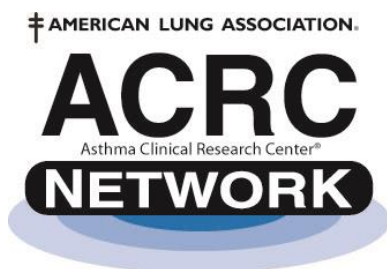


Effect of Positive Airway Pressure on Reducing Airway Reactivity in Patients with Asthma (CPAP) Trial

Manual of Procedures Version 2.0



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1 December 2013

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Revision history

Version 0.1 (17 Aug 2012)

Based on protocol v1.6 (13 Apr 12)

Version 2.0 (1 Dec 2013)

Based on protocol v1.7 (18 Apr 13)

Based on PPMs subsequent to MOP Version 0.1

Incorporates revisions, clarifications, and corrections to MOP Version 0.1

Updated Table of Contents

| | <i>Section title</i> |
|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Section # | Change/addition |
| 1.2 | <i>Eligibility criteria</i> <ul style="list-style-type: none">• Added note: “‘on’ prescribed therapy does not necessarily mean subject must be currently using medication. Subject however must be prescribed a medication by a physician for at least the past 12 months and is stable to be enrolled in the study. If a subject does not seem stable and is having asthma problems due to not using their medication, it is best not to enroll the subject at this time.”• Added note: “Also, subjects cannot participate in the CPAP trial if they share the same bed with an individual who uses CPAP” |
| 1.3 | <i>Study visit time windows and data collection schedule</i> <ul style="list-style-type: none">• Added “weeks” to “visit window”• New – added Quality of life questionnaires (WQ) to be administered at V2 and V6 |
| 2.1 | <i>Order of procedures</i> <i>Trial Schema terminology</i> <ul style="list-style-type: none">• Reordered signing consent prior to evaluation of eligibility for better clarification |
| 2.2 | <i>Screening visit (V1)</i> <ul style="list-style-type: none">• Added note: “Disposable one way valve mouthpieces can be used for peak flow at V1”• Added: If PC₂₀ is greater than 8 mg/mL for FEV₁, participant is not eligible; “terminate the challenge after the 16mg/mL concentration”• Added: Data enter Screening (SC) form into the data system before the randomization visit if the participant is eligible “(even if the methacholine challenge test is still scheduled)”. The Screening (SC) form must be data entered “immediately after completing a successful V1 (i.e. no STOPS on the SC form) and” before a participant can be randomized at V2.• Added note: “If there is a STOP on the Screening (SC) form, do not data enter the form, but make sure you update the Participant Screening Log (PS) to reflect the reason why participant failed screening.” |

- 2.3 *Randomization visit (V2)*
- **New** – added Quality of Life Questionnaires (WQ)
 - **Added:** “On the main data system page, perform treatment assignment by completing the ‘CPAP Treatment Assignment (Randomization)’. This will provide the assigned kit ID for the participant. This step must be completed before distributing the study kit to the participant.”
-

- 2.5 *Adherence clinic visit (V4)*
- **Changed:** time frame window from 1-2 weeks after randomization to “1-3 weeks after randomization”
 - **Added:** Remove SD card A from the device and ship to the DCC “immediately after the visit”
 - **Added:**
 - “After the DCC reviews SD card (A), the DCC will send a CPAP compliance report showing device usage during the week after randomization as well as recommendations for the participant.
 - Review the compliance report, compare it to the adherence flowcharts, and contact the participant if needed to resolve any issues with CPAP adherence
 - Show the participant their usage report at their next clinic visit
 - Contact the DCC for any questions”
-

- 2.6 *Follow up clinic visit (v5)*
- **Added:** “Show the participant their usage report based on their SD card (A)” Remove SD card B from the device and ship to the DCC “immediately after the visit”
 - **Added:**
 - “After the DCC reviews SD card (B), the DCC will send a CPAP compliance report showing device usage as well as recommendations for the participant.
 - Review the compliance report, compare it to the adherence flowcharts, and contact the participant if needed to resolve any issues with CPAP adherence
 - Show the participant their usage report at their next clinic visit
 - Contact the DCC for any questions”
-

- 2.7 *End of treatment visit (V6)*
- **New** – added Quality of Life Questionnaires (WQ)
 - **Added:** “Review the CPAP compliance report with the participant based on SD Card (B)” .Remove SD card C from the device and ship to the DCC “immediately after the visit.”
-

- 2.10 *Missed procedures/ missed visits*
- **Added:** At V6, participants should be instructed to use the CPAP device until their V6 is performed “including the methacholine challenge test. If the methacholine test is rescheduled for V6, make sure the participant uses the CPAP device until then. Complete a Treatment Termination (TT) form when participant returns the CPAP device.”
 - **Added note:** “Forms that are expected and required at baseline (V1

- and V2) and are missing are to be reported as protocol deviations.”
- **Added note:** There must be a minimum of one week between visits “after V4.”

3.4

Study supplies

- **Added:** “Maintaining an inventory of study supplies is the responsibility of the clinical and satellite centers. This will include ordering study supplies as needed.”
- **Added:** “Disposable one way valve mouthpieces are available upon request at the DCC. To order please complete a General Order (GO) form”
- **Added** to Data Coordinating Center will distribute the following:
 - “A laminated flowchart on the 11-step methacholine procedure sequence
 - A laminated flowchart on acceptability and reproducibility of spirometry maneuvers
 - 1 laminated example of good CPAP adherence
 - 1 laminated example of poor CPAP adherence”

4.1.1

Spirometry procedures

- **Changed** requirement that all sites will use KoKo spirometry software version 4.14 to “version 4.11”
- **Added:** “During the study, the new version 4.15 will be sent out to clinics along with a PPM and instructions to download”
- **Added:** “At V1” to the end of: At least 3 acceptable and 2 reproducible efforts should be obtained. If this cannot be obtained after approximately 8 attempts, then the testing should be halted
- **Added:** “race” to ethnicity in the table for pulmonary function predicted values

4.2.2

Methacholine challenge test – 11 step

Purpose and schedule

Rescheduling

- **Added:**
 - “Both Methacholine Challenge Testing (MC) forms are to be data entered in the system
 - Guidelines on waiting times to reschedule:
 - Low FEV1:
 - At V1: participant is ineligible, wait 4 weeks and rescreen participant
 - At follow up visits: it is recommended that a rescheduled challenge should be performed no earlier than 2 weeks from the first challenge
 - Failing to achieve acceptability and reproducibility at V1: rescheduled challenge should be performed no earlier than 1 week from the first challenge”
 - **Added note:** “If V6 methacholine is to be rescheduled, the CPAP device must be kept with the participant, and the participant should use the device until their methacholine challenge is performed. The Treatment Termination (TT) form and the Study Evaluation (EV) form

should be completed after the participant returns the CPAP device and masks (end of treatment).”

4.2.5 *Contraindications*

General contraindications

- **Added:** “At V1” to the end of : An acceptable methacholine test depends on the ability of a participant to perform acceptable spirometric maneuvers. If a participant is unable to perform reproducible (2 efforts) and acceptable (3 efforts) pre-spirometry tests at each of the pre-diluent and post-diluent sessions, the methacholine challenge test should not be conducted at V1.

4.2.12 *Administration of 11-step methacholine challenge*

- **Per PPM 15**, the following clarifications were made:

Pre-diluent lung function

1. Record pre-diluent spirometry
 - “At V1:”
 - If acceptability and reproducibility requirements are not met, do not proceed
 - Must obtain 3 acceptable and 2 reproducible efforts
 - Minimum of 3 efforts and maximum of 8 efforts
 - “At V5, V6, and V7”
 - If acceptability and reproducibility are not met after performing 8 maneuvers, select the highest FEV₁ from an acceptable maneuver (or the highest if none are acceptable) and proceed with the next step of the challenge”

Post-diluent

- **Clarified** post-diluent requirements:
- “At V1:
 - Must obtain 3 acceptable and 2 reproducible efforts
 - Minimum of 3 efforts and maximum of 8 efforts
 - Record the highest acceptable FEV₁ as post-diluent FEV₁ on Methacholine Challenge Testing (MC) form
 - If acceptability and reproducibility requirements are not met, do not proceed”
- “At V5, V6, and V7”
 - Minimum of 3 efforts and maximum of 8 efforts
 - Record the highest acceptable FEV₁ as post-diluent FEV₁ on Methacholine Challenge Testing (MC) form
 - Record the highest acceptable FEV₁ as post-diluent FEV₁ on Methacholine Challenge Testing (MC) form
 - If acceptability and reproducibility are not met after performing 8 maneuvers, select the highest FEV₁ from an acceptable maneuver (or the highest if none are acceptable) and proceed with the next step of the challenge”

Administration of Methacholine concentrations

- **Added:** “At V1: If PC₂₀ is greater than 8 mg/mL for FEV₁, participant is not eligible; terminate the challenge after the 16mg/mL concentration and continue with the recovery phase.”

Administration of bronchodilator

- **Added to note:** Notify physician if post-bronchodilator FEV₁ remains less than 90% of pre-diluent “after administering bronchodilator twice.”

4.2.13 *ATS methacholine challenge testing sequence*

- **Changed** title to “CPAP methacholine challenge testing sequence”
- **Per PPM 15 - Replaced** flowchart with updated flowchart (version date 25 Mar 2013)

4.3 *Exhaled Nitric Oxide (NIOX MINO)*

- **Per PPM 19 – Replaced** all section on eNO procedures with new instructions for NIOX MINO®

4.4.3.2 *Blood draw for DNA and plasma*

- **Added note:** “If DNA cannot be drawn at V2, draw blood at a following clinic visit and use spare labels to label form and specimens. Record as a protocol deviation”

4.4.3.3 *Blood draw for Inflammatory Profile*

- **Added note:** “If blood cannot be drawn at a certain visit, draw blood at a following clinic visit and use spare labels to label form and specimens. Record as a protocol deviation.”

