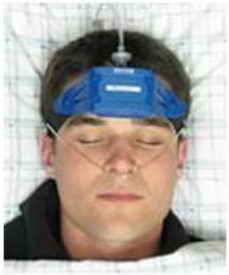
Home monitoring for OSA: Subjects will be given an ARES™ Unicorder (pictured) or a similar device (such as Embletta) and a separate wrist pulse oximeter (Nonin WristOx2 Model 3150) to take home and wear for 2 nights, with a pre-addressed mailer to return the devices to the sleep lab. The ARES Unicorder is routinely used in clinical practice for home monitoring of OSA. The ARES Unicorder is worn on the forehead and does not require additional wires to external devices. It measures oxygen saturation and pulse rate from reflectance oximetry, airflow from a nasal cannula/pressure transducer, snoring via acoustic microphone and head movement actigraphy and head position from accelerometers. The device also provides audible alerts during the study if poor quality airflow or SpO2 is detected so the subject can reposition the device. The wrist pulse oximeter



will be used to correct for the drift in oxygen saturation found in previous studies with the ARES^{TM} Unicorder.

Analysis of Respiratory Data from ARES: Data from the monitor will be autoscored and then manually reviewed by a single trained sleep technician at NYU SOM. Data from ARES will be de-identified; only the study ID will be used in monitoring. Apneas will be scored when there is a reduction in airflow to less than 10% of baseline. We have extensive experience using the ARES device and have validated it against NPSG (Noctornal Polysomnography) in over 300 subjects in multiple research studies[57,58].

SA3. Relate nasal resistance to CPAP adherence in patients with OSA and show that reduction of expiratory pressure using Cflex will improve CPAP adherence. Patients with OSA will be randomized in a double blind cross over design to receive CPAP or CPAP$_{Flex}$ and adherence will be measured as average hours of use over 2 weeks.

Protocol for SA3 1. From the ARES studies, we expect to identify ~500 subjects with OSA. We expect about 10% to refuse to even try CPAP. All others would be recruited to be randomly *assigned* to CPAP *or* CPAP$_{Flex}$ as a first treatment, and crossed over to the other after completing the first arm of the protocol.

2. Initially, the subject will be treated using the AutoCPAP program which varies the pressure, generally between 5 and 15 cm water, depending on the obstruction. If used regularly (for at least 4 hours a night for 2 nights), a fixed pressure will be automatically assigned. If the subject does not regularly use CPAP, treatment will continue using the autotitrate program. The technician will monitor CPAP treatment to ensure adequate treatment when the subject uses CPAP. The automated AHI is monitored to ensure efficacy of therapy (AHI of <10 events per hour of sleep). If the AHI is >10 events per hour of sleep the data is reviewed by a designated sleep physician and the pressure is modified or the patient is recommended for an in laboratory sleep study if indicated.
3. Adherence monitoring will be made from the CPAP machine for 1 month with first intervention, then switched to the alternate intervention and adherence monitored for another month. Data from last 2 weeks of each period will be used for objective adherence comparisons between interventions. Periods of reported non-use by the subject due to illness or travel will not be included in the treatment periods. The trial periods may be extended for up to 1 month due to instrument (CPAP machine or modem) failure. Instrument failure is not expected to exceed 10% of the users. At the end of the trial, subjects will be asked to return the modem either by mail or in person. If the subject returns the modem in person, he/she will be asked to repeat the nasal lavage sample. The subject will be informed that the purpose of this sample is to collect preliminary data. The pre-CPAP and post-CPAP samples will be compared to determine if CPAP use has any effect on markers in the lavage sample.

4. Subjective assessment of sleepiness, quality of life and satisfaction with therapy will be obtained using questionnaires administered at the start and end of each period.

Procedures for SA3

Initiation of Therapy: Within 6 months of the home monitoring identify OSA, subjects will return to the clinic for CPAP therapy and will undergo mask fitting and desensitization and CPAP education during this visit. CPAP education will follow a written protocol common to both sites. During the first two weeks of therapy, the research co-coordinator will call the patients each week to discuss any mask or CPAP related issues. If the subject experiences any problems, he/she may

return to the clinic for additional support or mask replacement. If more than 6 months elapse after the home monitoring and the subject wishes to participate in the CPAP trial, the subject will be asked to repeat the initial assessment including questionnaires, rhinomanometry, nasal lavage, and home sleep testing.

