# American Lung Association

# Asthma Clinical Research Centers Network

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## Effect of Positive Airway Pressure on Reducing Airway Reactivity in Patients with Asthma

## (CPAP)

**U01 HL 108730 (Holbrook, Busk)**

**Version 1.8**

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# 1. Abstract

It is now well established that failure to rhythmically apply strain to airway smooth muscle leads to change in the biomechanics of the smooth muscle characterized by shortened resting length and increased sensitivity to pharmacologic constrictors. Patients with asthma have physiologic airway characteristics that recapitulate this condition – increased airway tone and increased sensitivity to methacholine. It is our underlying hypothesis that asthma, although it may be initiated by allergic airway inflammation, is promoted by decreased tidal force fluctuations during recumbent sleep. If this is true, then treatments that increase tidal force fluctuations of airways should reverse these abnormalities. One treatment that increases tidal force fluctuations is continuous positive airway pressure (CPAP). CPAP prevents a fall in end expiratory lung volume and prevents closure of airways in dependent regions of the lung thereby permitting the stresses of tidal breathing to apply strain to airways. Preliminary data in 15 asthmatics showed that 1 week of 10cm $H_2O$ nocturnal CPAP was associated with a remarkable 2.7-fold increase in the concentration of methacholine causing a 20% fall in $FEV_1$ ($PC_{20}$). The objective of this study is to conduct a randomized, sham-controlled, multicenter study of 5 and 10 cm $H_2O$ CPAP in order to verify these findings; to assess the effect of nocturnal CPAP on airways reactivity; to determine the durability of the effect over 12 weeks; to assess the safety, tolerability and adherence to this treatment; and to explore if there are clinically meaningful benefits. The study will be conducted at 18 centers of the American Lung Association-Asthma Clinical Research Centers (ALA-ACRC) with the Data Coordinating Center (DCC) at Johns Hopkins University. A substudy of High Resolution Computed Tomography (HRCT) will also be conducted to compare the structural changes in the airways across treatment groups and to correlate structural changes with the physiological changes.

# 2. Introduction

## 2.1. Title

Effect of Positive Airway Pressure on Reducing Airway Reactivity in Patients with Asthma (CPAP)

## 2.2. Sponsors

The American Lung Association; National Institutes of Health/National Heart Lung Blood Institute U01 HL 108730 (Holbrook, Busk)

## 2.3. Investigators and study centers

Network Chair

| | |
|---|---|
| Bailey, William | University of Alabama |

Main Study Principal Investigators
Busk, Michael; Holbrook, Janet

Participating Centers

| | |
|---|---|
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| Smith, Lewis | Illinois Consortium |
| Castro, Mario | Washington University/ St. Louis University |
| Dozor, Allen | Maria Fareri Children's Hospital at Westchester Medical Center and New York Medical College |
| Irvin, Charles | Northern New England Consortium |
| Lima, John | Nemours Children's Clinic |
| Hanania, Nicola | Baylor College of Medicine |
| Sundy, John | Duke University Medical Center |
| Katial, Rohit | National Jewish Health |
| Salzman, Gary | University of Missouri, Kansas City School of Medicine |
| Cohen, Rubin | Hofstra North Shore – LIJ School of Medicine |
| Happel, Kyle | Louisiana State University Health Sciences Center, The Ernest N. Morial Asthma, Allergy and Respiratory Disease Center |
| Reibman, Joan | Columbia University – New York University Consortium |
| Mastronarde, John | Ohio State University Medical Center/ Columbus Children's Hospital |
| Wasserman, Stephen | University of California, San Diego |
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| Gerald, Lynn | University of Arizona |
| Teague, Gerald | University of Virginia |

*(Additional clinics may be added)*

Data Coordinating Center

| | |
|---|---|
| Holbrook, Janet | Johns Hopkins University |

## 2.4. Support

ResMed Ltd, a company for the development and manufacturing of medical products based in Australia, will provide CPAP devices and sham CPAP devices for the trial

## 2.5. Background and significance

Asthma is a common and morbid disease characterized by increased airway smooth muscle constriction to non-specific agonists – a characteristic that is correlated with asthma severity. Nationwide, asthma afflicts 23 million Americans, and is the most common chronic disabling illness in children. Asthma causes nearly 11 million ambulatory physician encounters and 440,000 hospitalizations annually.[1]

A characteristic of asthma is airways hyper-reactivity; an increased sensitivity to stimulants of airway constriction.[2] In the past twenty years, an accumulating body of information has shown that airways reactivity can be induced in airways in-vitro and in-vivo by prevention of intermittent stretching of the airway smooth muscle. Thus, it is a reasonable inference that some component of the airways reactivity associated with asthma is due to decreased stretching of airways, causing the airway smooth muscle to alter its contractile properties. It has been suggested that asthmatics partially defend against this effect by maintenance of elevated end-expiratory lung volume (Functional Residual Capacity (FRC)) through tonic contraction of respiratory muscles[3]. Sleep, however, abolishes this protective effect, as it is accompanied by a reduction of respiratory muscle tone, causing a reduction in FRC. One of the consequences of this is the nocturnal decrease in the ability of a deep inspiration to cause dilation of airways – a loss of airway-parenchymal interdependence.[4] Low FRC may also account in part for several of the unexplained characteristics of asthma – worsening obstruction in the early morning, increased asthma prevalence with obesity, and the failure of deep inspiration to dilate airways and reverse bronchoconstriction.

If this scenario is true, then imposing increased strain on airways with nocturnal positive airway pressure might lead to increased stretching of the airways, hence, decreased airways reactivity. Indeed, it has been demonstrated in animals that sustained mechanical strain of the airways using continuous positive airway pressure (CPAP) produced a marked decrease in airways reactivity. [5, 6] Moreover, it has also been demonstrated that CPAP only at night was sufficient to decrease airways reactivity in these animals. CPAP also decreased airways reactivity in a rabbit model of asthma with atopic airway inflammation and airway hyper-reactivity.[7]

In human studies, Chan and coworkers[8] evaluated 9 patients with obstructive sleep apnea (OSA) and mild asthma. Two-week periods of nocturnal CPAP of 8 cm $H_2O$ improved A.M. and P.M. peak expiratory flow rates before and after bronchodilators compared to no CPAP. Ciftci applied nocturnal CPAP for 2 months and noted a decrease in asthma symptoms.[9] Lafond and colleagues reported that applying nocturnal CPAP for OSA improved asthma quality of life, but did not alter airways reactivity.[10] We speculate that this may have been because the level of CPAP used to treat OSA did not adequately expand the lung in this severely obese population (mean BMI = 37).

Lin et al reported that 9 stable asthma subjects without OSA had an acute decrease in methacholine reactivity and increase in bronchodilator response during application of CPAP for 30 minutes, but did not test longer-term use[11]. In addition, preliminary data from a pilot study carried out by Tepper et al. at Indiana University in 15 asthmatics without OSA illustrated that 1 week of nocturnal CPAP caused a significant decrease in airways reactivity assessed by methacholine challenge testing, with a 2.75-fold increase in the provocative concentration ($PC_{20}$) for methacholine.

Although current therapies for asthma, such as long-acting bronchodilators and inhaled corticosteroids, are effective in prevention of symptoms for the vast majority of asthmatics[12], they are limited by high cost, poor adherence, and increasing concern about long-term adverse effects. [13, 14] Thus, there is a compelling need for new, safe and effective approaches to asthma treatment. The extensive literature on airway smooth muscle physiology, our findings in animal models of asthma, and our preliminary findings in humans, all strongly suggest that nocturnal CPAP will decrease airways reactivity in patients with asthma at least as much as conventional drug treatments. Furthermore, CPAP is widely used for the treatment of obstructive sleep apnea and has a strong track record of safety for long term home use.