4.4.3.4 *Eosinophil count*

- **Added:**
“Analysis arrangements
 - Make arrangements for local analysis, at local CLIA – approved laboratory
 - Use whatever method used at the laboratory for eosinophil count (cells per µL). Both flow cytometry and manual counting are acceptable methods. Eosinophil counting must be reported as cells/µL, NOT as percentage.
 - To convert % eosinophil to cells/µL:
 - Multiply % eosinophil by number of white blood cells
 - Typical count for white blood cells is 4,000 - 10,000 cells/µL
- Example:
1% eosinophils x 5,000 white blood cells/µL = 50 eosinophil cells/µL
- Obtain collection and processing/storage instructions from lab”

4.4.4 *Specimen labeling*

Pre-printed labels for CV form

- **Added:** “Add a clear tape on the CV form label as well”

Spare labels

- **Added:** “Important Note: If specimens are collected on a different visit than expected, please use the spare labels for the specimens.”

- **Deleted:** “activation of spare labels”

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| 4.4.5 | <i>Specimen shipping</i> <ul style="list-style-type: none">• This section was replaced by a new section for specimen shipping |
| 4.6 | <i>Peak flow measures</i> <ul style="list-style-type: none">• Added note: “Disposable one way valve mouthpieces can be used for peak flow at V1” |
| 5.1.4 | <i>Preparations to use the CPAP device</i> <ul style="list-style-type: none">• Added note: “The on/off button is yellow when the device is on standby (hooked up to an outlet but the air pressure is off) and blue when the pressure is on.” |
| 5.6 | <i>Safety warnings</i> <ul style="list-style-type: none">• Added: “The following are recommendations that the coordinator should communicate to the participants to ensure the safety and effectiveness of the device.” |
| 5.8 | <i>Adherence factors</i> <i>Follow-up and monitoring adherence</i> <ul style="list-style-type: none">• Added: “In addition, the DCC will review the SD Cards shipped and provide a CPAP compliance report showing device usage as well as recommendations for improving adherence. The DCC reviews the adherence based on:<ul style="list-style-type: none">○ <i>Consistency:</i> the number of nights the participant uses the device in the specified period○ <i>Continuousness:</i> the number of hours the participant uses the device every night <p>Compare the CPAP compliance reports for each participant to the adherence flowcharts and review the usage with the participant at their next Clinic visit”</p> |
| 6.1.1 | <i>Study kits: Overview</i> <ul style="list-style-type: none">• Added: “Study kit label that has Kit ID and serial number is covered by an orange sheet of paper” |
| 6.1.3 | <i>Kit receipt and storage</i> <ul style="list-style-type: none">• Added:<ul style="list-style-type: none">○ “Satellite clinic should have a separate DA log○ Store study kits in a secure, locked location with limited public access○ Store kits separately; e.g., store kits on a designated shelf” |
| 6.1.5 | <i>Kit return and shipment</i> |

- **Changed** address of device shipment to:
 “Data Coordinating Center
 911 S. Ann St
 Baltimore MD 21231
 Phone: 443-287-3170
 Fax: 775-871-4030
 ! Address changed to:
 415 N Washington St.
 2nd floor
 Baltimore, MD 21231
- Immediately upon shipment, notify Device Distribution Center by emailing or faxing the CPAP Device Transmittal Sheet (CT) (email ryasin@jhsph.edu or fax to 775-871-4030)”

6.1.6 *Kit recycling*

- **Clarified** warning: “If device need to be replaced, order a new kit (comes with new masks) and ship the old kit with old masks back”

6.1.9 *Compliance monitoring*

- **Added:**
 - Discuss compliance and CPAP use “based on the CPAP SD card compliance reports provided by the DCC”
 - Show participant their CPAP compliance report and device usage”

6.1.10 *Kit replacements*

- **Deleted** instructions about ordering replacement kits through the data system
- **Replaced with:** “To place an order for a replacement kit, contact the DCC (Razan Yasin [ryasin@jhsph.edu; 443-287-5796] or the main number at the DCC (443-287-3170))”
- **Added:** Complete one new Device Distribution and Return (DD) form “to record the return of the old kit and the issuing of a new kit.
 - If the exchange occurs on the same day, please enter the ID of the “kit dispensed” on item 7 of the form”

6.1.10.2 *Other accessories replacement*

- **Added:** “If any of the accessories need to be replaced, keep the older item in a zip lock bag and label it with Participant ID, Kit ID, and date. Keep the zip lock bag in the participant kit box and ship with the rest of the equipment after V7”

6.2.2 *Temporary or permanent termination of study treatment*

- **Added:** “It is recommended to encourage the participant to come for the follow up clinic visits even if they are not using the device. If the participant informs the clinic that they will not be coming back for the rest of the study visits, complete the exit tasks with the participant (Section 2.9)”

6.2.3 *Unmasking*

- **Deleted** instructions for unmasking through the data system
- **Added:** “Complete Unmasking (UM) form”

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| 7.1 | <p><i>HRCT – Design and outcome measures</i></p> <ul style="list-style-type: none"> • Added: “Substudy Principal Investigator: Dr. Robert Brown” |
| 7.6 | <p><i>HRCT visits</i></p> <p><i>Screening visit (V1) of the main CPAP study:</i></p> <ul style="list-style-type: none"> • Changed 30 “seconds” to 30 “minutes” <p><i>Tasks (for both HRCT S1 and S2)</i></p> <ul style="list-style-type: none"> • Added: “do NOT burn the reader software” on the disks |
| 7.8 | <p><i>HRCT certification requirements</i></p> <ul style="list-style-type: none"> • Clarified that one scanner is to be used for the HRCT substudy. |
| 7.8.1 | <p><i>Phantom scanning requirements</i></p> <p><i>Equipment and materials</i></p> <ul style="list-style-type: none"> • Changed “COPDGene” Lung Phantom to “CPAP” Lung Phantom <p><i>Tasks</i></p> <ul style="list-style-type: none"> • Added: “do NOT burn the reader software” |
| 7.8.1.1 | <p><i>Phantom scanning procedure</i></p> <ul style="list-style-type: none"> • Added version date (1 Jan 2013) to refer to the updated Appendix A |
| 7.8.2 | <p><i>Scanner requirements</i></p> <ul style="list-style-type: none"> • Changed instructions to reflect that each site should use only ONE scanner for the HRCT substudy. The phantom MUST be scanned for the scanner to be used. Complete a Phantom Acquisition (PT) form |
| 7.9.4 | <p><i>HRCT Contraindications and participant assessment</i></p> <ul style="list-style-type: none"> • Deleted “or less” from “Inability to lie flat for 30 minutes” |
| 8.1 | <p><i>List of forms, questionnaires, logs</i></p> <ul style="list-style-type: none"> • Added Quality of life questionnaires (WQ): Assess general and asthma-specific quality of life • Deleted: DNA Specimen Transmittal sheet • Changed specimen transmittal sheet purpose to: “Accompanies specimens ready to be shipped: printed directly from the data system after specimens are scanned)” |
| 8.3 | <p><i>ID codes</i></p> <p><i>Personal Identification Number (PIN)</i></p> <ul style="list-style-type: none"> • Deleted: PIN is activated “by DCC staff” • Added: PIN is activated “to access the ACRC website automatically after registration” • Deleted: “contact DCC staff to activate the PIN” <p><i>Clinical Center ID</i></p> <ul style="list-style-type: none"> • Changed “Hofstra University School of Medicine” to “Hofstra North Shore – LIJ School of Medicine” • Changed “National Jewish Medical and Research Center” to “National Jewish Health” |

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| 10.2 | <p><i>Satellite clinics</i></p> <ul style="list-style-type: none"> • Added: Satellite clinics are an adjunct to their main clinical center (see Section 8.3 for list of main clinical centers and respective ID codes) “but need to be certified separately after the review and approval of the lead coordinator at the main clinical center” |
| 10.4 | <p><i>Data audits and data quality queries</i></p> <ul style="list-style-type: none"> • Added: “Methacholine audits <ul style="list-style-type: none"> ○ All methacholine KoKo printouts will be audited by the DCC for correctness and completeness. Clinics are to submit methacholine reports to the DCC for overreading on a weekly basis. Reports will be graded on three criteria as follows: <ol style="list-style-type: none"> 1. Were the baseline maneuvers acceptable as per the study MOP? 2. Was the appropriate number of efforts performed at each stage? 3. Was the challenge halted at the appropriate stage? ○ Each criterion is graded on a pass/fail basis; scores are then totaled and converted to a letter grade for the purpose of clinical feedback. Meeting all three criteria is marked as an “A” (3/3), two criteria is a “B” (2/3), one is a “C” (1/3), and failing to meet any of the criteria on a single challenge will result in a “D” grade (0/3). ○ The DCC will issue a monthly report to clinics informing them of their grades to date and of any late or outstanding reports. The DCC may also follow up individually with clinics or staff to address performance or operational issues in more detail. Coordinators should send all Methacholine KoKo reports to Razan Yasin (ryasin@jhsph.edu).” |
| 11.2 | <p><i>ACRC Centers</i></p> <ul style="list-style-type: none"> • Added: “Columbus Children’s Hospital” to OSU |
| Appendices | <p><i>Appendix A: Phantom scanning procedures</i></p> <ul style="list-style-type: none"> • Per PPM# 13 – attached the updated version of Appendix A – 1 Jan 13 <p><i>Appendix B: HRCT scanning procedures</i></p> <p><i>Section 6</i></p> <ul style="list-style-type: none"> • Changed: the value of natural radiation we are exposed to all the time gives you about “3 mSv (0.3 rem)” each year (<i>previously 0.3 mSv and .03 rem</i>) <p><i>Section 7</i></p> <ul style="list-style-type: none"> • Added: “Please save the DICOM images without any reader on the disks” |
| Throughout | <p>Other minor clarifications and abbreviations throughout the document Other grammatical errors/typos were fixed throughout the document for clarification</p> |

1. Study overview

1.1. Design and outcome measures

Title

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

Objective

To test the primary hypothesis that twelve weeks of treatment with nocturnal CPAP will decrease airways reactivity to methacholine.