Randomization and Blinding: OSA patients will be randomly allocated to CPAP or $CPAP_{Flex}$ stratified by site and low (log[Reff]≤1.0) and high (log[Reff]>1.0) resistance by the statistician. This will be accomplished by generating an allocation table of randomly permuted blocks of assignments to study condition (CPAP vs $CPAP_{Flex}$) for each site. Outcome of the randomized choice of treatment will be provided to an unblinded individual (one at each site) who is not part of the analysis of the study data, and who will set the allocated CPAP device at the start of each treatment period. Devices will be tracked by serial number. Although subjects will be blinded to the therapy type, they may be able to perceive a difference in the mask pressure during expiration. CPAP and $CPAP_{Flex}$ machines are identical otherwise and no feedback will be provided to subjects regarding the type of treatment. The unblinded individual (not the PI) will maintain a master file containing numbered sealed envelopes containing the serial number, patient ID and designation code for each treatment period and subject. Except in an emergency situation these envelopes will not be opened until the study has been completed and all data have been entered/cleaned. The unblinded individual will document any premature unblinding that may occur. All data review relevant to adherence/titration scoring will be presented to the scorer as a flow signal alone, keeping the pressure data unvisualized so as not to reveal the presence of $CPAP_{Flex}$. The automated report will indicate if there are significant deviations from prescribed pressure.

Monitoring of CPAP Efficacy and Adherence: Efficacy will be evaluated by (i) reviewing residual AHI and inspiratory flow limitation at optimal pressure as recorded on the device and (ii) review of raw airflow signal. Nightly adherence at the optimal pressure is recorded on the device and also transmitted to the sleep center.

Cross over to alternate therapy: Four weeks after the first intervention (ie CPAP or $CPAP_{Flex}$), the device will be switched to the alternate mode by remote modem connection. The switch will take place after the subject has completed the telephone satisfaction questionnaire.

Subjective Assessment: At the end of each intervention period subjects will fill out ESS, Functional Outcomes of Sleep Questionnaire (FOSQ) and a satisfaction questionnaire.[59] At the second clinic visit (for the CPAP training and mask fitting), subjects will be given two stamped envelopes, addressed to the research coordinator. The envelopes will each contain one copy of the ESS and FOSQ. After approximately 3 weeks of the first therapy mode, the subject will be called by a member of the study team. The investigator will interview the subject to complete the satisfaction questionnaire by phone. The satisfaction questionnaire must be completed prior to the switch to the alternate treatment period. The investigator will also remind the subject to complete the ESS and FOSQ and return it by mail. This will be repeated for the second therapy mode. The satisfaction questionnaire must be completed to conclude the CPAP trial. At the end of each the end of each treatment period, a study investigator will attempt to reach the subject at least 3 times to complete the satisfaction questionnaire. If the subject cannot be contacted, a letter will be sent requesting the subject to contact the investigator. During this contact period, the treatment period will be extended. If the subject does not respond within two weeks, he/she will be considered lost to follow-up.

[redacted]

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3.1. Duration of Study

The study period is four years.

3.2 Study Sites

Environmental and Occupational Health Institute (EOHSI), Piscataway, NJ, Mt. Sinai School of Medicine, New York and NYU School of Medicine, New York. Only de-identified data will be shared between the study sites.

[redacted]

3.5.1 Inclusion Criteria

Subjects identified as new onset snoring (pre-post-9/11score of ≤2 to 3-4) or non-snorer (score of ≤2 to ≤2)

3.5.2 Exclusion Criteria

(i) Gross skeletal alterations affecting the upper airway (eg.micrognathia) (ii) Unstable chronic medical conditions known to affect OSA (CHF, stroke) (iii) Pregnancy or intent to become pregnant within the period of the protocol (v) Inability to sign informed consent form (iv) habitual snorer or diagnosis of OSA prior to 9/11/01 (pre-9/11 score of 3-4) (v) a perforated septum (vi) treatment for sleep apnea including surgery, current (within the past 2 months) use of a mandibular advancement device, or current (within the past 2 months) use of CPAP (vii) First WTCHP monitoring visit after 2/1/13 (viii) if the V1 questionnaire regarding snoring prior to September 11, 2001 is unavailable, the patient will be asked if he/she currently snores. Patients with no V1 snoring questionnaire who currently snore will be excluded.