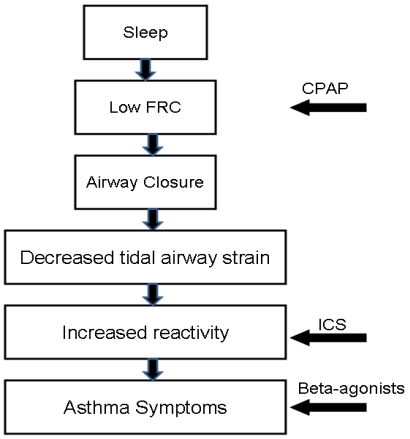



*Figure 1: Simplified model of hypothesized role of CPAP in treatment of asthma. CPAP augments nocturnal tidal stretching of airway smooth muscle which reverses intrinsic pathobiology of airway smooth muscle. ICS and beta-agonists are directed at other components of asthma – inflammation and increased airway tone.*

The objective of this phase II trial is to conduct a randomized, sham-controlled, multicenter study of 5 and 10 cm $H_2O$ CPAP in order to confirm the following; to assess the effect of nocturnal CPAP on airways reactivity; to determine the durability of the effect over 12 weeks; to assess the safety and tolerability and adherence to this treatment; and to explore if there are clinically meaningful benefits.

We also hypothesize that the combination of increased airway tone and low FRC at night leads to closure of airways in the dependent regions of the lung - leading to decreased tidal strain on airways and a change in the state of airway smooth muscle. A substudy of High Resolution Computed Tomography (HRCT) will evaluate the role of airway tone and altered airway physiology in asthma. Imaging will allow us to compare the structural changes in the airways across treatment groups and to correlate structural changes with the physiological changes. The substudy is described in more details in Section 8.

If this trial demonstrates that sustained mechanical strain can reverse one of the fundamental defects in asthmatic airway smooth muscle, it will provide the conceptual basis for an entirely novel approach to the treatment of asthma - one that does not rely on pharmacologic modulation of inflammation or bronchoconstriction. This would be a major breakthrough and potentially refocus the treatment of asthma from treatment of inflammation and bronchoconstriction to one that addresses innate abnormalities of airway smooth muscle.

***The goals of this trial are to:***

- Evaluate whether chronic nocturnal CPAP decreases airways reactivity to methacholine in patients with asthma
- Determine whether there is a dose response effect by evaluating 2 levels of CPAP (10 cm $H_2O$, 5 cm $H_2O$) and Sham (less than 1 cm $H_2O$)
- Assess the impact of CPAP on asthma control and symptoms
- Determine adherence, safety, and tolerability of CPAP
- Conduct a mechanistic substudy to determine whether chronic nocturnal CPAP alters airway-parenchymal interdependence and maximal airway caliber.

***Rationale for levels of CPAP***

In animal studies, CPAP of 6 cm $H_2O$ pressure placed the animals at an end-expiratory lung volume above the tidal volume range and near mid lung volume. As the chest wall of humans is stiffer than rabbits, our preliminary data used CPAP of 8 to 10 cm $H_2O$, which is typical of pressures safely used to treat obstructive sleep apnea. This level of CPAP will place end-expiratory lung volume in the mid-lung volume range. In our preliminary studies, this level of CPAP caused a significant reduction in airways reactivity. However, we do not know whether lower levels will be similarly effective. Therefore we will evaluate whether a pressure of 5 cm $H_2O$ will produce a decrease in airways reactivity and whether there is a critical threshold or a dose-response relationship.

***Rationale for a Phase II study***

We will consider our proof of principle established if we can demonstrate a sustained (12 week) decrease in airways reactivity with CPAP treatment. It successful, this trial will inform the design of future phase III trials in selection of patients, relevant outcome measures, and power calculations. Adherence, safety and tolerability of CPAP will also be key outcomes to guide further development of this treatment approach.

***Rationale for duration of treatment***

Preliminary data show that 5-7 days of treatment with 8-10 cm $H_2O$ of CPAP had a beneficial effect on airways reactivity to methacholine. A major goal of this trial is to determine whether this treatment effect is sustained or perhaps even progresses over time. Twelve weeks is a reasonable and feasible period of time to answer this question for the proposed proof of principle study. Interim measurements will be made at 6 weeks to determine whether there are time-dependent changes in treatment effect.

# 3. Study design

The study is a 16-week multi-center, 3-parallel arm, randomized, sham-controlled trial to assess the effect of positive airway pressure on reducing airways reactivity in patients with asthma. Participants are randomly assigned in equal allocation to one of three treatments: CPAP 10 cm $H_2O$ vs. CPAP 5 cm $H_2O$ vs. CPAP Sham (less than 1 cm $H_2O$). The treatment period is 12 weeks with airways reactivity assessed at baseline, 6 and 12 weeks of treatment and after a 2 week washout.

## 3.1. Hypothesis

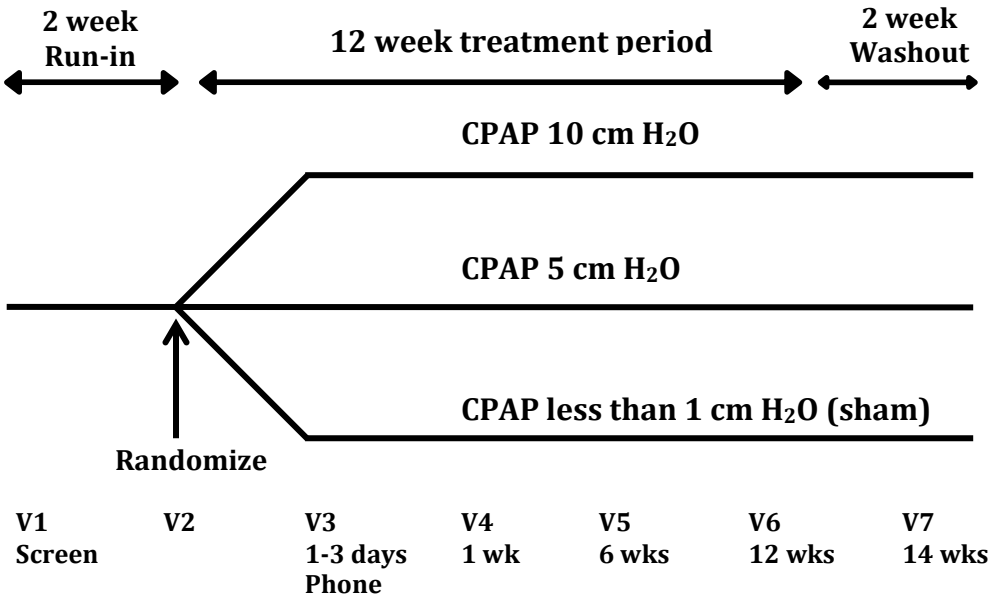
To conduct a multi-center, randomized, 3-parallel arm, sham–controlled phase II clinical trial in 200 participants with asthma to test:

***Primary hypothesis***
Twelve weeks of treatment with nocturnal CPAP will decrease airways reactivity to methacholine.

***Secondary hypotheses***
Nocturnal CPAP will improve asthma symptoms and will be well-tolerated.

***Exploratory questions***
- Is there an optimal level of CPAP in terms of efficacy vs. tolerability?
- Is there a subgroup of patients most likely to benefit (e.g. obese, non-atopic, low inflammatory burden, most adherent)?

## 3.2. Trial schema




## 3.3. Treatment groups

Eligible participants will be randomized to receive one of three parallel treatments:

- Nocturnal CPAP 10 cm $H_2O$, or
- Nocturnal CPAP 5 cm $H_2O$, or
- Nocturnal Sham CPAP (less than 1 cm of $H_2O$)

CPAP will be administered using the ResMed S9 CPAP machines with a heated humidifier. These are state-of-the-art machines that are highly portable, with quiet blowers, and electronic adjustment and monitoring of CPAP levels. SD Data cards record up to 365 days of adherence data acquired by monitoring respiratory fluctuations in pressure. CPAP levels will be pre-adjusted. Sham CPAP devices have modified masks that maintain a pressure at the mask of less than 1cm $H_2O$ while maintaining a sensation of flow across the face and retaining the capacity to measure respiratory flow variations as an indicator of active use.

## 3.4. Eligibility criteria

The planned sample size is 200 participants (67 per group) with stable asthma and airways reactivity and who do not have sleep disorders or other medical conditions that might interfere with participation or the interpretation of the study results. The aim is to include participants who have stable disease but with a range of severity and age, which will allow us to investigate the generalizability of the findings, and whether some subgroups are likely to benefit more. For blinding purposes, members from the same household cannot participate in the study at the same time.