To test the secondary hypothesis that nocturnal CPAP will improve asthma symptoms and will be well-tolerated.

To explore the questions:

- Is there is 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)?

Type of study

- Randomized, blinded, three arm parallel sham-controlled phase II trial
- Multicenter, 18 clinical centers
- Fixed sample size; 192

Study treatment

- Nocturnal CPAP 10 cmH₂O – *high*
- Nocturnal CPAP 5 cmH₂O – *medium*
- Nocturnal Sham CPAP (less than 1 cmH₂O) – *low*
- Allocation ratio 1:1:1
- For use every night

Primary outcome

- Change in PC₂₀

Secondary Outcome Measures

- Change in Asthma Symptom Score measured by the Asthma Control Test (ACT)
- Change in FEV₁ measured by pre-diluent spirometry before each methacholine test
- Changes in nocturnal asthma awakenings, and asthma symptom free days recorded daily on the participant's diary card
- Rates of episodes of poor asthma control (EPAC)* determined by data collected on the diary cards and during visits
- The Asthma Symptom Utility Index (ASUI)
- Change in asthma-specific quality of life measured by the Marks Asthma Quality of Life Questionnaire (Marks AQLQ)
- Side effects/adverse events assessed by to open-ended questions and questionnaires


- Change in sleep quality measured using Sleep questionnaires: Epworth Sleepiness Scale and Pittsburgh Sleep Quality Index. Multivariable Apnea Prediction (MAP) Questionnaire will be used to exclude baseline sleep apnea. The Berlin Sleep Questionnaire will be used as an external measure of the MAP
- Change in inflammatory markers measured to test whether treatment effects might be mediated by anti-inflammatory actions of CPAP
- Sino Nasal Questionnaire – 6 week to assess sinus symptoms
- Adherence of CPAP use assessed using an SD card and daily diary cards

Other data

- Baseline questionnaires to ascertain demographics, general information and health
- Genotyping performed on blood collected at V2
- Interval health history recorded at each clinic visit
- Exit interviews

*EPAC 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)*

 *Note:* An arbitrary two-week interval will be required before a new EPAC is counted to distinguish it from an extension or relapse of a prior EPAC


1.2. Eligibility criteria

The goal is to enroll 192 participants 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.

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 FEV₁ greater than or equal to 75% predicted at V1 (to minimize the likelihood that variability in FEV₁ will preclude participants from having methacholine challenges in follow-up visits)
- Airways reactivity: Methacholine bronchial challenge with PC₂₀ less than or equal 8 mg/mL for FEV₁ 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

 *Note:* 'on' prescribed therapy does not necessarily mean subject must be currently using medication. Subject however must be prescribed a medication by a physician for at least the past 12 months and is stable to be enrolled in the study. If a subject does not seem stable and is having asthma problems due to not using their medication, it is best not to enroll the subject at this time.

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; 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
 - (If participant used CPAP equivalents, such as BiPAP, contact the DCC. This will be determined on a case by case basis)
- Homelessness, lack of telephone access, or intention to move within the next 4 months of the trial

For blinding purposes, members from the same household cannot participate in the study at the same time. Also, subjects cannot participate in the CPAP trial if they share the same bed with an individual who uses CPAP

1.3. Study visit time windows and data collection schedule

| Visit | V1 | V2 | V3* | V4 | V5 | V6 | V7 |
|----------------------------------------------------------|---------|----|----------|-----|-----|------|-------|
| Target (weeks) | -2 | 0 | 1 day | 1 | 6 | 12 | 14 |
| Visit Window (weeks) | -4 to 0 | 0 | 1-3 days | 1-3 | 3-9 | 9-13 | 13-16 |
| 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- 11 step | • | | | | • | • | • |
| Asthma Control (ACT, ASUI) | | • | | | • | • | • |
| Asthma Quality of Life Measures (Marks AQLQ) | | • | | | • | • | • |
| MAP Questionnaire, Berlin Sleep Questionnaire | • | | | | | | |
| Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index | • | | | | • | • | • |
| Sino-Nasal Questionnaire (SNQ-6)- 6 week | | • | | | • | • | • |
| Quality of Life Questionnaires (WQ) | | • | | | | • | |
| Exit interview | | | | | | • | • |
| Physical examination | | • | | | | | |
| Randomization, device & mask dispensing | | • | | | | | |
| Blood for DNA / serum storage | | • | | | | | |
| Blood for Inflammatory Profile | | • | | | | • | • |
| Exhaled nitric oxide (eNO) | | • | | | | • | • |
| Return CPAP device & mask | | | | | | • | |
| Collect CPAP SD cards | | | | • | • | • | |
| CPAP Troubleshoot | | • | • | • | • | | |
| Adverse event screen | | • | • | • | • | • | • |
| Return asthma Diary Cards | | • | | • | • | • | • |

* V3 is a phone call between V2 and V4

A minimum of one week separation is required between visits after V4

(V#) Visit Number
 (CL) Clinic Visit
 (PH) Phone Visit
 (pre-BD) pre-Bronchodilator

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

2. Study visits/contacts

2.1. Order of procedures

Overall study visits


There is no specified order for study visit procedures except as noted below. However, it is recommended that the quality of life, sleep, and asthma control questionnaires be completed at the beginning of the visit so that the responses are not influenced by study visit procedures

Randomization visit

The online randomization should be completed after all other V2 procedures and lung function tests are performed (including questionnaires, specimen collection, and review of CPAP Diary Cards (DC), if any), and before distributing study kit to participant

Required order of lung function procedures

- Procedures for exhaled nitric oxide, and spirometry (pre-bronchodilator - part of 11 step-methacholine challenge test) can interfere with each other. Exhaled nitric oxide (eNO) must be measured before spirometry or at least one hour after return to baseline lung function as documented by spirometry
 - Exhaled nitric oxide (eNO)
Conducted before
 - Pre-bronchodilator spirometry (11 step-methacholine challenge test)

 Note: Not all of these tests are done at each visit

- A pregnancy test is to be conducted, if applicable, prior to methacholine challenge testing.
- Spirometry (pre-bronchodilator only) is to be conducted prior to methacholine challenge testing. Albuterol is to be held prior to conducting methacholine challenge testing - short acting should be held 4 hours prior to methacholine challenge testing, long acting should be held 24 hours prior to methacholine challenge testing. See Section 4.2.6 for a complete list of medication holds.
- **Participants should be encouraged to use their CPAP device the night before methacholine testing.**

Required order for blood draws

- Collection of tubes should be conducted in the order as listed:
 - Blood for CRP and IL-6 (in tiger top serum separator tube).
 - Blood for eosinophil count (in 6 mL lavender top tube).
- Blood for DNA (in 10 mL lavender top tube). Collection of blood at Randomization (V2) should be performed after confirming participant eligibility, but before randomization and kit assignment.

Timing for methacholine challenge testing and blood draws

Both methacholine testing results and IL-6 levels can vary during a day. Whenever possible, clinic visits should be scheduled for the same time of day to avoid diurnal variation in these measurements.

Trial Schema terminology

| Pre-screening | Registration | Enrollment | Randomization |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> ▪ Participant information is entered into the Participant Screening Log (PS). ▪ Participant may not have signed consent. | <ul style="list-style-type: none"> ▪ A participant is <i>registered</i> when the participant ID is assigned. | <ul style="list-style-type: none"> ▪ Signs consent ▪ Participant is evaluated for eligibility. ▪ Completes V1, with methacholine challenge completed or planned to be completed | <ul style="list-style-type: none"> ▪ Participant is assigned study treatment. |

Definition of enrollment in CPAP: completed V1, with a methacholine challenge completed or planned to be completed.

2.2. Screening visit (V1)

Overview

Screening includes the consenting process, initial evaluation for eligibility, assessing risk of sleep apnea and quality of sleep, pregnancy testing (for women of child bearing potential), pre-BD spirometry and the 11-step methacholine challenge test. It will also include the distribution of CPAP Diary Cards (DC), Peak Flow Meters, and Asthma Action Plan Card (AAP).