3.5.3 Subject Recruitment

Two recruitment methods for the WTCHP responders at Rutgers Robert Wood Johnson Medical School (RWJMS) may be used for the study.

Clinic recruitment

The primary recruitment for the WTCHP responders at Rutgers RWJMS will be in-person during a clinic visit. Prior to each appointment, the WTCHP staff mail appointment packets to responders. The packets contain a letter confirming their appointment, a copy of the WTCHP consent, and approved at-home questionnaires. As part of this mailing packet, a pre-visit flyer (Pre-Visit Study Announcement) announcing the study will be included. As WTC responders return to the clinic for an annual monitoring or treatment exam, the clinic staff will check the medical chart for eligibility. A member of the clinic staff will confirm that the patient has agreed to be contacted for future studies and that the subject had not reported habitual snoring (snoring several nights a week) prior to 9/11. A study flyer will be placed in the file. If the patient appears to be eligible, a nurse or physician will inform the patient about the study, give the patient a copy of the approved flyer and ask if they are interested. If the patient is interested in participating, they will be asked to provide their name, email/street address, and phone number on a postcard so that a member of the research team can speak with him/her about the research study. A box labeled with the study name will be placed in the waiting room to collect postcards from interested patients. The box is under observation by clinic staff and will be emptied by the research staff each day. If the patient cannot be reached by phone and did provide their street address, a follow up letter will be mailed to them. The letter will ask the patient to contact the research staff if he/she is still interested in the study. If the email address was provided, an approved email will be sent asking the subject to contact the research staff.

Interested patients will also be given the option of speaking with a study investigator during the clinic visit. The study investigator (the research coordinator/assistant) will meet with him/her in a private area to inform the potential subject about the study and go through the screening script. In addition, flyers and postcards will be placed in the clinic waiting room. Information about the study will also be posted on the EOHSI website (http://eohsi.rutgers.edu/content/research-volunteers).

Mail recruitment
If the recruitment rate of WTCHP responders at Rutgers RWJMS via clinic visit is insufficient to meet recruitment goals, names of WTCHP responders at Rutgers RWJMS (the same study population) will be recruited by mail. Under WTCHP guidelines, for any mailing, names of responders at Rutgers RWJMS must be obtained from the Data Coordinating Center (DCC) for the WTCHP. Once the DCC has mailed the names to Dr. Udasin, the medical records will be checked to select responders who did not report habitual snoring prior to 9/11/01. The responders who did not snore will be sent a letter from Dr. Udasin, the principal investigator and medical director of the Rutgers RWJMS Clinical Center of the WTCHP. The letter will give the responders information about the study and let them know that they will be called by one of the study investigators. The letter will be followed by a phone call within a few weeks. This will give the responder some time to consider the study prior to being called by the study investigator.

To supplement the two recruitment methods, information about the study will be posted on the EOHSI website (http://eohsi.rutgers.edu/content/research-volunteers).

3.5.4 Consent Procedures

Clinic Recruitment: If the subject has asked to be contacted about the study (placed a contact card in the clinic box), a study investigator (research assistant, research coordinator) will call the subject and read the study screening script for clinic contacts.
Mail Recruitment: If the subject has been recruited by mailing, a member of the clinic staff will call the subject and read the study screening script for DCC contacts.

After reading the script (either for clinic contacts or DCC contacts), if the subject is interested in participating, their contact information will be recorded, a copy of the consent form will be mailed, and an appointment will be made for the first clinic visit. The subject will be called the preceding workday to confirm the appointment. The subject will be asked if he/she is experiencing seasonal allergies or had a recent cold. If yes, the appointment will be re-scheduled so that all symptoms have subsided at least 2 weeks prior to the appointment.

Clinic contacts only: If the subject is in the clinic and requests information about the study, the screening may be done in-person, in a private office. If eligible, the subject will be given a consent form to read. After reading it, the investigator will review the study and answer any questions. The consent form will be signed by the subject and the investigator. The subject will be given a copy of the signed document. An appointment will be made for the clinical visit.