### 3.4.1. Inclusion criteria

- 15 – 60 years of age at V1
- Physician diagnosis of asthma and on prescribed asthma medication for at least the past 12 months at V1
- Pre-bronchodilator $FEV_1$ greater than or equal to 75% predicted at V1 (to minimize the likelihood that variability in $FEV_1$ will preclude participants from having methacholine challenges in follow-up visits)
- Airways reactivity: Methacholine bronchial challenge with $PC_{20}$ less than or equal 8 mg/mL for $FEV_1$ at V1
- Stable asthma defined by no change in treatment, ED visit, hospitalization, or urgent health care visit for asthma for the 8 weeks prior to screening
- Non-smoker for more than 6 months and less than or equal to 10 pack-year history of smoking
- Ability and willingness to provide informed consent
- If receiving immunotherapy, must have had stable therapy for the 8 weeks prior to screening
- Spend a minimum of six hours per night in bed on average
- Willingness to sleep 5 days a week on average in the same place for the next 4 months.
- For women of child bearing potential; not pregnant, not lactating and agree to practice and adequate birth control method (abstinence, combination barrier and spermicide, or hormonal) for the duration of the study

### 3.4.2. Exclusion criteria

- Weight less than or equal to 66 lbs. (30kg) at V1
- BMI greater than or equal to 35 at V1
- Acute respiratory illness in the month prior to screening
- Systemic corticosteroid therapy during the 3 months preceding screening
- History of sleep apnea by self-report
- High risk of sleep apnea as assessed by Multivariable Apnea Prediction (MAP) Index[15]; high risk defined as probability that is equal to or greater than 20%
- Chronic diseases (other than asthma) that in the opinion of the investigator would interfere with participation in the trial or put the participant at risk by participation, e.g. non-skin cancer, chronic diseases of the lung (other than asthma), chronic heart diseases, endocrine diseases, liver, kidney or nervous system diseases, or immunodeficiency, any pre-existing conditions that may be contraindications to positive airway pressure including: severe bullous lung disease, pneumothorax, pathologically low blood pressure, dehydration, cerebrospinal fluid leak, recent cranial surgery, trauma, bypassed upper (supraglottic) airway
- Known sleep disorders that are currently under treatment by a sleep specialist
- Known intolerance to methacholine
- Absolute contraindications to methacholine that include: current use of beta-adrenergic blocking agent, heart attack or stroke in the last 3 months, uncontrolled hypertension, known aortic aneurysm
- Use of investigative drugs or intervention trials in the 30 days prior to screening or during the duration of the study
- Prior use of CPAP for any reason
- Homelessness, lack of telephone access, or intention to move within the next 4 months of the trial.

## 3.5. Data collection schedule

| Visits | V1 | V2 | V3 | V4 | V5 | V6 | V7 |
|---|---|---|---|---|---|---|---|
| **Target (weeks)** | **-2** | **0** | **1 day** | **1** | **6** | **12** | **14** |
| **Type of visit** | **CL** | **CL** | **PH** | **CL** | **CL** | **CL** | **CL** |
| Consent, eligibility evaluation | ● | | | | | | |
| Baseline asthma medical history | ● | | | | | | |
| Interval asthma / Health history | | ● | | ● | ● | ● | ● |
| Pregnancy testing (if indicated) | ● | | | | ● | ● | ● |
| Spirometry (pre-BD) | ● | | | | ● | ● | ● |
| Methacholine challenge | ● | | | | ● | ● | ● |
| Asthma Control (ACT, ASUI) | | ● | | | ● | ● | ● |
| Asthma Quality of Life Measure (Marks AQLQ ) | | ● | | | ● | ● | ● |
| MAP Questionnaire, Berlin Sleep Questionnaire | ● | | | | | | |
| Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index | ● | | | | ● | ● | ● |
| Sino Nasal Questionnaire (6 week) | | ● | | | ● | ● | ● |
| Quality of Life Questionnaires (WQ) | | ● | | | | ● | |
| Exit interview | | | | | | ● | ● |
| Physical examination | | ● | | | | | |
| Randomization | | ● | | | | | |
| Blood for DNA / serum storage | | ● | | | | | |
| Blood for Inflammatory Profile | | ● | | | | ● | ● |
| Exhaled nitric oxide (eNO) | | ● | | | | ● | ● |
| Collect CPAP SD cards | | | | ● | ● | ● | |
| Adverse event screen | | ● | ● | ● | ● | ● | ● |
| Return asthma diary cards | | ● | | ● | ● | ● | ● |

(V#) Visit Number
(CL) Clinic Visit
(PH) Phone Visit
(pre-BD) pre-Bronchodilator
A minimum of one week is required between visits after V4

(ACT) Asthma Control Test
(ASUI) Asthma Symptom Utility Index
(Marks AQLQ) Marks Asthma Quality of Life Questionnaire
(MAP) Multivariable Apnea Prediction

## 3.6. Study visit procedures

V1 Screening visit (weeks -2 to 0) (4 hours)

- Explanation of study
- Obtain informed consent (and assent when appropriate)
- Baseline eligibility forms
- Baseline asthma medical history
- Sleep questionnaires (MAP, Berlin, Epworth, Pittsburgh)
- Pregnancy test for persons of child-bearing potential
- Methacholine challenge testing (may require separate visit)
- Asthma action plan based on baseline peak flow rate (PEFR)
- Distribution of asthma education materials
- Distribution of baseline diary cards and portable peak flow meter
- Fitting sample CPAP masks
- Establish study visit schedule

V2 Randomization visit (week 0) (3-4 hours)

- Verification of consent
- Explanation of study expectations
- Review diary cards
- Review eligibility criteria
- Interval medical history
- Brief physical examination
- Randomization
- Fitting of the CPAP mask
- Instructions on CPAP and provide CPAP equipment
- Asthma control – ACT, ASUI and Marks AQLQ
- Sino Nasal Questionnaire-6 week
- Blood collection (up to 30 ml) for inflammatory markers and DNA/serum storage
- Exhaled nitric oxide (eNO)
- Adherence counseling
- Adverse event screen

V3 Phone follow up (day 1) (15 minutes)

- Assess for issues related to use of CPAP and adherence
- Schedule additional clinic visits for refitting mask if necessary
- Reinforce daily diary completion and PEFR monitoring
- Adverse event screen
- Confirm first follow-up visit date

V4 Interval visit (week 1) (1-2 hours)

- Return, review asthma diary cards
- Adherence counseling, resolve problems with using CPAP device
- Adverse event screen
- Interval asthma/health history
- Collect CPAP cards

V5 Interval visit (week 6) (2-3 hours)

- Return, review asthma diary cards
- Adherence counseling, resolve problems with using CPAP device
- Adverse event screen
- Interval asthma/health history
- Asthma control – ACT, ASUI and Marks AQLQ
- Sleep questionnaires (Epworth, Pittsburgh)
- Sino Nasal Questionnaire- 6 week
- Pregnancy test for persons of child-bearing potential
- Methacholine challenge testing
- Collect CPAP cards

V6 Final treatment visit (week 12) (3-4 hours)

- Return CPAP device
- Return, review asthma diary cards
- Adverse event screen
- Interval asthma/health history
- Asthma control– ACT, ASUI and Marks AQLQ
- Sleep questionnaires (Epworth, Pittsburgh)
- Sino Nasal Questionnaire- 6 week
- Blood collection (up to 20 ml) for inflammatory markers
- Exhaled nitric oxide (eNO)
- Pregnancy test for persons of child-bearing potential
- Methacholine challenge testing
- Collect CPAP cards
- Exit interview

V7 Washout visit (14 weeks) (3-4 hours)

- Return, review asthma diary cards
- Adverse event screen
- Interval asthma/health history
- Asthma control – ACT, ASUI and Marks AQLQ
- Sleep questionnaires (Epworth, Pittsburgh)
- Sino Nasal Questionnaire- 6 week
- Blood collection (up to 20 ml) for inflammatory markers
- Exhaled nitric oxide (eNO)
- Pregnancy test for persons of child-bearing potential
- Methacholine challenge testing
- Exit interview

## 3.7. Outcomes

### 3.7.1. Primary outcomes

Methacholine reactivity- Change in $PC_{20}$
Airways reactivity will be measured with methacholine challenge testing, following modified ATS guidelines using the dosimeter technique[16]. Methacholine reactivity will be measured at baseline, 6, 12, and 14 weeks.