Time frame

- Target: 2 weeks prior to Randomization (V2)
- Window: 0 to 4 weeks prior to Randomization (V2)
- Duration: 4 hours

Equipment and materials

- Informed consent(s)
- V1 forms and V1 checklist (VC1)
- CPAP practice kit (sample device and masks)
- Spirometer
- Methacholine challenge test instructions, supplies, and equipment
- Participant binder, ACRC tote bag and magnet
- Mini-Wright Peak Flow Meters
- General asthma education materials

Tasks

- Explain study to participant.
- Review consent with participant or parent/guardian, and assent (assent required for participants less than 18 years of age; may be part of consent form per local IRB requirements).
- Sign and date consent, and assent (if applicable); provide copy to participant.
- Have participant complete a release statement as applicable (see sample release statement in Section 3.6.2 of MOP).
- Show participant sample CPAP device and fit them with the masks.
- Participants should see and fit the masks at the screening visit. This will give them an idea of what is expected from them in the study.
 - Coordinators should assess the participant's readiness and confidence to use CPAP every night for 12 weeks. If the participant does not feel comfortable wearing the mask at the screening visit, or is not willing to use it for the next 12 weeks, it might be better not to enroll the participant in the study at this time.
 - **For blinding purposes, DO NOT hook up the mask to the device, and do not turn on the sample CPAP device while participant is wearing the sample mask. Sample devices and masks are used for demonstration purposes only.**

HRCT

- If clinic is participating in the HRCT substudy, explain substudy to participant, review HRCT consent, sign and date HRCT consent; provide copy to participant.
- Participant must be 18 years of age or older to participate in the substudy (*Consent may be part of the main CPAP consent per local IRB requirements*)

Sample masks should be disinfected between participants. Refer to MOP Section 5.5

- Assign participant an ID using the next sequentially numbered label on Clinic Label Sheet (see example in Section 8.3.1 of MOP).
 - Register participant ID in CPAP data system.
 - Place label in box on item 2 of Screening (SC) form.
- Complete Participant Information (PI) form.
- Have participant complete:
 - Multivariable Apnea Prediction Questionnaire (MP).
 - Calculate the sleep apnea probability using the online calculator.
 - If probability of sleep apnea is greater than or equal to 20%, participant is not eligible.
 - Berlin Sleep Questionnaire (BQ).
 - Epworth Sleepiness Scale (ES) questionnaire.
 - Pittsburgh Sleep Quality Index (SQ) questionnaire.
- Complete forms
 - Screening (SC) form
 - Baseline Asthma and Medical History (BA) form
- Distribute and review:
 - CPAP Schedule of Visits (SOV) with dates and times for all subsequent visits recorded, if possible.
 - Participant binder.
 - Peak Flow Meter and Instructions for Measuring Peak Flow (IPF).
 - Provide instruction, both verbal and written, on how to use.
 - Have participant perform 3 peak flows, record the highest of three efforts Screening (SC) form and on Asthma Action Plan Card (AAP).
 - Note: Disposable one way valve mouthpieces can be used for peak flow at V1
 - Instruct participant to bring peak flow meter to all study visits.
 - Asthma Action Plan Card (AAP).
 - Fill in personal best peak flow from the highest of three efforts, and calculate zone cut-offs using the online calculator on the CPAP website. Record zone cut-offs on the card and give to participant. Refer to MOP Section 8.2.2.
 - CPAP Diary Cards (DC) and Instruction for CPAP Diary Card (IDC). Refer to MOP Section 8.2.1.
 - Canvas bag with ACRC logo and ACRC magnet.
 - General Asthma education materials.
 - Instructions for Preparation for Methacholine Challenge Test (IMC).
- Conduct or schedule 11 step-Methacholine challenge testing procedures.
 - Methacholine challenge may be conducted before or after the screening visit is completed.
 - Conduct a pregnancy test, if applicable, before the methacholine challenge test.
 - Collect pre-bronchodilator spirometry data and record on Methacholine Challenge Testing (MC) form.
 - If FEV₁ is less than 75% predicted, participant is not eligible; terminate screening; notify asthma care provider.
 - Conduct 11- step methacholine challenge according to procedures detailed in MOP Section 4, and record results on the Methacholine Challenge Testing (MC) form.
 - Height and weight should be measured the same day of the methacholine test.
 - It is recommended to use the Methacholine Testing Worksheet (MW).
 - If PC₂₀ is greater than 8 mg/mL for FEV₁, participant is not eligible; terminate the challenge after the 16mg/mL concentration; notify asthma care provider.

- Pre-bronchodilator spirometry and methacholine challenge testing may be conducted on a separate day than the other V1 procedures/questionnaires. Participants will continue to V2 if they will meet all eligibility criteria.
- After the visit, send Primary Physician Introduction letter to primary asthma physician (sample letter in Section 3.6.1 of the MOP). Include a copy of methacholine results.
- Data enter Screening (SC) form into the data system before the randomization visit if the participant is eligible (even if the methacholine challenge test is still scheduled). The Screening (SC) form must be data entered immediately after completing a successful V1 (i.e. no STOPS on the SC form) and before a participant can be randomized at V2.
- Update Participant Screening Log (PS).
- Data enter the remaining forms within 10 working days for eligible participants.
- If screen failure or incomplete screening:
 - Do not data enter SC form or other data forms.
 - Update Participant Screening Log (PS).
 - Records of all screen failures should be kept with study materials.

HRCT

If participant consented for the HRCT substudy, send Primary Physician Introduction letter informing the physician about participation in substudy (this may be part of the main CPAP study **letter as well**)

Note: If there is a STOP on the Screening (SC) form, do not data enter the form, but make sure you update the Participant Screening Log (PS) to reflect the reason why participant failed screening.

Forms (abbreviation)

- Baseline Asthma and Medical History (BA).
- CPAP Diary Card (DC)
- Methacholine Challenge Testing (MC).
- Participant Information (PI)*.
- Screening (SC) form.

Questionnaires (abbreviation)

- Epworth Sleepiness Scale (ES)
- Berlin Sleep Questionnaire (BQ)
- Multivariable Apnea Prediction (MAP) Questionnaire (MP)
- Pittsburgh Sleep Quality Index (SQ)

Information Sheets (abbreviation)

- Asthma Action Plan Card (AAP)*
- Instructions for CPAP Diary Cards (IDC)*
- Instructions for Methacholine Challenge Test (IMC)*
- Instructions for Measuring Peak Flow (IPF)*
- CPAP Schedule of Visits (SOV)*

Logs and Administrative forms (abbreviation)

- Methacholine Challenge Worksheet (MW)*
- Participant Screening Log (PS)
- CPAP V1 task checklist (VC1)*

**Not entered into database*

2.3. Randomization visit (V2)

Overview

V2 includes confirmation of eligibility, brief physical exam, asthma related questionnaires, sinus symptoms questionnaire, blood draw, exhaled nitric oxide, and, if applicable, HRCT scanning for clinics participating in the substudy. For participants that are randomized the visit also includes the dispensing of CPAP devices and masks and initiating CPAP therapy.

Time frame

- Target: 2 weeks after Screening visit (V1)
- Window: 0 to 4 weeks after V1
- Duration: 3-4 hours

Equipment and materials

- V2 forms and V2 checklist (VC2)
- Assigned study kit
- Soap
- Distilled water, *if applicable*
- NIOX MINO
- Specimen collection, processing and storage supplies
- CPAP Diary Cards (DC), if needed
- CPAP Wallet Card
- CPAP Participant Instructional Video on flash drive - *Guide to using your CPAP*.

Tasks

- Administer the Asthma Symptom Utility Index (AS).
- Have participant complete self-administered questionnaires:
 - Asthma Control Test (TA) questionnaire.
 - Marks Asthma Quality of Life Questionnaire (MQ).
 - Sino-Nasal Questionnaire (SNQ-6) – 6 week (NQ).
 - Quality of Life Questionnaires (WQ)
- Complete physical exam procedures and Physical Exam (PE) form.
- Collect CPAP Diary Cards (DC) distributed at V1.
 - Review CPAP Diary Cards with participant, provide feedback as needed.
 - Edit as appropriate.
- Collect interval medical history data, record on Clinic Visit (CV) form.
- Measure exhaled nitric oxide (eNO), record on Nitric Oxide (NO) form.
- Record methacholine challenge testing results for eligibility on the Randomization (RZ) form.
- Review participant eligibility for study treatment using Randomization (RZ) form.
- **If participant meets all eligibility criteria and before assigning a study kit**, collect, process, and store blood specimens for inflammatory (required) and genetic (optional) analyses per MOP Section 4.4.
- **If participant meets all eligibility criteria**, key Randomization (RZ) form into the data system.
 - On the main data system page, perform treatment assignment by completing the ‘CPAP Treatment Assignment (Randomization)’. This will provide the assigned kit ID for the participant. This step must be completed before distributing the study kit to the participant.

- Record the study kit ID on the Randomization (RZ) form (generated from data system).
- Record the study kit ID on the Device Dispensing and Return (DD) form.
- Ensure that all items in the study kit have the same kit ID (Device, nasal mask, nasal pillows, SD cards).
- Distribute assigned CPAP study device to participant and review instructions for set up and safety tips. Refer to MOP Section 5.
 - Label device and other accessories with Participant ID.
 - Choose the proper mask for the participant. **Participant should be fitted to both types of masks (nasal mask and nasal pillows)**. Once participant is comfortable with a type and size mask, dispense **only one** mask to them to take home.
 - Initiate CPAP therapy with participant.
 - Resolve any problems with the mask or device.
 - Record ID and type of mask dispensed to participant on Device Dispensing and Return (DD) form.
- Distribute and review:
 - CPAP Device User Instructions (ICD).
 - CPAP Diary Cards (DC) and Instructions for Diary Cards (IDC).
 - Soap.
 - Distilled water, *if applicable*.
 - CPAP Wallet Card.
 - CPAP Participant Instructional Video on flash drive.
- Screen for adverse events.
- Review instructions for use of Asthma Action Plan Card (AAP).
- Complete Device Dispensing and Return (DD) form.
- Complete Study Kit Accountability Log (DA).
- Key remaining forms into CPAP data system within 10 working days.
- If participant is not eligible to be randomized, update the Participant Screening Log (PS). Do not data enter the Randomization (RZ) form.