If the subject wishes to think about participating, he/she will be given a copy of the consent form to take home. The investigator will record contact information and contact the subject in a few days. If the subject wishes to participate, an appointment will be made for the clinic visit. Consent will be obtained on the day of the clinic visit as outlined below.

Consent Signature
Clinic and DCC contacts: Subjects may return the signed consent form by mail. Once the consent form is received, an investigator will call the subject, answer any questions, and confirm participation. These subjects may then do the home sleep monitoring prior to their first clinic visit.

The monitor will be mailed with a signed copy of the consent form. If the clinic visit is scheduled first, on the day of the clinic visit, the consent form will be reviewed with the subject by a member of the study team. All questions will be answered. If the subject wishes to enroll, he/she will be asked to sign and date the consent form. The study investigator will also sign and date the consent form. The subject will be given a copy of the signed document.

3.5.5 Subject Costs and Compensation

After the completion of the clinic visit and the ARES home monitoring, subjects will be provided payment of $100 dollars as compensation for their time. Subjects who have been diagnosed with sleep apnea and placed on CPAP will be allowed to keep the machine after completion of the study, if desired. Subjects will have an opportunity to refuse to participate at any time during the study.

4. Study Variables

4.1 Independent Variables or Interventions

Both CPAP and $CPAP_{Flex}$ are standard treatments for sleep apnea. This study will test the efficacy of each treatment based on independent measures of nasal resistance.

4.2 Dependent Variables or Outcome Measures

[redacted]

Evaluation of sleep apnea will be based on sleep study performed in the home.

4.3 Risk of Harm

The physical risks to the study are minimal. All procedures are non-invasive and often performed in clinical settings. [redacted]Participants may experience slight discomfort from the pressure of the strap of the ARES monitor. The strap may be loosened. Additionally, in rare cases (<0.5%), participants have had a mild skin allergy to the synthetic fabric on the strap. The participants will be instructed to discontinue use of the monitor if any skin reaction is suspected. Some participants may be concerned about the diagnosis of sleep apnea. These subjects will discuss the diagnosis with the study physician and receive treatment with CPAP. Some people find CPAP uncomfortable. The subject may choose to continue or discontinue the use of CPAP. The other risk of the study is the disclosure of PHI. Every effort will be made to keep all PHI confidential.

4.4 Potential for Benefit

Patients with OSA will receive treatment. They will have an opportunity to evaluate two modes of treatment with CPAP (CPAP and $CPAP_{Flex}$) and select the most comfortable mode. Subjects diagnosed with OSA will be allowed to keep their CPAP machines following the study period, unless they specifically indicate that they do not wish to use it, in which case the devices will be returned to the sleep laboratory.

Normal subjects will not benefit directly from participation in this study. However, the data from the study will provide new knowledge about conditions common to WTC exposed individuals.

Evaluation of standard therapies in this population will help provide guidelines to physicians caring for these patients.

[redacted]

6. Data and Safety Monitoring

All procedures in the study are minimal risk. Both CPAP and CPAPFlex have equal efficacy for the treatment of OSA. The PI will monitor this study for all patient safety issues. The PIs, Dr. Sunderram along with Dr. Ayappa (MSSM), will review these data as soon as they are available on each subject. Subjects will be given an access number to call during the work day during the study. Aggregate data reviews will be conducted annually at a minimum, and presented for review by the Rutgers-RWJMS, MSSM IRB and NYU IRB.

7. Reporting Results

7.1 Individual Results

All patients will be given the results of their overnight sleep monitoring. Those diagnosed with OSA will be asked to meet with the study physician to review the results and discuss the diagnosis and treatment options. At the end of the study, those subjects who participated in the CPAP evaluation will be given a report documenting the appropriate titration for treatment and recommendations for follow-up. Subjects will also be asked if they wish to share the study results with the WTCHP clinic. If so, the subjects will be asked to sign an authorization allowing the study staff to release the records to the WTCHP clinic. No release of study information will be made without a written authorization.

7.2 Aggregate Results

Subjects will be given the option to receive a summary of the study results. Additionally, the summary results will be available on Clinical Trials.gov.

7.3 Professional Reporting

Results of the study will be published in peer-reviewed journals and may be presented at professional meetings. A description of this clinical trial will be available on ClinicalTrials.gov, as required by U.S. Law.