### 3.7.2. Secondary outcomes

- Change in Asthma Symptom Score as measured by the Asthma Control Test (ACT). ACT will be administered at baseline, 6, 12, and 14 weeks. This instrument, which has been validated for ages 12-84 years, and is a 4-week recall questionnaire that measures issues of asthma control, symptoms, use of rescue inhalers, activity limitation, and nocturnal awakenings[17]
- Change in $FEV_1$ as measured by pre-diluent spirometry before each methacholine challenge test
- Changes in nocturnal asthma awakenings, and asthma symptom free days as recorded daily on the participant's diary card
- Rates of episodes of poor asthma control (EPAC) as determined by data collected on the diary cards and data collected during visits. EPAC is defined as:
    - Decrease of morning peak expiratory flow (PEFR) by more than 30% (from baseline personal best) for 2 consecutive days (definite yellow zone event), OR
    - Addition of oral corticosteroid (prednisone or prednisolone) to treat asthma symptoms, OR
    - Unscheduled contact with a health care provider (ED visit, physician office, hospital) for asthma symptoms, OR
    - Increased use of rescue medication(s) from baseline (i.e., either 4 or more additional puffs of bronchodilator or 2 or more additional nebulizer treatments in one day)
- The Asthma Symptom Utility Index (ASUI) will be administered at baseline, 6, 12, and 14 weeks. It is a 2-week utility-weighted asthma symptom questionnaire.[18]
- Change in asthma-specific quality of life as measured by the Marks Asthma Quality of Life Questionnaire (Marks AQLQ). Marks AQLQ is validated for 18 years and older.[19]
- Side effects/adverse events will be assessed by responses to open-ended questions, as well as responses to questionnaires at each visit and rated in severity. Targeted symptoms, e.g. nasal dryness and tolerability will be asked directly. Serious adverse events will be reported at any time an investigator is aware of them.
- Change in sleep quality will be measured using sleep questionnaires: Epworth Sleepiness Scale[20,21] and Pittsburgh Sleep Quality Index[22]. These questionnaires assess the effect of nocturnal CPAP on sleep quality, which can be affected by asthma[23]. Multivariable Apnea Prediction (MAP) Questionnaire[24] will be used to exclude baseline sleep apnea. The Berlin Sleep Questionnaire [25 26 27] will be used as an external measure of the MAP.
- Change in inflammatory markers will be measured at baseline, 12 and 14 weeks to test whether treatment effects might be mediated by anti-inflammatory actions of CPAP such as occur with abrogation of nocturnal hypoxemia or inhalation of humidified filtered air.[28, 29]

- Sino Nasal Questionnaire – 6 Week score will be measured at baseline, 6, 12, and 14 weeks to assess sinus symptoms over the last 6 weeks, since participants will be using nasal masks.
- Adherence of CPAP use will be assessed using an SD card that records usage of the device for up to 365 days. SD cards will be collected at weeks 1, 6, and 12. Adherence will also be assessed from daily diary cards.

### 3.7.3. Other data

- Baseline questionnaires are administered to ascertain demographics, general information and health (including race, gender, SES, and asthma history), as well as information about asthma symptoms and medication use. These data along with clinical measures such as height and weight will be used to characterize the population and allow for analysis of subgroups.
- Genotyping will be performed on blood collected at V2. DNA will be isolated for the purposes of evaluating the genetic basis of asthma phenotyping and of determining associations between genomic variants and CPAP and sham interventions. Dr. John Lima, PI of the ACRC Nemours Children's clinic, Jacksonville FL and Director of the Center for Pharmacogenomics and Translational Research will direct the genotyping assessments
- Interval health history is recorded at each clinic visit. With participant permission, records of all hospitalizations and, if necessary, deaths are obtained for verification of diagnoses and assessment of safety issues.
- Exit interviews are administered at the two last visits to determine global assessments of treatment, adequacy of informed consent procedures, satisfaction with study procedures and personnel, and effectiveness of the blinding procedures.

# 4. Study treatment

## 4.1. Description of study device and treatment

CPAP devices and masks that are being used in this study have received 510(k) clearance for commercial use by ResMed. These include ResMed S9 Elite™ and ResMed S9 Escape™ CPAP devices, and ResMed Swift™ FX, and ResMed Mirage™ FX Masks. The CPAP devices themselves are identical to the FDA 510(k) cleared commercial devices with the exception that the CPAP level is adjusted to a pre-set fixed level. For the purposes of blinding, the manufacturer will remove the model names (Escape/Elite) from the units, so that both units will look identical. Displays that give information on the level of CPAP are masked by the manufacturer. Access to the device screen for adjustment of settings requires additional steps, and care will be taken to prevent accidental access.

Each device will have a device identification number that is linked to the factory-set level of CPAP. When a participant is assigned a treatment arm, the appropriate device and mask will be distributed to the participant at the randomization visit. The active machines and masks are identical to the commercial product. The sham CPAP devices will be set to deliver less than 1cm $H_2O$ pressure by using a modified mask that allows for more leak than the unmodified mask. Factory calibration will be done to insure that all delivered CPAP devices are within tolerance (+ or - 1cm). Thus the sham device will have a similar flow rate and noise level to that of the non-sham devices. All machines will be set to have a ramp up

time of 15 minutes. This feature allows the pressure to increase slowly and less noticeably (typically as the person falls asleep).
Details about device instructions for use and mask fitting will be provided to study staff in a Manual of Procedures. Dr. Alan Schwartz, who is an expert in sleep medicine with more than 20 years of experience with prescribing and troubleshooting CPAP, will serve as the medical expert overseeing the application of these devices and training the research personnel in the fitting of masks and deployment of the systems.

The CPAP devices can monitor the number of hours that CPAP is actually being used by measuring respiratory pressure fluctuations. Daily use statistics can be stored for up to 365 days on a single SD card that is collected at 1, 6 and 12 weeks of treatment. This will be used in counseling participants to adhere to the study treatment.

## 4.2. Risks and side effects of study treatment

The ResMed CPAP devices being used in this research are FDA 510(k) cleared medical devices that pose minimal risk and are widely used in the community for treatment of obstructive sleep apnea (OSA). CPAP side effects and adverse events have been reported to be minor and reversible according to the practice parameters for the use of CPAP by the American Academy of Sleep Medicine Report [30].

The levels of CPAP used in this trial are well below the maximum recommended level of 20 cm $H_2O$ for treatment of OSA [31].Theoretical risks of CPAP include barotrauma to the lung and reduction in systemic venous return. However, these serious risks have not been reported in the OSA population in the past 30 years[32] nor have they been observed when CPAP has been applied to reduce work of breathing in acute asthma attacks[33]. A common, bothersome side-effect is that the mask fits uncomfortably and impairs the user's ability to sleep. This is overcome by attention to fitting of the mask and having available range of sizes and styles for the patient to test. Coordinators are also trained for proper mask fitting. Another common side effect of CPAP is drying of the nose from the air flow. This will be minimized by the use of air that will be warmed and humidified, which not only improves comfort but is thought to improve adherence with treatment. Other common side effects include:

a. Mask allergies, skin or eye irritations
b. Dry mouth or throat
c. Congestion, runny nose, sneezing, sinusitis
d. Nosebleeds
e. Ear discomfort
f. Stomach bloating and discomfort [34, 35]

We do not expect CPAP to have more than minimal risks when used by participants with asthma. We believe that the CPAP device should decrease the risk of an asthmatic exacerbation or attack for three reasons. First, patients will be breathing filtered air (hypoallergenic), which poses less risk of triggering an asthmatic attack. In the preliminary study of 15 asthmatics with 8-10cm $H_2O$ CPAP and sham by Tepper et al., there was no induction of asthma exacerbations even in the absence of heated humidified air. There is the possibility that there will be a treatment benefit from both active and sham CPAP resulting from the nocturnal inhalation of filtered humidified air. If this is the case, we would expect all groups to improve over time, and will have concomitant improvement in biomarkers of airway inflammation. Although this would not support our underlying hypothesis, this result would lead to other approaches to treating airways reactivity.

Second, patients with some degree of underlying bronchospasm will find breathing on low to moderate levels of CPAP more comfortable. These levels can lower the work of breathing and help them sleep better. Third, CPAP is likely to open the airways, which according to our primary hypothesis should lead to bronchorelaxation and decreased bronchospasm in general. The literature on the use of CPAP in patients who have concomitant sleep apnea and asthma has not reported any worsening of asthma[36].