Forms (abbreviation)

- Clinic Visit (CV)
- CPAP Diary Card (DC)
- Device Dispensing and Return (DD)
- Nitric Oxide (NO)
- Physical Exam (PE)
- Randomization (RZ)

Information Sheets (abbreviation)

- Asthma Action Plan Card (AAP)*
- CPAP Device User Instructions (ICD)*
- Instructions for CPAP Diary Cards (IDC)*
- CPAP Wallet Card*
- CPAP Participant Instructional Video on flash drive*

Questionnaires (abbreviation)

- Asthma Symptom Utility Index (AS)
- Marks Asthma Quality of Life Questionnaire (MQ)
- Sino-Nasal Questionnaire (SNQ-6) – 6 week (NQ)
- Asthma Control Test (TA)
- Quality of Life Questionnaires (WQ)

HRCT

For participants enrolled in the HRCT substudy, S1 should be completed after randomization in the main CPAP study, and before participant initiates CPAP use. Refer MOP Section 7.

Log/Administrative forms (abbreviation)

- Study Kit Accountability Log (DA)*
- Participant Screening Log (PS)*
- Unusual Event (UE) form or Serious Adverse Event (SR) form if applicable
- CPAP V2 task checklist (VC2)*

* *Not entered into database*

2.4. Phone visit (V3)

Overview

Participant is contacted by phone 1 day after randomization. The primary purpose of this visit is to assess participant use of the CPAP device and fit of the CPAP mask, provide troubleshooting instructions for participants if they are having problems with the device or mask, and provide adherence counseling for CPAP use and CPAP Diary Cards (DC) completion. This visit is also used to assess safety concerns.

Time frame

- Target: 1 day after randomization
- Window: needs to occur between Randomization and V4
- Duration: 15 minutes

Equipment and materials

- V3 form (PC)

Tasks

- Conduct telephone interview using Phone Contact (PC) form.
 - Note: Do not complete a PC form for any additional unscheduled calls.*
- Resolve any problems the participant may be having with the device or mask.
- If a clinic visit is needed to fit a different mask type, schedule a clinic visit with participant for refitting. Conduct Visit 4 (V4) a week after randomization (target window is 1-2 weeks).
- Screen for adverse events.
- Adherence counseling:
 - Remind participant to use the CPAP device every night.
 - Remind participant to refer to their CPAP Device User Instructions (ICD) or CPAP. Participant Instructional Video on flash drive.
 - Remind participant to use their Asthma Action Plan Card (AAP), if necessary.
 - Review instructions for completion of CPAP Diary Cards (DC).
 - Reinforce peak flow monitoring.
 - Discuss any other potential problems participant may have with study procedures.
- Confirm date of first follow-up visit (V4) and remind participant to bring:
 - The CPAP device and mask.
 - Peak Flow Meter.
 - CPAP Diary Cards (DC).

Form (abbreviation)

- Phone Contact (PC)

Log/Administrative forms (abbreviation)

- Unusual Event (UE) form or Serious Adverse Event (SR) form if applicable

2.5. Adherence clinic visit (V4)

Overview

The primary purpose of this visit is to assess participant adherence to CPAP and the use of the device, assess mask fit, resolve any problems with the CPAP device or mask, and provide adherence counseling.

Time frame

- Target: 1 week after randomization
- Window: 1 to 3 weeks after randomization
- Duration: 1-2 hours

Equipment and materials

- V4 forms and V4 checklist (VC4)
- Replacement SD card
- Original assigned study kit
- CPAP Diary Cards (DC), if needed

Tasks

- Collect CPAP Diary Cards (DC) distributed at V2.
 - Review CPAP Diary Cards (DC) with participant, provide feedback as needed.
 - Edit as appropriate.
- Collect interval medical history data, record on Clinic Visit (CV) form.
- Adherence monitoring – refer to Section 6.1.9
 - Remove SD card A from the device and ship to the DCC immediately after the visit.
 - Insert a new SD card B into the device.
- Inspect the assigned CPAP device.
 - Make sure filter and water tub are in place and is in good condition.
- Review instructions of using the CPAP device and mask with participant.
- Troubleshoot and resolve any problems participant may have with device or mask.
- Fit participant to a different mask if they are having trouble with the original mask dispensed at V2.
 - Record ID and type of mask dispensed and returned on Device Dispensing and Return (DD) form.
- Have participant demonstrate the device set up and mask fitting.
- Review safety tips with participant.
- Adherence counseling. Remind participant:
 - Their use of device is monitored on the study device.
 - They are getting humidified and filtered air by using the study device.
- Review:
 - Instructions for use of Asthma Action Plan Card (AAP).
 - Instructions for Peak Flow Meter measurements.
 - Study visit schedule.
- Distribute:
 - CPAP Diary Cards (DC), and review Instructions for CPAP Diary Cards (IDC).
 - Instructions for Methacholine Challenge Test (IMC).
 - Soap, if needed.

- Screen for adverse events.
- Key forms into CPAP data system within 10 working days.
- After the DCC reviews card (A), the DCC will send a CPAP compliance report showing device usage during the week after randomization as well as recommendations for the participant.
 - Review the compliance report, compare it to the adherence flowcharts, and contact the participant if needed to resolve any issues with CPAP adherence
 - Show the participant their usage report at their next clinic visit
 - Contact the DCC for any questions

Forms (abbreviation)

- Clinic Visit (CV)
- CPAP Diary Card (DC)
- Device Dispensing and Return (DD)

Information Sheets (abbreviation)

- Instructions for Methacholine Challenge Test (IMC)*

Log/Administrative forms (abbreviation)

- Unusual Event (UE) form or Serious Adverse Event (SR) form if applicable
- CPAP V4 task checklist (VC4)*

* *Not entered into database*

2.6. Follow up clinic visit (V5)

Overview

The purpose of this visit is to collect data (interval history, 11-step methacholine challenge test, and questionnaires). It is also to resolve any problems with the CPAP device or mask, and provide adherence counseling.

Time frame

- Target: 6 weeks after randomization
- Window: 3 to 9 weeks after randomization
- Duration: 2-3 hours

Equipment and materials

- V5 forms and V5 checklist (VC5)
- Replacement SD card
- Original assigned study kit
- Spirometer
- Methacholine challenge test supplies, and equipment
- CPAP Diary Cards (DC), if needed

Tasks

- Administer the Asthma Symptom Utility Index (AS).
- Have participant complete:
 - Epworth Sleepiness Scale (ES) questionnaire.
 - Pittsburgh Sleep Quality Index (SQ) questionnaire.

- Sino-Nasal Questionnaire (SNQ-6)- 6 week (NQ).
- Marks Asthma Quality of Life Questionnaire (MQ).
- Asthma Control Test (TA) questionnaire.
- Collect CPAP Diary Cards (DC) distributed at V4.
 - Review CPAP Diary Cards (DC) with participant, provide feedback as needed.
 - Edit as appropriate.
- Adherence monitoring – refer to Section 6.1.9.
 - Show the participant their usage report based on their SD card (A)
 - Remove SD card B from the device and ship to the DCC immediately after the visit
 - Insert a new SD card C into the device.
- Inspect the assigned CPAP device.
 - Make sure filter and water tub are in place and is in good condition.
- Collect interval medical history data, record on Clinic Visit (CV) form.
- Conduct 11 step-Methacholine challenge testing procedures.
 - Conduct a pregnancy test, if applicable, before the methacholine challenge test.
 - Collect pre-bronchodilator spirometry data and record on Methacholine Challenge Testing (MC) form.
 - If FEV₁ is less than 70% predicted, do not conduct the methacholine challenge testing.
 - Conduct 11- step methacholine challenge according to procedures detailed in MOP Section 4.2, and record results on the Methacholine Challenge Testing (MC) form.
 - Height and weight should be measured the same day of the methacholine test.
 - It is recommended to use the Methacholine Testing Worksheet (MW).
- Troubleshoot and resolve any problems participant might have with device or mask.
- Fit participant to a different mask if they are having trouble with the original mask dispensed.
 - Record ID and type of mask dispensed and returned on Device Dispensing and Return (DD) form.
- Review instructions of using the CPAP device and mask with participant.
- Have participant demonstrate the device set up and mask fitting.
- Review safety tips with participant.
- Adherence counseling. Remind participant:
 - Their use of device is monitored on the study device.
 - They are getting humidified and filtered air by using the study device.
- Review:
 - Instructions for use of Asthma Action Plan Card (AAP).
 - Instructions for Peak Flow Meter measurements.
 - Study visit schedule.
- Distribute:
 - CPAP Diary Cards (DC), and review Instructions for CPAP Diary Cards (IDC).
 - Instructions for Methacholine Challenge Test (IMC).
 - Soap, if needed.
- Screen for adverse events.
- Key forms into CPAP data system within 10 working days.
- After the DCC reviews SD card (B), the DCC will send a CPAP compliance report showing device usage as well as recommendations for the participant.
 - Review the compliance report, compare it to the adherence flowcharts, and contact the participant if needed to resolve any issues with CPAP adherence
 - Show the participant their usage report at their next clinic visit

- Contact the DCC for any questions

Forms (abbreviation)

- Clinic Visit (CV)
- CPAP Diary Card (DC)
- Device Dispensing and Return (DD)
- Methacholine Challenge Testing (MC)

HRCT

For participants enrolled in the HRCT substudy, S2 should be completed 10 to 12 weeks after randomization in the main CPAP study. Refer to MOP Section 7.