8. Bibliography

1. Lioy PJ, Georgopoulos P. The anatomy of the exposures that occurred around the World Trade Center site: 9/11 and beyond. *Ann N Y Acad Sci.* Sep 2006;1076:54-79.

2. Sunderram J, Udasin I, Kelly-McNeil K, et al. Unique features of obstructive sleep apnea in World Trade Center responders with aerodigestive disorders. *J Occup Environ Med.* Sep 2011;53(9):975-980.
3. Herbert R, Moline J, Skloot G, et al. The World Trade Center disaster and the health of workers: five-year assessment of a unique medical screening program. *Environ Health Perspect.* Dec 2006;114(12):1853-1858.
4. Moline JM, Herbert R, Levin S, et al. WTC medical monitoring and treatment program: comprehensive health care response in aftermath of disaster. *Mt Sinai J Med.* Mar-Apr 2008;75(2):67-75.
5. Lioy PJ, Pellizzari E, Prezant D. The World Trade Center aftermath and its effects on health: understanding and learning through human-exposure science. *Environ Sci Technol.* Nov 15 2006;40(22):6876-6885.
6. Chen LC, Thurston G. World Trade Center cough. *Lancet.* Dec 2002;360 Suppl:s37-38.
7. McGee JK, Chen LC, Cohen MD, et al. Chemical analysis of World Trade Center fine particulate matter for use in toxicologic assessment. *Environ Health Perspect.* Jun 2003;111(7):972-980.
8. Levin S, Herbert R, Skloot G, et al. Health effects of World Trade Center site workers. *Am J Ind Med.* Dec 2002;42(6):545-547.
9. Skloot G, Goldman M, Fischler D, et al. Respiratory symptoms and physiologic assessment of ironworkers at the World Trade Center disaster site. *Chest.* Apr 2004;125(4):1248-1255.
10. Herbstman JB, Frank R, Schwab M, et al. Respiratory effects of inhalation exposure among workers during the clean-up effort at the World Trade Center disaster site. *Environ Res.* Sep 2005;99(1):85-92.
11. de la Hoz RE, Shohet MR, Chasan R, et al. Occupational toxicant inhalation injury: the World Trade Center (WTC) experience. *Int Arch Occup Environ Health.* Feb 2008;81(4):479-485.
12. de la Hoz RE, Shohet MR, Wisnivesky JP, Bienenfeld LA, Afilaka AA, Herbert R. Atopy and upper and lower airway disease among former World Trade Center workers and volunteers. *J Occup Environ Med.* Sep 2009;51(9):992-995.
13. Noah TL, Zhou H, Zhang H, et al. Diesel exhaust exposure and nasal response to attenuated influenza in normal and allergic volunteers. *Am J Respir Crit Care Med.* Jan 15 2012;185(2):179-185.
14. Romieu I, Barraza-Villarreal A, Escamilla-Nunez C, et al. Dietary intake, lung function and airway inflammation in Mexico City school children exposed to air pollutants. *Respir Res.* 2009;10:122.
15. Kongerud J, Madden MC, Hazucha M, Peden D. Nasal responses in asthmatic and nonasthmatic subjects following exposure to diesel exhaust particles. *Inhal Toxicol.* Aug 2006;18(9):589-594.
16. Nikasinovic L, Just J, Sahraoui F, Seta N, Grimfeld A, Momas I. Nasal inflammation and personal exposure to fine particles PM2.5 in asthmatic children. *J Allergy Clin Immunol.* Jun 2006;117(6):1382-1388.
17. Dalton PH, Opiekun RE, Gould M, et al. Chemosensory loss: functional consequences of the world trade center disaster. *Environ Health Perspect.* Sep 2010;118(9):1251-1256.
18. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med.* Apr 29 1993;328(17):1230-1235.