In regards to using a sham CPAP in asthmatics, previous experience has indicated that sham CPAP can be an effective placebo device for CPAP-naïve participants[37]. Similarly modified masks as sham masks have been used in other studies[38,39] without an increase in the established side effects or occurrence of previously unobserved side effects.
In terms of tolerability of sham CPAP, we will analyze sleep quality questionnaires to assess if there is any sleep disruption risks in sham vs. treatment groups.

## 4.3. Handling of CPAP devices

Study devices will be supplied by a central device distribution center (the DCC) and shipped to the investigators. The study device will be kept in a secure, limited access, storage area. Each box of study device will be identified by protocol name. Study device receipt and distribution will be documented in the device accountability log. At week 12, participant should return the CPAP device and all its accessories to the clinic site.

## 4.4. Asthma treatment

All participants enrolled in this study will continue their routine asthma care with their asthma care provider including pharmacotherapy and environmental interventions. CPAP will be used as an additional possible treatment. It is the policy of the ALA-ACRC that each study participant have an identified asthma care provider who is not the study physician directing the clinical site. If a potential participant does not have a regular asthma care provider then the participant is provided one, usually by another physician at the study site.

Participants will receive asthma education materials, and a personalized asthma action plan summarizing the procedures for home care in the event of asthma symptoms or a drop in peak flow. At the screening visit (Visit 1), the study coordinator will give the participant an asthma action card with instructions for its use. The card identifies three zones: the zones will be “green” (greater than 80% of baseline PEF),”yellow” (50—79% of baseline PEF), and “red” (less than 50% of baseline PEF). Zones will be based on peak flow readings at Visit 1. These personal cut-offs will be entered onto the Asthma Action Plan Card. This card is the size of a credit card and has been used successfully in several previous ALA-ACRC asthma trials.

The asthma action plan card instructs participants to seek medical attention immediately if they are experiencing a serious asthma attack. Participants who experience less serious asthma symptoms or a drop in peak flow into the yellow zone or red zone are instructed to take 2 puffs of their rescue inhaler and wait 15-20 minutes. If symptoms persist or peak flow does not return to the green zone, participants are instructed to take 2 more puffs of the inhaler and wait 15-20 minutes up to 2 more times. If after a total of 3 administrations of the rescue inhaler, symptoms persist or peak flow is not in the green zone participants are instructed to seek medical care immediately.

Participants will be asked to hold their inhaled asthma controller medications for 12-48 hours prior to study visits that include a methacholine challenge test so as to obtain a valid methacholine challenge test. They will be permitted to use their rescue bronchodilator for relieve of symptoms up to six hours prior to methacholine challenge testing. They will inhale a bronchodilator after the end of the methacholine test (unless less than or equal 10% drop from baseline values occurred during the test)

# 5. Specific procedures

## 5.1. Randomization

Treatment assignment will be randomly allocated in a 1:1:1 ratio with stratification by clinic using a permuted block randomization scheme. Randomization will occur at V2 after the participant meets all eligibility criteria. The clinic staff will complete a randomization form for each eligible participant and enter it into a web-based randomization system. Eligibility criteria are verified via computer program, which then provides a study treatment assignment number according to an encrypted table on the server; the assignment number will correspond to a specific CPAP device and associated supplies (e.g., mask, tubing).

Blinding to treatment assignment is challenging for a CPAP trial, although previous experience has indicated that sham CPAP can be an effective placebo device for CPAP-naïve participants[40]. In order to blind study team members, we will distribute the numbered CPAP devices from the DCC. As a further measure to ensure masking, we will try to the extent possible to have clinics assign different staff to fit and train participants in the use of the CPAP device, than the staff assigned to collect outcome data. The rationale for the masking is to avoid bias in the collection of study data, particularly those that are patient reported outcomes.

## 5.2. Unmasking

It is our general position that unmasking of treatment assignment is rarely necessary. If adverse events occur that may be related to the study treatment, then the study treatment is stopped and the patient continues scheduled follow-up. Envelopes with treatment assignment are provided to the clinic in the case a treating physician feels it is important to know the treatment assignment. In addition, we provide a computer link and phone number where authorized personnel can receive unmasking information from the Coordinating Center. All participants are provided with a wallet card that provides information that they are participating in a clinical trial and gives the contact numbers of personnel at the clinic.

## 5.3. Methacholine challenge testing

Pre-bronchodilator spirometry and methacholine challenge testing will be performed at V1, V5, V6, and V7. Spirometry reference values will be those of Hankinson et al from NHANES[41]. Eleven breaths each of doubling concentrations of methacholine (Provocholine™) are inhaled from a calibrated DeVilbiss™ 646 nebulizer, starting at 0.03 mg/mL until a 20% or greater fall in $FEV_1$ occurs or a maximum of 32 mg/mL is inhaled. Results are computed as the logarithmic interpolated concentration that causes a 20% fall ($PC_{20}$). Methacholine challenge tests should be administered at the same time of the day, preferably in the morning with prior medication holds of asthma medications in accordance to the ATS recommendations. Methacholine challenge tests will also be carried out according to ATS and institutional guidelines at each participating clinical center by study-

certified technicians. A physician and a resuscitation kit will be available during each test to treat any adverse response to the methacholine challenge test. Consistency of testing is enforced by the use of identical spirometers (Koko, nSpire Health, Longmont, CO.), customized testing and reporting software, dosimeters, calibrated nebulizers, and central review and certification of technicians. The participating study sites have experience with these procedures which are in use in our current trials.

## 5.4. Treatment failure

Patients may be withdrawn from the treatment if they have a serious adverse event or are intolerant of the treatment. All patients will be asked to return for study visits in order to maintain the intent to treat paradigm for the primary analysis. Patients will be treated by their usual asthma care provider according to best medical judgment regardless of whether they continue to use CPAP.

## 5.5. Study termination

Participants are asked to return for a study visit 2 weeks after discontinuation of CPAP so we can evaluate the persistence of effect after the treatment is stopped. We will not recommend use of CPAP for patients to treat their asthma based on the information collected in this study alone. We will provide patients with a sealed envelope that discloses their treatment assignment at the termination of the study which they may choose to present to their care provider for the purpose of guiding future treatments. Participants will be instructed to open the envelopes after they leave the clinic to maintain blinding of the study staff.

If the subject leaves the study prematurely either voluntarily or for other reasons, the information obtained to that point will be used for the study and analysis. Leaving the study early will not affect participant regular medical care.

## 5.6. Specimen collection

Inflammatory biomarkers include blood eosinophil counts, IL-5, and exhaled Nitric Oxide (eNO) as markers of allergic inflammation, and IL-6, CRP, IL-8, and TNF-alpha as markers of nocturnal hypoxemia. Eosinophil counts will be measured in the local clinic labs, as well as eNO, which will be measured with the NIOX Mino [42, 43]. Serum from the blood collection will be prepared at clinics and stored at Nemours Children's clinic in Jacksonville FL for further analysis. Serum will be held for exploratory supplementary measures of cytokines.

The DCC supplies shipping labels, containers, and transmittal slips. All sites are required to be certified in biosafety for handling biological specimens in accordance with local university policy and applicable law.

Blood: up to 30 mL of blood is collected by venipuncture at V2 and up to 20 ml at V6 and V7 for eosinophil counts, DNA isolation (V2 only), and inflammatory markers. Participants are not required to agree to supply DNA in order to be eligible for the study.

## 5.7. Certification of clinical centers and staff

Clinical centers must be certified by the DCC prior to enrolling patients into the trial and clinical staff must be certified before they can participate in data collection or data entry. Certification requirements include clinics filing current copies of local IRB approvals and

conflict of interest statements with the DCC, clinic coordinators attendance of a training meeting, certification for individual staff members responsible for key study procedures such as methacholine testing and completion of a knowledge assessment form.

### 5.8. Adherence to study treatment

In order to reinforce adherence to study treatment, we will demonstrate the use of the study device to participants, maintain a range of mask sizes and types in the clinic to ensure comfortable fits, and use humidification to prevent nasal drying. We will assess compliance and identify potential issues early with the phone visit 1-3 days after starting CPAP and a clinic visit after 1 week. We will also assess feedback of electronic monitoring records at all follow-up clinic visits [44, 45]. If needed, additional visits for mask refitting and equipment trouble-shooting will be conducted. Staff at each center will be trained in the proper selection and fitting of CPAP masks and our research coordinators will review CPAP usage data from the device to review adherence with participants to reinforce the importance of adherence with therapy.