Questionnaires (abbreviation)

- Asthma Symptom Utility Index (AS)
- Epworth Sleepiness Scale (ES)
- Marks Asthma Quality of Life Questionnaire (MQ)
- Sino-Nasal Questionnaire (SNQ-6) – 6 week (NQ)
- Pittsburgh Sleep Quality Index (SQ)
- Asthma Control Test (TA)

Information Sheets (abbreviation)

- Instructions for Methacholine Challenge Test (IMC)*

Log/Administrative forms (abbreviation)

- Methacholine Challenge Testing worksheet (MW)*
- Unusual Event (UE) form or Serious Adverse Event (SR) form if applicable
- CPAP V5 task checklist (VC5)*

* *Not entered into database*

2.7. End of treatment visit (V6)

Overview

The purpose of this visit is to document CPAP treatment termination, return study device and mask to clinic, collect specimens, conduct 11-step methacholine challenge test, and measure eNO

Time frame

- Target: 12 weeks after randomization
- Window: 9 to 13 weeks after randomization
- Duration: 3-4 hours

Equipment and materials

- V6 forms and V6 checklist (VC6)
- NIOX MINO
- Original assigned study kit
- Spirometer
- Methacholine challenge test supplies, and equipment
- Specimen collection, processing and storage supplies
- CPAP Diary Cards (DC), if needed

Tasks

- Administer the Asthma Symptom Utility Index (AS).
- Have participant complete:
 - Epworth Sleepiness Scale (ES).
 - Pittsburgh Sleep Quality Index (SQ).
 - Sino-Nasal Questionnaire (SNQ-6)- 6 week (NQ).
 - Marks Asthma Quality of Life Questionnaire (MQ).
 - Quality of Life Questionnaires (WQ)
 - Asthma Control Test (TA).
 - Study Evaluation (EV).
- Collect CPAP Diary Cards (DC) distributed at V5.
 - Review CPAP Diary Cards (DC) with participant, provide feedback as needed.
 - Edit as appropriate.
- Adherence monitoring – refer to Section 6.1.9.
 - Review the CPAP compliance report with the participant based on SD Card (B)
 - Remove SD card C from the device and ship to the DCC immediately after the visit.
- Collect blood specimen for inflammatory biomarkers (required) per MOP Section 4.4.
- Collect interval medical history data, record on Clinic Visit (CV) form.
- Measure exhaled nitric oxide (eNO), record on Nitric Oxide (NO) form.
- Conduct 11 step-Methacholine challenge testing procedures.
 - Conduct a pregnancy test, if applicable, before the methacholine challenge test.
 - Collect pre-bronchodilator spirometry data and record on Methacholine Challenge Testing (MC) form.
 - If FEV₁ is less than 70% predicted, do not conduct the methacholine challenge testing.
 - Conduct 11- step methacholine challenge according to procedures detailed in MOP Section 4, and record results on the Methacholine Challenge Testing (MC) form.

- Height and weight should be measured the same day of the methacholine test.
- It is recommended to use the methacholine testing worksheet (MW).
- Inspect the returned CPAP device.
 - Make sure filter and water tub are in place and is in good condition.
 - Make sure all device parts are returned to clinic (See MOP section 6.1.5).
- Place all returned device and accessories in the original study kit box.
- Complete a Device Dispensing and Return (DD) form. Record ID and type of mask returned.
- Complete a Treatment Termination (TT) form.
- Record on Study Kit Accountability Log (DA).
- Review:
 - Instructions for use of Asthma Action Plan Card (AAP).
 - Instructions for Peak Flow Meter measurements.
 - Study visit schedule.
- Distribute:
 - CPAP Diary Cards (DC), and review Instructions for CPAP Diary Cards (IDC).
 - Instructions for Methacholine Challenge Test (IMC).
- Screen for adverse events.
- Key forms into CPAP data system within 10 working days.

Forms (abbreviation)

- Clinic Visit (CV)
- CPAP Diary Card (DC)
- Device Dispensing and Return (DD)
- Methacholine Challenge Testing (MC)
- Nitric Oxide (NO)
- Treatment Termination (TT)

HRCT

If S2 is scheduled on the same day of V6, it must be completed PRIOR to the methacholine challenge testing. Refer to MOP Section 7.

Questionnaires (abbreviation)

- Asthma Symptom Utility Index (AS)
- Epworth Sleepiness Scale (ES)
- Study Evaluation (EV)
- Marks Asthma Quality of Life Questionnaire (MQ)
- Sino-Nasal Questionnaire (SNQ-6) – 6 week (NQ)
- Pittsburgh Sleep Quality Index (SQ)
- Asthma Control Test (TA)
- Quality of Life Questionnaires (WQ)

Information Sheets (abbreviation)

- Instructions for Methacholine Challenge Test (IMC)*

Log/Administrative forms (abbreviation)

- Study Kit Accountability Log (DA)*
- Methacholine Challenge Testing worksheet (MW)*
- Unusual Event (UE) form or Serious Adverse Event (SR) form if applicable
- CPAP V6 task checklist (VC6)*

* *Not entered into database*

2.8. Final washout visit (V7)

Overview

The purpose of this visit is to collect data, conduct 11-step methacholine challenge testing, eNO, specimen collection, and complete questionnaires after a 2-week washout period from CPAP treatment.

Time frame

- Target: 14 weeks after randomization
- Window: 13 to 16 weeks after randomization
- Duration: 3-4 hours

Equipment and materials

- V7 forms and V7 checklist (VC7)
- NIOXMINO
- Spirometer
- Methacholine challenge test supplies, and equipment
- Specimen collection, processing and storage supplies
- *Original assigned kit box, if not returned at V6*

Tasks

- Administer the Asthma Symptom Utility Index (AS).
- Have participant complete:
 - Epworth Sleepiness Scale (ES).
 - Pittsburgh Sleep Quality Index (SQ).
 - Sino-Nasal Questionnaire (SNQ-6) - 6 week (NQ).
 - Marks Asthma Quality of Life Questionnaire (MQ).
 - Asthma Control Test (TA).
 - Study Evaluation (EV)
- Collect CPAP Diary Cards (DC) distributed at V6.
 - Review CPAP Diary Cards (DC) with participant.
 - Edit as appropriate.
- Collect blood specimen for inflammatory biomarkers (required) per MOP Section 4.4.
- Collect interval medical history data, record on Clinic Visit (CV) form
- Measure exhaled nitric oxide (eNO), record on Nitric Oxide (NO) form.
- Conduct 11 step-Methacholine challenge testing procedures.
 - Conduct a pregnancy test, if applicable, before the methacholine challenge test.
 - Collect pre-bronchodilator spirometry data and record on Methacholine Challenge Testing (MC) form.
 - If FEV₁ is less than 70% predicted, do not conduct the methacholine challenge testing.
 - Conduct 11- step methacholine challenge according to procedures detailed in MOP Section 4.2, and record results on the Methacholine Challenge Testing (MC) form.
 - Height and weight should be measured the same day of the methacholine test.
 - It is recommended to use the Methacholine Testing Worksheet (MW).
- If participant returns device and masks at V7 instead of V6, complete a Device Dispensing and Return (DD) form. Record ID and type of mask returned.
 - Remove SD card from the device and ship to the DCC.

- Make sure filter and water tub are in place and in good condition.
- Make sure all device parts are returned to clinic.
- Record on Study Kit Accountability Log (DA).
- Screen for adverse events.
- Give participant:
 - Exit envelope which includes:
 - Participant exit letter (see prototype in Section 3.6.4).
 - Sealed treatment unmasking envelope (attached inside the study kit box).
 - Copy of final methacholine results.
- Send physician exit letter (see prototype in Section 3.6.3) to participant's primary asthma care physician.
- Complete Unmasking (UM) form, if not done previously. Make sure that study kit ID corresponds to the Device Dispensing and Return (DD) form for kit dispensed to the Participant (compare to participant ID).
- Ship study kit back to the Device Distribution Center. Refer to MOP Section 6.
- Key forms into CPAP data system within 10 working days.

Forms (abbreviation)

- Clinic Visit (CV)
- CPAP Diary Card (DC)
- Device Dispensing and Return (DD)
- Methacholine Challenge testing (MC)
- Nitric Oxide (NO)
- Unmasking (UM)

Questionnaires (abbreviation)

- Asthma Symptom Utility Index (AS)
- Epworth Sleepiness Scale (ES)
- Study Evaluation (EV)
- Marks Asthma Quality of Life Questionnaire (MQ)
- Sino-Nasal Questionnaire (SNQ-6) – 6 week (NQ)
- Pittsburgh Sleep Quality Index (SQ) Asthma Control Test (TA)

Log/Administrative forms (abbreviation)

- Study Kit Accountability Log (DA)*
- Methacholine Challenge Testing Worksheet (MW)*
- Unusual Event (UE) form or Serious Adverse Event (SR) form if applicable
- CPAP V7 task checklist (VC7)*

* *Not entered into database*

2.9. Exit tasks

Purpose

To complete study visits with participant and notify them of their assigned study treatment via sealed treatment envelope after participant completes V7.

Timeframe

- Conducted at V7, or when participant notifies clinic they will not come back for study visits.

Materials

- Participant exit letter (see Section 3.6.4 for prototype; may need to be approved by local IRB before use).
- Sealed treatment assignment envelope (found inside the study kit box). Make sure study kit ID corresponds to kit ID dispensed to participant at V2.
- Physician exit letter (see Section 3.6.3 for prototype).
- Copy of final methacholine results.

Tasks

- Make sure participant has returned study CPAP device and masks. (*Study device and masks should have been returned at V6.*)
 - Make sure a Treatment Termination (TT) form and a Device Dispensing and Return (DD) form have been completed at V6, or whenever participant stopped treatment.
 - Have participant complete Study Evaluation (EV) questionnaire.
 - Give the participant:
 - Participant exit letter signed by Study Physician.
 - Sealed treatment assignment envelope.
 - Copy of final methacholine results.
 - Review contents of the exit letter with participant.
 - Complete Unmasking (UM) form.
 - Send physician exit letter.
 - Key forms into CPAP data system within 10 working days.
- ▶ If participant exit tasks are to be completed before their V7 (e.g. participant leaving the area), try to complete as many exit tasks as possible at the clinic (e.g. questionnaires, methacholine testing, return of CPAP device, study evaluation).
- ▶ If participant does not return to clinic for V7, conduct Study Evaluation (EV) questionnaire over the phone, and mail unmasking envelope and written materials to the participant.