19. Young T. Rationale, design and findings from the Wisconsin Sleep Cohort Study: Toward understanding the total societal burden of sleep disordered breathing. *Sleep Med Clin.* Mar 1 2009;4(1):37-46.
20. Remmers JE, deGroot WJ, Sauerland EK, Anch AM. Pathogenesis of upper airway occlusion during sleep. *J Appl Physiol.* Jun 1978;44(6):931-938.
21. Suratt PM, Turner BL, Wilhoit SC. Effect of intranasal obstruction on breathing during sleep. *Chest.* Sep 1986;90(3):324-329.
22. Ayuse T, Inazawa T, Kurata S, et al. Mouth-opening increases upper-airway collapsibility without changing resistance during midazolam sedation. *J Dent Res.* Sep 2004;83(9):718-722.
23. Tanaka Y, Honda Y. Nasal obstruction as a cause of reduced PCO2 and disordered breathing during sleep. *J Appl Physiol.* Sep 1989;67(3):970-972.
24. de la Hoz RE, Aurora RN, Landsbergis P, Bienenfeld LA, Afilaka AA, Herbert R. Snoring and obstructive sleep apnea among former World Trade Center rescue workers and volunteers. *J Occup Environ Med.* Jan 2010;52(1):29-32.
25. Webber MP, Lee R, Soo J, et al. Prevalence and incidence of high risk for obstructive sleep apnea in World Trade Center-exposed rescue/recovery workers. *Sleep Breath.* Jul 1 2010.
26. Kohler M, Bloch KE, Stradling JR. The role of the nose in the pathogenesis of obstructive sleep apnoea and snoring. *Eur Respir J.* Dec 2007;30(6):1208-1215.
27. Virkkula P, Maasilta P, Hytonen M, Salmi T, Malmberg H. Nasal obstruction and sleep-disordered breathing: the effect of supine body position on nasal measurements in snorers. *Acta Otolaryngol.* Jun 2003;123(5):648-654.
28. Morris LG, Burschtin O, Lebowitz RA, Jacobs JB, Lee KC. Nasal obstruction and sleep-disordered breathing: a study using acoustic rhinometry. *Am J Rhinol.* Jan-Feb 2005;19(1):33-39.
29. Tagaya M, Nakata S, Yasuma F, et al. Pathogenetic role of increased nasal resistance in obese patients with obstructive sleep apnea syndrome. *Am J Rhinol Allergy.* Jan-Feb 2010;24(1):51-54.
30. Young T, Finn L, Kim H. Nasal obstruction as a risk factor for sleep-disordered breathing. The University of Wisconsin Sleep and Respiratory Research Group. *J Allergy Clin Immunol.* Feb 1997;99(2):S757-762.
31. Young T, Finn L, Palta M. Chronic nasal congestion at night is a risk factor for snoring in a population-based cohort study. *Arch Intern Med.* Jun 25 2001;161(12):1514-1519.
32. McNicholas WT. The nose and OSA: variable nasal obstruction may be more important in pathophysiology than fixed obstruction. *Eur Respir J.* Jul 2008;32(1):3-8.
33. Punjabi NM, Caffo BS, Goodwin JL, et al. Sleep-disordered breathing and mortality: a prospective cohort study. *PLoS Med.* Aug 2009;6(8):e1000132.
34. Sanders MH, Montserrat JM, Farre R, Givelber RJ. Positive pressure therapy: a perspective on evidence-based outcomes and methods of application. *Proc Am Thorac Soc.* Feb 15 2008;5(2):161-172.
35. McArdle N, Douglas NJ. Effect of continuous positive airway pressure on sleep architecture in the sleep apnea-hypopnea syndrome: a randomized controlled trial. *Am J Respir Crit Care Med.* Oct 15 2001;164(8 Pt 1):1459-1463.
36. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, et al. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for