## 6. Statistical design

### 6.1. Justification of sample size

The sample size calculation is based on the $PC_{20}$ results obtained from 61 participants in the MeCIS phase II study [46] who were asthmatics similar to those in this trial. The mean $PC_{20}$ was 2.8 mg/mL with a standard deviation of 3.3 mg/mL. With a sample size of 67 per group (n = 200 total) we have 80% power (type 1 error = 0.025, 2-sided) to detect a 1.7-fold increase in mean $PC_{20}$ for each of the CPAP arms as compared to the sham arm and more than 95% power to detect a 2-fold increase. Thus, we have ample power to confirm our preliminary data that that 1 week of CPAP showed a 2.75-fold increase in $PC_{20}$ even with adherence as low as 60%. The type 1 error rate is adjusted to account for multiple comparisons among the 3 treatment groups and the sample size is inflated by 15% to account for missing data and other sources of heterogeneity.

| Detectable Difference (mg/mL) | Power (n = 200 total) |
|---|---|
| 1.5 | 33% |
| **2.0** | **80%** |
| 2.5 | 96% |
| 3.0 | 99% |

| Detectable Difference (mg/mL) | Total Sample Size (3 groups, 80% power) |
|---|---|
| 1.5 | 550 (183 per group) |
| **2.0** | **200 (67 per group)** |
| 2.5 | 112 (37 per group) |
| 3.0 | 79 (26 per group) |

### 6.2. Primary analysis

The primary statistical analysis will be an unadjusted comparison of 12-week change in methacholine $PC_{20}$ between each of the active groups and the sham treatment group. Generalized estimating equations (GEE) will be used to model the change in $PC_{20}$ over time. A saturated mean model, i.e., each time-point, treatment group and interaction between time and treatment are incorporated into the mean model, and an unstructured covariance model will be used. If imbalances in influential baseline variables are present, then secondary analyses using appropriate stratification or adjustments will be

done. Analyses will be done based upon principle of intention to treat, i.e. all data from all randomized participants will be included in the analysis.

Methacholine data presents analytical challenges because of missing data due to failure to achieve a $PC_{20}$ at the highest concentration or missing data because the participant has baseline lung function too low to perform the test. In part, we are protecting against this by using a 32 mg/mL maximal methacholine concentration and enrolling patients with a safety margin of lung function and airways reactivity. Based on our MeCIS study[47], we expect this type of missing data to occur in about 5% of participants. For participants who do not decline 20% at the highest dose of methacholine, we will use multiple imputation techniques to adjust for missing data while ensuring that the imputed values are above the highest concentration (32 mg/mL). For other types of missing data, sensitivity analyses including imputations based upon best and worst case scenarios as well as imputation based upon the methacholine dose-response slope will be performed. GEE, which are robust for data that is missing at random, will be used for modeling the outcomes. We will run additional sensitivity analyses in which the $PC_{20}$ is imputed to be below the lowest does of methacholine for participants who have pre-diluent $FEV_1$ less than 70% of the predicted value and are therefore unable to take the test.

## 6.3. Subgroup analysis

Subgroup analyses will be done by testing for interaction between treatment and relevant subgroups that may benefit the most (e.g. obesity, adult onset, non-atopic, nocturnal asthma, persistent asthma, low lung function, adherence with treatment).[48]

## 6.4. Secondary analysis

Secondary analyses will focus on the effects of additional covariates (age, gender, BMI, atopic status, baseline inflammatory status, and adherence), alternate outcomes ($FEV_1$, asthma diary data, asthma control, quality of life, and inflammatory biomarkers), and dose-response models using the level of CPAP and adherence measurements. For all three, the models will be similar to those used for the primary outcome, i.e., GEE with a saturated mean model and unstructured covariance matrix. Analyses using level of CPAP and adherence measures will be performed to explore potential dose-response relationships for both the primary outcome ($PC_{20}$) as well as other measures of lung function.

## 6.5. Adherence analysis

Data from daily diaries and data downloaded from CPAP devices will be used to evaluate adherence to the treatment regimens. Evaluation of treatment effects in subgroups of adherent versus non-adherent participates will be performed. These analyses will also utilize time-dependent covariates to characterize adherence. Adherence with CPAP in OSA is similar to that of inhaled corticosteroids (ICS) therapy in asthma (50-80%).[49] The study is powered to account for 60% adherence (greater than or equal to4 hours / night on average). We recognize the importance of enforcing and measuring this for valid interpretation of our results. In our preliminary studies, the mean CPAP use of 4 hours/night was effective.

# 7. Data and safety monitoring

## 7.1. Data and safety monitoring board

An independent Data and Safety Monitoring Board (DSMB) to review the CPAP trial is approved by NHLBI and by ALA. The DSMB will meet twice a year, usually by teleconference, to review data related to participant safety and other related issues, such as center performance standards or recruitment issues. The DSMB may request more frequent meetings if necessary to fulfill its charge. It may also request additional safety reports on a more frequent basis. No formal interim efficacy analyses or stopping guidelines are proposed because the study is not a clinical efficacy study. Safety and performance concerns that require recommendations by the DSMB will be based on the relative balance between patient safety and the potential scientific benefits of conducting the study.

At the end of each DSMB meeting, the board will make formal recommendations regarding trial continuation and clinical performance. The DSMB may recommend that the study be stopped early if there is evidence that the risk-benefit ratio does not warrant continuation of the trial. These recommendations will be submitted to ALA, the ACRC Steering Committee, the NHLBI, and to the participating center's IRBs.

A serious adverse event (SAE) is an adverse event that results in one of the following outcomes: death, a life-threatening event, hospitalization (initial or prolonged), disability or permanent damage, congenital anomaly/birth defect, or required intervention to prevent permanent impairment or damage (devices). SAEs may also result in other serious important medical event which may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent any of the outcomes previously listed in this definition. SAEs also include any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects, and should be reported to the DCC on study forms as appropriate.

Clinical center personnel (i.e. coordinator, PI) will monitor participant safety via study visits and interim telephone calls. When an investigator or clinical center staff member becomes aware of an SAE, it should be reported to the DCC within 72 hours of the clinic learning of the event. SAEs will be reported to all the DSMB members in a timely fashion for review. This initial review will determine whether there is a recommendation for an immediate change in the protocol or halt to the study until such time as the matter can be discussed among the DSMB members or to determine if more information or discussion is needed. An ad hoc meeting will be arranged to discuss the event if deemed necessary by the DSMB. In addition, the DCC will distribute reports of SAEs from one center to all of the centers for review by the local IRBs. SAE's that are considered to be unexpected and related to use of the CPAP device will be reported to all clinical centers and to the FDA as a MEDWatch report.

SAEs, unanticipated problems and protocol deviations will be reported to the IRBs and NIH in accordance with their reporting requirements. In addition, any plan of action in response to those reports or actions taken by IRBs in response to those reports will be reported to the DSMB, ALA, and ACRC Steering Committee as an expedited, ad hoc report.

Non-serious adverse events will be recorded on study forms and reviewed by the DSMB at their regular meetings.

## 7.2. Protection of human subjects

### 7.2.1. Recruitment and consent procedures

Participants will be recruited by each participating clinic. Recruitment strategies include local American Lung Association campaigns, solicitation in physician offices, clinics, workplaces, schools and public media advertisements. All public advertisements are subject to approval by the local IRB and must indicate that it is a research study. The DCC will help coordinate recruitment among clinics and promote sharing of effective recruitment strategies within the network. The trial will be registered on www.ClinicalTrials.gov.

Potential enrollees and their legal guardian (for pediatric participants) will be approached either in person, by telephone or by mail to establish general eligibility criteria. A general description of the study, including frequently asked questions and a consent form will be provided prior to their initial screening visit. Potential enrollees will attend a screening visit, they will meet with the study coordinator and the local physician co-investigators to review the study and answer questions. They will be asked to sign consent, and if appropriate provide assent, and undergo the screening procedures at that visit. Eligible participants will have a methacholine test prior to the randomization visit.

The consent form will be subject to approval by the clinical center IRB. A copy of the consent form will be given to each participant, and the signed original will be kept in the participant's research chart. Individual consent for the methacholine challenge test and genotyping may be required depending upon institutional requirements. Subjects 15 to 17 years of age may also need to provide assent according to local IRB policies. Sites will provide assent forms or modified consent forms for these participants per local IRB policies. The legal guardians of participants in this age range must also sign the consent form.