Forms (abbreviation)

- Treatment Termination (TT) (*if not completed at V6*)
- Unmasking (UM)

Questionnaires (abbreviation)

- Study Evaluation (EV)

2.10. Missed procedures/ missed visits

Time frame (for enrolled participants)


- After time window has closed for a specified study visit or phone contact and any of the following were missed:
 - All requirements for a visit or phone contact (missed visit).
 - One or more of the procedures or forms required for a visit (missed data at a visit).

Tasks

- Attempt to schedule next visit or phone contact at a more convenient time, preferably early in the time window.
- If you are unable to contact participant,
 - Attempt to contact at all telephone numbers listed (home, work, cell) on Participant Information (PI) form.
 - Make calls at different times of the day.
 - Attempt to e-mail participant.
 - Send a letter to participant.
- Record specific procedures missed or reason visit or phone contact was missed on Missed Data (MD) form.
- Record CPAP Diary Cards (DC) not returned as missing on Missed Data (MD) form (e.g. at V6 record as missing any CPAP Diary Cards (DC) not returned, or returned blank, that were to be done since V5 CV form).

Procedures for participants who have missed one or more visits or phone contacts

- Once randomized, a participant is never considered “off study” until after the scheduled follow-up period ends; i.e., after V7 window closes
- Continue attempts to contact participant unless told not to contact.
- Return for study visits after an absence of any length is acceptable and encouraged.
- Be sure Missed Data (MD) forms are up-to-date.
 - Do NOT conduct Randomization Visit (V2) outside of window. If V2 cannot be scheduled within 4 weeks of screening, participant is to be re-screened, i.e. V1 should be conducted again.
 - V4 and V6 should be conducted, even if the visit is outside of window. It is important to check on participant use of the device at V4, and to collect the methacholine results of end of treatment at V6. Coordinator should conduct these visits even if they are outside of window.
 - At V6, **participants should be instructed to use the CPAP device until their V6 is performed including the methacholine challenge test.** If the methacholine test is rescheduled for V6, make sure the participant uses the CPAP device until then. Complete a Treatment Termination (TT) form when participant returns the CPAP device.
 - Do not conduct V5 outside of window. If the participant misses V5 and the window closes, conduct V6 and end treatment.
- For V3, V5, and V7, a Missed Data (MD) form is required at the close of each time window of visits missed.
- Forms that are expected and required at baseline (V1 and V2) and are missing are to be reported as protocol deviations.

 *Note:* There must be a minimum of one week between visits after V4.

Forms (abbreviation)

- Missed Data (MD)
- Participant Information (PI)*

*Not entered into database

2.11. Rescreening and recycling

Rescreening

Purpose

To perform the screening process again by re-evaluating a participant who previously did not meet eligibility criteria during screening at V1 or by re-evaluating a participant who did not successfully complete randomization visit (V2).

Tasks

- Maintain folder on participants who were not able to meet entry criteria at V1, but who may be eligible in the future.
 - Mark paperwork as “screen failure” and keep in file.
- After a 4-week waiting period you may try to re-screen a participant.
- Use the participant ID and name code as originally assigned.
- Re-do V1 procedures.
- Complete a new set of forms for V1.
- If participant is eligible, enter new forms into the database.
- **DO NOT** delete original forms from the database.

Note: There is not a limit on the number of times a participant can be re-screened, but clinics should use their discretion as to what is reasonable.

Recycling

Purpose

- Attempt to randomize a participant into the trial who previously failed to meet eligibility criteria at Randomization Visit (V2)
- There is **NO** recycling for participants in CPAP. If a participant does not meet eligibility criteria at V2, the participant **must be** rescreened, i.e. V1 should be conducted again.
- Contact the DCC for permission and instructions about recycling for unusual circumstances.

2.12. Scheduling visits

V1- 11-step Methacholine Challenge Testing

Pre-bronchodilator spirometry and methacholine challenge testing should be performed at V1. However, if the participant did not hold the asthma medications as required, do not perform methacholine challenge test. A methacholine challenge test must be conducted before randomization to confirm eligibility.

HRCT See Section 7 for details about HRCT scheduling

Combining V1 and V2

V1 and V2 may be performed in one day. However the following points must be followed:

- Some items on the Clinic Visit (CV) form refer to the time since the last clinic visit. If V1 and V2 are combined, consider the last three weeks when responding to these items.
- eNO must be performed prior to methacholine challenge testing.
- Specimen collection must be performed after confirming eligibility and before randomization.

3. Clinic certification, personnel certification, and study supplies

3.1. Clinic Certification

Purpose

- Provide confirmation and documentation that the main ACRC Clinical Center and any additional satellite centers have obtained the required approvals, facilities, equipment, personnel, and training necessary to conduct CPAP.
- Ensure consistent conduct of study procedures over time within and across clinics so that findings from all clinics are comparable.

When

- Before an ACRC Clinical Center or satellite clinic may recruit participants and conduct study procedures for the Effect of Positive Airway Pressure on Reducing Airway Reactivity in Patients with Asthma (CPAP) .

HRCT

Clinics participating in the HRCT substudy must complete HRCT certification. See Section 7

3.1.1. Consent statement and consent checklist

The Data Coordinating Center will provide an Informed Consent template for clinics to use when creating the Informed Consent Documents for CPAP. The template contains all information which must be present on all clinical center consent documents. Clinical centers are not required to use this template, however, it is provided as a tool to make the development of clinics' Informed Consent document easier.

- All consents (adult, parental, and assent) should be reviewed and approved by the Data Coordinating Center prior to IRB submission.
- When clinical centers send their Informed Consent statements to the DCC, they should use the Informed Consent Checklist, which is provided by the DCC and is located on the CPAP website.
- The items listed on the checklist are mandatory items which are required to be present somewhere in the consent. The clinical center should review the checklist and note on which page each item can be found.
- In addition, the clinical center should e-mail a copy of their consent in Microsoft Word, with the item number from the checklist added to the document as a comment. Example is shown below:

The people working on the study at this clinic will collect information about you. This includes things learned from the procedures described in this consent form and other information including your name, address, date of birth, and other details. Your name and other identifying information will be kept private. Generally, only people on the research team will know that you are in the research study and will see your information. A unique number and special code will be used in place of your name on samples and for data entry. The number and code cannot be linked to your name except at the clinical center where you complete visits. Data collected from your study visits will be labeled with only the unique number and special code. Study data will be sent to the Data Coordinating Center at The Johns Hopkins University in Baltimore, Maryland.

Comment [RZY64]: 25a

Comment [RZY65]: 25b

The consents will be reviewed at the DCC and, once approved, should be submitted to the clinical center's IRB for their approval. If the IRB returned the consent statement to the clinical center with proposed changes, the clinical center should contact the DCC to approve any additions or subtractions from the document. If a DCC re-review is required, the clinical center should again include the consent checklist with any applicable changes made.

3.1.2. Clinic certification form submission instructions

The Clinic Certification (CC) form should be completed and submitted by the Lead Coordinator at each main Clinical Center. The Center Director/PI must review and sign the form prior to submission to the DCC. The CC form is used to confirm the clinic has the following:

Documentation

- Letter or stamp of IRB approval of the CPAP informed consent form
- Original checklist if no changes were made to consent, or an updated checklist if changes were made to consent after DCC pre-approval.

Facilities

- Secure area for study kit storage
- Private area to conduct participant interviews and study visits
- Secure storage area for storage of study supplies, documents, and forms

Equipment and materials

- KoKo spirometer to measure FEV₁ and FVC
- KoKo spirometer software (Version 4.14)
- Equipment to measure height and weight
- NIOX MINO eNO equipment
- Equipment for methacholine challenge testing
 - KoKo dosimeter
 - Nebulizer cups, pre-calibrated for CPAP
- Computer for data entry with the following specifications
 - Microsoft Windows
 - Microsoft Internet Explorer (version 5.5 or above)
 - Adobe Acrobat Reader (5.0 or above—available free from www.adobe.com)
 - Printer (recommended)

3.1.3. Satellite Clinic Certification form submission instructions


Satellite Centers should complete the Satellite Clinic Certification (ST) form. The ST form is similar to the CC form but is meant to be completed by a coordinator at the satellite clinic and signed by the Co-PI at the satellite clinic. After completion, this form should be sent first to the Lead Coordinator at the main clinical center who will review it and send it to the DCC.

3.2. Personnel Certification form submission instructions

Any personnel at a clinic center who will perform functions for CPAP must be certified for that function by the DCC prior to conducting any procedures. All personnel are required to complete a Personnel Certification (CE) and any applicable certification tasks prior to submitting the CE form.

3.2.1. Study roles and certification responsibilities

Clinic Coordinator

- Complete Personnel Certification (CE) form
 - Signed Personnel Assurance (PA) statement
 - Completed sample CPAP Diary Cards (DC) (see Instructions for Diary Cards (IDC) and Section 8.2.1 on how to correctly complete CPAP Diary Cards (DC))
 - Coordinator should complete a one-week CPAP Diary Card (DC) based on a scenario provided by the DCC and can be found on the CPAP website. Complete CPAP Diary Cards (DC) approximating the experience of a participant.
 - After completing the CPAP Diary Card (DC) as a participant, review as a coordinator and complete the rest of the Diary Card (DC)
 - Pass the on-line General Knowledge Assessment (GEN) and print confirmation page
 - Pass the on-line CPAP Device Troubleshooting Assessment (DEV) and print confirmation page
 - Review of CPAP device setup and mask fitting using the clinic practice kit provided by the DCC
-  *Note:* It is recommended to watch the CPAP Coordinator Instructional Video prior to taking the CPAP Device Troubleshooting (DEV) assessment online.