obstructive sleep apnoea: a randomised parallel trial. *Lancet.* Jan 19 2002;359(9302):204-210.
37. Patel SR, White DP, Malhotra A, Stanchina ML, Ayas NT. Continuous positive airway pressure therapy for treating sleepiness in a diverse population with obstructive sleep apnea: results of a meta-analysis. *Arch Intern Med.* Mar 10 2003;163(5):565-571.
38. George CF. Reduction in motor vehicle collisions following treatment of sleep apnoea with nasal CPAP. *Thorax.* Jul 2001;56(7):508-512.
39. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. *Proc Am Thorac Soc.* Feb 15 2008;5(2):173-178.
40. Sugiura T, Noda A, Nakata S, et al. Influence of nasal resistance on initial acceptance of continuous positive airway pressure in treatment for obstructive sleep apnea syndrome. *Respiration.* 2007;74(1):56-60.
41. Engleman HM, Wild MR. Improving CPAP use by patients with the sleep apnoea/hypopnoea syndrome (SAHS). *Sleep Med Rev.* Feb 2003;7(1):81-99.
42. Nakata S, Noda A, Yagi H, et al. Nasal resistance for determinant factor of nasal surgery in CPAP failure patients with obstructive sleep apnea syndrome. *Rhinology.* Dec 2005;43(4):296-299.
43. Aloia MS, Stanchina M, Arnedt JT, Malhotra A, Millman RP. Treatment adherence and outcomes in flexible vs standard continuous positive airway pressure therapy. *Chest.* Jun 2005;127(6):2085-2093.
44. Pepin JL, Muir JF, Gentina T, et al. Pressure reduction during exhalation in sleep apnea patients treated by continuous positive airway pressure. *Chest.* Aug 2009;136(2):490-497.
45. Sharafkhaneh A, Giray N, Richardson P, Young T, Hirshkowitz M. Association of psychiatric disorders and sleep apnea in a large cohort. *Sleep.* Nov 2005;28(11):1405-1411.
46. Webber MP, Lee R, Soo J, et al. Prevalence and incidence of high risk for obstructive sleep apnea in World Trade Center-exposed rescue/recovery workers. *Sleep & breathing = Schlaf & Atmung.* Sep 2011;15(3):283-294.
47. El-Solh AA, Ayyar L, Akinnusi M, Relia S, Akinnusi O. Positive airway pressure adherence in veterans with posttraumatic stress disorder. *Sleep.* Nov 2010;33(11):1495-1500.
48. Berry RB, Hill G, Thompson L, McLaurin V. Portable monitoring and autotitration versus polysomnography for the diagnosis and treatment of sleep apnea. *Sleep.* Oct 2008;31(10):1423-1431.
49. Kuna ST, Gurubhagavatula I, Maislin G, et al. Noninferiority of functional outcome in ambulatory management of obstructive sleep apnea. *Am J Respir Crit Care Med.* May 1 2011;183(9):1238-1244.
50. Mulgrew AT, Fox N, Ayas NT, Ryan CF. Diagnosis and initial management of obstructive sleep apnea without polysomnography: a randomized validation study. *Ann Intern Med.* Feb 6 2007;146(3):157-166.
51. Storaas T, Steinsvag SK, Florvaag E, Irgens A, Aasen TB. Occupational rhinitis: diagnostic criteria, relation to lower airway symptoms and IgE sensitization in bakery workers. *Acta Otolaryngol.* Nov 2005;125(11):1211-1217.
52. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep.* Dec 1991;14(6):540-545.
53. Quan SF, Howard BV, Iber C, et al. The Sleep Heart Health Study: design, rationale, and methods. *Sleep.* Dec 1997;20(12):1077-1085.

54. Vogt K, Jalowayski AA, Althaus W, et al. 4-Phase-Rhinomanometry (4PR)--basics and practice 2010. *Rhinol Suppl.* 2010(21):1-50.
55. Masdeu MJ, Seelall V, Patel AV, Ayappa I, Rapoport DM. Awake measures of nasal resistance and upper airway resistance on CPAP during sleep. *J Clin Sleep Med.* Feb 15 2011;7(1):31-40.
56. Laumbach RJ, Fiedler N, Gardner CR, et al. Nasal effects of a mixture of volatile organic compounds and their ozone oxidation products. *J Occup Environ Med.* Nov 2005;47(11):1182-1189.
57. Ayappa I, Norman RG, Seelall V, Rapoport DM. Validation of a self-applied unattended monitor for sleep disordered breathing. *J Clin Sleep Med.* Feb 15 2008;4(1):26-37.
58. Ayappa I, Norman RG, Suryadevara M, Rapoport DM. Comparison of limited monitoring using a nasal-cannula flow signal to full polysomnography in sleep-disordered breathing. *Sleep.* Sep 15 2004;27(6):1171-1179.
59. Kushida CA, Berry RB, Blau A, et al. Positive airway pressure initiation: a randomized controlled trial to assess the impact of therapy mode and titration process on efficacy, adherence, and outcomes. *Sleep.* Aug 2011;34(8):1083-1092.
60. Cohen J. A power primer. *Psychol Bull.* Jul 1992;112(1):155-159.
61. Rosner B. *Fundamentals of biostatistics.* 7th ed. Boston: Brooks/Cole, Cengage Learning; 2011.