### 7.2.2. Potential risks and procedures to minimize risk to the participants

The risks associated with the study treatment were described in Section 4.2 of this protocol. Participation in this research protocol requires some routine clinical procedures that entail more than minimal risk. These include methacholine challenge tests and blood draws. In addition, there are risks to participant's confidentiality and financial risks that are associated with study participation.

***CPAP treatment (See Section 4.2)***

***Pulmonary function testing*** (as part of the methacholine testing) requires deep and forceful respiratory efforts. It is a commonly performed and safe examination that is widely performed in patients with lung disorders. Some patients report chest soreness the day following the procedure. Some patients may experience light-headedness during the forced expiration. The risk of syncope is mitigated by having the patient perform the test in the seated rather than standing position, with direct observation of the patient during the testing.

***Methacholine challenge testing*** often induces a mild cough, but very rarely induces enough bronchoconstriction to induce dyspnea. The safety of this test has been well described in collaborative asthma research studies with appropriate instructions and when attention is paid to routine safety precautions[50,51]. These safety precautions will be part of our procedures and include the following: training and certification of personnel conducting the test; administration of the test according to ATS and institutional guidelines at each

participating clinical center; confirming that a physician and a resuscitation kit are available during each test to treat any adverse response to the methacholine challenge test. We will also review the resuscitation kits and emergency response plans as part of the clinic certification requirements to ensure materials are up-to-date and appropriate plans are in place.

Participants do not undertake the challenge test if they have acute asthma symptoms or if the baseline $FEV_1$ is less than 70% predicted (75% predicted for eligibility at V1). The test is terminated when the $FEV_1$ declines to 80% of the value obtained with diluent inhalation. The participant will inhale a bronchodilator at the end of the test (unless less than or equal 10% drop from baseline values occurred during the test) and participants will not leave the testing area until their lung function returns to 90% value of their baseline, or until they are released by the study physician.

The methacholine challenge test is a well-established means of evaluating the degree of airway responsiveness[52]. It has been shown to be a safe and easily reversible bronchial testing for asthmatics[53]. In this study, it will be administered to the participants before randomization, and 6 weeks, 12 weeks, and 14 weeks after randomization, making the duration between tests sufficient to minimize the burden on the participant. There is also a minimum of 1 week required between visits in the study after Visit 4. As mentioned previously, it is our policy that the participant does not leave the testing area until their lung function returns to normal.

***Exhaled Nitric Oxide, eNO*** Participants will also undergo measurement of exhaled nitric oxide (eNO) according to standardized techniques[54.] The risks of this test are minimal. Collection of eNO involves inhalation to total lung capacity while in a seated position followed by slow exhalation against resistance for 10 seconds. Both children and adults can perform this without difficulty. A trained technician will be present to supervise and support the participant in order to minimize discomfort.

***Blood*** will be obtained for DNA and measurement of inflammatory markers. Risks of blood draw are minimized by limiting the amount drawn to no more than 60 mL at each visit where blood is drawn for a total maximum of 240 mL over 6 weeks. Patients have venipuncture in the seated or lying position to minimize syncopal events and pressure is applied after the procedure.

The risks of DNA analysis are primarily related to the possibility that an outside agency not approved by the participant might obtain and use the information in such a way that it would harm the participant. To minimize this risk, DNA samples will be identified only by a numeric identifier, and no genetic analysis will be performed other than that associated with asthma and airway diseases. These results will not be a part of a participant's general medical record. Genetic information or other information obtained from participants will not be supplied to any outside agency except as authorized by the consent statement. Genetic information will be shared with other investigators in the network through study ID codes and not by name. Genetic results may be presented in publications and meetings but individual names will not be identified.

***Questionnaires***: Each participant will complete questionnaires of health status, asthma specific symptoms, and quality of life. There is always the risk that information from a study can be disseminated in ways that can risk the privacy of a person with attendant social and occupational harm. Refer to Section 7.2.5 for more information about data confidentiality.

***Psychological or financial risks:*** The participant is not charged for use of the CPAP devices or any of the study procedures. Although unlikely, there may be unforeseen psychological or financial risks for participants in this trial. For example, participants may have unrealistic expectations of benefit from treatment received in a trial, or may have psychological distress from having a diagnosis of asthma or other concomitant diseases discovered during screening evaluation. Participants may also have to undergo financial loss from their occupations to attend clinic visits. Most participants, however, receive psychological benefit from participating in a study that may help others, and the financial costs are mitigated by small honoraria for participation in the study.

If a participant suffers an injury as a consequence of participation in this study, they would be responsible for the medical costs as the University and NIH do not have a program to reimburse patients for such costs.

The procedures to minimize risk in this trial are similar to those successfully used in current or previous clinical and translational research, and thus are likely to be effective.

### 7.2.3. Vulnerable populations

Children between the ages of 15 and 18 will be eligible for participation in this trial and are considered a vulnerable population. Sites will provide assent forms or modified adult consent forms for these participants per polices of the local IRB.

There have been several studies of CPAP for treatment of OSA in children. CPAP has been shown to be safe, effective, and well-tolerated by children and adolescents with OSA[55 56 57 58 59 60]. Levels of airway pressure required in children for OSA treatment are similar to levels used in adults[61 62]. Because asthma is the most common chronic disabling illness in children[63], we think it is important to include children, ages 15 to 17 in our study. We believe adolescents, 15-17 years of age, are sufficiently mature to use the CPAP device and mask, and to participate with adequate adherence in this trial. Masks that are used for this trial come in various sizes that will be suitable for adolescents included in the study.

Pregnant and lactating persons will be excluded from this trial because methacholine challenge testing is relatively contra-indicated in these conditions. In order to participate in the trial, persons of child-bearing potential must have a negative pregnancy test at V1, no plans to become pregnant, and be using an effective form of birth control. A pregnancy test will be administered before each methacholine challenge test, as well as before HRCT scans for those participating in the substudy. Any participants who become pregnant will be withdrawn from the treatment and methacholine testing components of the study and the pregnancy will be followed to full term to assess the perinatal outcomes. For the purposes of this study, pregnancy will be considered a reportable serious adverse event.

### 7.2.4. Treatment of adverse events

Treatment of adverse events will be performed in accordance with the Institutional IRB policies and as described in the informed consent document. Neither the NIH, the American Lung Association, nor Johns Hopkins University, have a program for providing treatment or compensation for participants in research studies. Some universities however do agree to indemnify participants who may be harmed by participation in research studies at their institutions.

### 7.2.5. Data confidentiality

Participant data, which includes identifiable personal health information (PHI), are collected at each of the clinical sites. PHI will be stored at each of the clinical sites in accordance with HIPAA regulations and local university and hospital policies. This includes the storage of PHI in locked cabinets or rooms, limited access to secure data areas by certified study personnel, password protection for electronic medical records, and explanation of HIPAA regulations on the study consent form. Data such as lung function or laboratory tests that are collected as part of this study may be transmitted to the patients treating physicians with the consent of the participant. Participants will be informed in the consent that PHI may also be disclosed for auditing purposes by the NIH or other regulatory bodies and is subject to subpoena.

PHI is not transmitted to the DCC or central laboratory in that all specimens and records are identified by a study ID, and other identifying information such as name or hospital ID number are not entered into the central study database. Source records that are transmitted to the DCC for data quality audits have identifying information redacted.

No highly confidential information is routinely collected, although the data collection does include PHI, so a breach of confidentiality would constitute a HIPAA violation. If a patient is harmed from this study as a consequence of negligence, then the investigators or University might be liable for damages.

We will advise participants that the U.S. Department of Health and Human Services has the right to inspect medical records relating to this research for the purposes of verifying data. Demographic information on the subjects is released only to characterize populations for the National Institutes of Health. Where data are shared with other research entities, it will comply with the HIPAA definition of a limited dataset, and appropriate IRB approvals and waivers will be obtained.

# 8. HRCT substudy

## 8.1. Title

Effects of CPAP on Airway Size in Patients with Asthma

## 8.2. Principal investigator

Robert H. Brown, M.D., M.P.H.
Imaging Analysis Center
Johns Hopkins Bloomberg School of Public Health, Baltimore MD

## 8.3. Objective

The High Resolution Computed Tomography (HRCT) substudy is proposed to examine whether 12 weeks of nocturnal CPAP causes morphological changes (increased airway size or decreased air trapping) in individuals with airways hyper-responsiveness.

## 8.4. Background and significance

The goal of the main trial is to determine whether the application of positive pressure to the airways of asthmatics can diminish airways reactivity. There are several potential causes of the decreased airway reactivity. One possibility is larger airways either at TLC, FRC, or both. Another possibility is decreased air trapping secondary to CPAP treatment. A third possibility is there may be upper airway relief of obstruction that leads to decreased reactivity. Prolonged distention of the airways with CPAP in ferrets resulted in airway dilation at a specific lung volume through decreased tone of the airway smooth muscle leading to increased airway dilation at a specific lung volume. [64]

The overall goal of this substudy is to ascertain whether similar findings of airway dilation after CPAP are present in human asthmatics using high resolution computed tomography (HRCT). Our laboratory has had extensive experience imaging airways in human asthmatics to determine the mechanical properties of the airways. Conventional pulmonary function tests are unable to assess airway stiffness or maximum airway size in response to the stress of lung inflation. HRCT is a direct, noninvasive, radiological technique that can accurately, reliably, and repeatedly measure luminal area and wall thickness of individual airways at multiple lung volumes in animals [65] [66] [67] [68] [69] and in human airways in vivo [70] [71] [72] [73]. In addition, HRCT imaging is uniquely capable of assessing regional changes in lung volume, which may differ in dependent vs. non-dependent regions of the lung. Also, HRCT can assess changes in tissue volume and density, which may result from changes in air trapping with chronic mechanical strain. Using HRCT in animal studies, it has been shown that CPAP produced an increase in airway size assessed in-vivo.[74]

In the substudy, HRCT will be used to make repeated measurements of airway luminal size, airway wall thickness in multiple airways (1st to 6th generation airways), and lung parenchymal density at two lung volumes in subjects with asthma, before and after 12 weeks of CPAP. Response of the airways to a deep inspiration will be used as a measure of the airway stress-strain relationships, and localized air-trapping will be used as an

indicator of regional airway tone. Thus, we will be able to confirm pre-clinical studies, and have greater insight into mechanisms of action of CPAP in asthma.

There are three novel aspects to this substudy 1) an improved understanding of the mechanisms of asthma with respect to the interaction of mechanical strain and airway dilation and responsiveness, 2) determination of the location of the areas most affected by this mechanical strain in vivo, and 3) a safe mechanical intervention as a potential new therapy for asthma.

## 8.5. Hypothesis

**Hypothesis 1**: Chronic mechanical strain using nocturnal CPAP treatment will decrease airways reactivity by increasing the mechanical interdependence between lung parenchyma and airways during a deep inspiration. This will be manifested by increased airway dilation during a deep inspiration (specific airway diameter) and will occur predominantly in the dependent lung zones.

**Hypothesis 2**: Chronic mechanical strain using nocturnal CPAP will lead to increased airway size in the dependent regions of the lung which will be manifested by a reduction in airway closure and regional air-trapping at end-expiration. Moreover, the magnitude in reduction of air trapping will be correlated with the magnitude of reduction in airways reactivity.

## 8.6. Eligibility criteria

A total of 54 adult subjects (18 per group), who are randomized in the main study, will be enrolled in the substudy. The substudy will be conducted at a subset of the ACRC clinics. Children below the age of consent (18 years old) will not be eligible for the substudy. Subjects will be asked to volunteer for this substudy. Whether or not they volunteer will not affect their ability to participate in the main protocol.

## 8.7. Study design

HRCT images of the lung parenchyma and airways will be acquired from individuals with asthma shortly before starting, and shortly before finishing CPAP treatment (total of two visits). Airway luminal area, airway wall thickness, and parenchymal density will be measured. These data will be obtained specifically for research purposes using standardized protocols for different model scanners. Variation between scanners is minimized by designating the same scanner to be used for all scans on an individual before and after CPAP treatment.

HRCT Visit 1 will be performed after randomization in the main CPAP study, and prior to initiation of CPAP.

HRCT Visit 2 will be performed between weeks 10 and 12 of CPAP, at a different day or prior of methacholine challenge testing.

CT scans will be done at approximately the same time of day as the methacholine challenge tests so the results can be correlated with changes in airways reactivity. Drug holds will also be similar to those used for methacholine challenge testing to minimize variability due to bronchodilator use.

Two CT scans will be performed each at different lung volume at each visit (Total of 4 scans for the study duration). The first volume will be at Total Lung Capacity (TLC), followed by another CT scan at Functional Residual Capacity (FRC). Study site coordinators will be provided with a script for the CT technologist to coach subjects in the appropriate breathing technique. For the HRCT scans:

- Albuterol will be held for at least 6 hours prior to scanning.
- A pregnancy test will be administered at each visit before imaging.
- Both inspiratory and expiratory scans will be carried out.
- The lungs and the upper airway will be included.
- The scanning protocol will begin below the lung bases and stop at the Nasopharynx.
- Scans will be performed with the subjects in the supine position

## 8.8. Outcomes

Changes in airways diameter and air trapping: The airway luminal areas, wall thickness and lung parenchyma (air, tissue, and total volume) will be measured using the validated[75,76,77] Pulmonary Workstation 2 software package (VIDA Diagnostics, Inc, Iowa City. IA). Air trapping will be defined as voxels less than -856 HUs at FRC.

## 8.9. Justification of sample size

With a sample size of 18 per group (n=54 total), we have 80% power (type 1 error = 0.025, 2-sided) to detect 20% increase in airway luminal size and more than 95% power to detect a 30% increase.

## 8.10. Data analysis

Data will be analyzed using both nonparametric and parametric statistics with correction for multiple comparisons. As a conservative approach, no assumptions will be made about the distribution of the data and a Wilcoxon rank-sum test will be used to compare airway luminal size and wall thickness before and after CPAP. P-values less than 0.05 will be considered significant.

Analyses will also be performed on measures of airway distensibility and lung parenchymal density. As a conservative approach, no assumptions will be made about the distribution of the data and a Wilcoxon rank-sum test will be used. Subsequently, parametric testing will be performed. Statistical corrections will be made for multiple comparisons.

## 8.11. Risk to participants and protections against risk

***HRCT Scans***

We are cognizant that this will involve a small amount of radiation exposure to our subjects. We have a long-established interaction with Dr. Mahadevappa Mahesh, the radiation physicist at the Johns Hopkins Hospital, and we have worked on several CT protocols over the years. For the current proposal, to limit the risk of imaging for our volunteers, we have determined what we consider the best balance between high quality data and minimal radiation exposure. We intend to perform four high-resolution chest CT

scans of the subjects. The chest CT protocol will be adjusted, based on the weight of the subjects. For average-size adults of (BMI 20-30), the effective dose estimation, per Dr. Mahesh, is about 4 mSv (0.4 rem) for inspiration scans and 3 mSv (0.3 rem) for expiration scans on female participants. For male participants, the effective dose estimated will be about 3.5 mSv (0.35 rem) for inspiration scans and 2.5 mSv (0.25 rem) for expiration scans. Thus the cumulative dose total for this study is estimated to be 14 mSv (1.4 rem) for female and 12 mSv (1.2 rem) for male participant respectively. This compares to the annual allowed limit on radiation workers of 50 mSv (5 rem) in the US. The risk of radiation overexposure will be mitigated by ensuring that all centers are certified for performance of the tests in a JCAHO accredited facility that performs required regular calibration of the scanners. Moreover, prior to subject enrollment, CT scanners at each site will be calibrated using a Lung Phantom (e.g. CPT674, The Phantom Lab, Salem, NY). While there are some variations between CT scanners, a standardization of the parameters and exposure levels has been developed to allow multiple scanners to output reliable quantitative measures and minimize risk across a given patient population.

As mentioned previously, children under the age of 18 will not be included in the HRCT substudy.

Although the scans are done only for research purposes, we are requiring that all CT scans be interpreted by a certified radiologist on site. The scans will be inspected for adequate inspiration, absence of motion artifact and inclusion of all parts of the chest. If any incidental findings are discovered during study, the clinical site study physician will be notified, the information will be given to the participant and with their permission, the information will also be transmitted to the participant's usual care-giver for appropriate medical care or follow-up.

### 8.12. Data confidentiality

For the HRCT substudy, all images will be de-identified at the scanning institution and a unique code will be assigned by the Data Coordinating Center

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