Data System Operator

Clinic staff who have been previously certified for ACRC data entry do not need to re-certify, however, they still need to complete the first three items below:

- Complete Personnel Certification (CE) form.
- Signed CPAP Personnel Assurance Statement (PA).
- Pass the on-line General Knowledge Assessment (GEN) and print confirmation page.
- Pass the on-line Data System Operator Knowledge Assessment (DSO) and print confirmation page.
- Use the practice Certification Data System to data enter practice forms and print confirmation pages (three forms).

Methacholine Tester

- Complete Personnel Certification (CE) form.
- Signed CPAP Personnel Assurance Statement (PA).
- Pass the on-line General Knowledge Assessment (GEN) and print confirmation page.
- Complete a Methacholine Challenge test on a (non-study) volunteer and provide the following:
 - Completed 11-step Methacholine Challenge Testing (MC) form.
 - Methacholine Challenge report.
 - Print out from the on-line CPAP 11-step Methacholine Challenge calculator.

eNO Operator

- Complete Personnel Certification (CE) form.
- Signed CPAP Personnel Assurance Statement (PA).
- Pass the on-line General Knowledge Assessment (GEN) and print confirmation page.
- Documented training by an Aerocrine representative or by a ACRC staff member already certified to perform eNO.

CPAP Device Specialist

- Complete Personnel Certification (CE) form.
- Signed CPAP Personnel Assurance Statement (PA).
- Pass the on-line General Knowledge Assessment (GEN) and print confirmation page.
- Pass the on-line CPAP device trouble-shooting assessment (DEV) and print confirmation page.
- Review of CPAP device set-up and mask fitting using the practice kit provided by the DCC.
- Watch CPAP Coordinator Instructional Video found on CPAP website or on copy provided to the clinic.

**Center Director/PI**

- Complete Personnel Certification (CE) form.
- Signed CPAP Personnel Assurance Statement (PA).
- Signed CPAP Methacholine Challenge Test Assurance Statement (MA).
 - Submit a copy of the completed statement to the certification coordinator at the DCC.
 - The original completed form should be kept on file at the clinical center.
 - The assurance statement refers to all CPAP methacholine challenge tests conducted at or for the clinical center and any affiliated clinical sites. The statement asserts the following:
 - All methacholine challenge tests conducted at the clinical center and satellite clinics will be conducted in accordance with the CPAP protocol and safety requirements.
 - Methacholine will be compounded by a qualified individual who has read and understands the protocol.
 - Staff members conducting the test will be trained and qualified in methacholine challenge testing.
- Pass the on-line General Knowledge Assessment (GEN) and print confirmation page.

Co-PI or Physician

- Complete Personnel Certification (CE) form.
- Signed CPAP Personnel Assurance Statement (PA).
- Signed CPAP Methacholine Challenge Test Assurance Statement (MA), if applicable.
- Pass the on-line General Knowledge Assessment (GEN) and print confirmation page.

Satellite Co-PI

- Complete Personnel Certification (CE) form.
- Signed CPAP Personnel Assurance Statement (PA).
- Signed CPAP Methacholine Challenge Test Assurance Statement (MA)
- Pass the on-line General Knowledge Assessment (GEN) and print confirmation page.

Lead Coordinator at the main Clinical Center should be certified at minimum as Clinic Coordinator.

Additional responsibilities of Lead Coordinators include:

- Completing the Clinical Center Certification (CC) form or Satellite Certification (ST) form, as applicable.
- Entering all staff into the CPAP directory in order to obtain a PIN and password, necessary to complete certification procedures.
- Reviewing all certification forms (CC, ST, CE) for completeness and correctness before submission to the DCC.
- Submission of all other required materials, including all IRB notices of approval for both protocol and consent(s), and satellite materials, if applicable). Certification materials should be submitted together as one package.

3.2.2. List of Certification Forms

Forms (abbreviation)

- Clinical Center Certification (CC) form
- Personnel Certification (CE) form
- CPAP Diary Card (DC)
- CPAP Methacholine Challenge Test Assurance Statement (MA)
- Methacholine Challenge Testing (MC)* form
- CPAP Personnel Assurance Statement (PA)
- Satellite Clinic Certification (ST) form

**Test reports must be included with this form. All identifiers must be blacked out.*

3.3. Data System Certification

Access to the CPAP data system will be restricted to clinical center staff certified for data entry. Each ACRC Clinical Center will be required to have at least one person certified for data entry, although having more than one person certified is advised. It is recommended that the Lead Coordinator be data entry certified since data entry certification is required to enter the Randomization (RZ) form.

Staff members who were certified as data system operators for previous ACRC studies do not have to be re-certified for CPAP.

The data system is accessed via the internet using Microsoft Internet Explorer (version 5.0 or higher) on a PC running Microsoft Windows. The data system is available from the CPAP web page at <http://www.jhcct.org/Secure/CPAP/CPAPHome.asp>. Access to the CPAP data system requires a PIN, password, and activation by the DCC.

- An attempt to access any part of the data system will lead the user to a login screen, requiring a clinic ID, PIN, and password.
- The “Certification Data System” link on the CPAP home page should be used to submit forms for data entry certification.
- After a staff member becomes certified, his or her PIN will be authorized for data entry. If the staff member was previously certified for data entry for another ACRC trial, they will not have to complete the data entry certification test again and they should use their unique password to enter the data system. If the staff member was not previously certified, use the default password of “changeme” (without quotation marks). The system will instruct the user to create a unique password the first time the user logs in to the data system. From that time forward, only the user’s unique passcode will work.

**CPAP certification data system links to SARA certification data system for the purposes of certification. If a coordinator has been certified to enter data for SOYA, STAN or LASST, they do not need to redo this exercise for CPAP. Please make a note of this when submitting other certification materials.*

3.4. Study supplies

Maintaining an inventory of study supplies is the responsibility of the clinical and satellite centers. This will include ordering study supplies as needed.

Bayview Medical Inc.

- Mini Wright Peak Flow Meters
 - Complete Peak Flow Meter Order (PO) form and fax it to Bayview Medical Inc (410-550-2617).
 - All orders received by 3 pm ET weekdays will arrive within five working days
 - Disposable one way valve mouthpieces are available upon request at the DCC. To order please complete a General Order (GO) form

Methapharm, Inc.

- Methacholine (Provocholine®) vials may be ordered at a discounted price using the Methapharm Provocholine Order (LP) form that is posted on the CPAP website:

(<http://www.jhcct.org/Secure/CPAP/CPAPHome.htm>)

Methapharm contact:

Tracey Feely
 Clinical Services Specialist
 tfeely@methapharm.com
 Direct: (+1) 519.751.3602 x.7223
 Methapharm Inc. | Tel: (+1) 519.751.3602 1.800.287.7686
 Fax: (+1) 519.751.9149
 81 Sinclair Boulevard, Brantford Ontario N3S 7X6 Canada
 www.methapharm.com

- Coordinators can complete the Methapharm Provocholine Order (LP) form online and email it to Tracey Feely, or fax it to the contact information above.

Aerocrine

- NIOX MINO (sensor/filter kits and replacement machine)
 - Contact maryan.fahim@aerocrine.com or 917-446-5429.
 - Identify yourself as ACRC CPAP study coordinator to get discounted price of \$600 for 50 test kits or \$1200 for 100 test kits.
 - Sensors alone are the same price as the kits.

Data Coordinating Center will distribute the following:

- Participant supplies
 - Asthma Action Plan Cards (AAP)
 - Canvas bags with ACRC logo
 - Labels for clinic contact information for participant binder
 - Magnets with ACRC logo
 - General Asthma Educational Materials
 - CPAP Wallet Cards
 - ACRC appointment cards
 - 1" participant binders with CPAP cover
 - Unmasking envelopes (inside each study kit box)
 - Soap for mask cleaning

- CPAP Device User Instructions (ICD) (inside each study kit box)
- CPAP Participant Instructional Video on flash drive -- *Guide to using your CPAP*
- Specimen collection
 - Blood for DNA
 - Vacutainers, 10mL, lavender top (EDTA)
 - 2.0mL cryovials, orange top
 - Blood for eosinophil
 - Vacutainers, 6mL, lavender top (EDTA)
 - Serum for inflammatory profile
 - Vacutainers, 10mL, tiger top (clot activator)
 - 2.0mL cryovials, orange top
 - Pre-printed barcode labels for Vacutainers and cryovials
- Methacholine supplies
 - Mouthpieces for nebulizer cups
 - Expiratory filters for T-piece
 - Step down adapters
 - T-pieces
 - Syringe filter for transferring MeCh solution to nebulizer cup (1 syringe per session)
 - Characterized nebulizers, *if needed*
 - A laminated flowchart on the 11-step methacholine procedure sequence
 - A laminated flowchart on acceptability and reproducibility of spirometry maneuvers
- ACRC general supplies
 - Marking pens for labels (cryopen)
 - Clinic label sheets
 - Disposable transfer pipettes
 - Cardboard boxes with dividers for specimen storage in freezer and shipping
- CPAP specific supplies
 - 1 Styrofoam head per clinic for mask demonstration purposes
 - 1 CPAP Coordinator Instructional Video on DVD per clinic
 - 1 practice kit per clinic
 - 1 laminated example of good CPAP adherence
 - 1 laminated example of poor CPAP adherence
- ACRC shipping supplies
 - Styrofoam shippers with outer cardboard box, large
 - Plastic biohazard specimen bags
 - Absorbent sheets
 - Dry ice label (UN 1845)
 - UN3373 label for biospecimens
- Original study kit box for returning study device
- HRCT substudy supplies
 - Disks (DVDs) for scan

Ordering additional supplies from Data Coordinating Center

- Order supplies as needed
- Complete CPAP Supply Order (CO) form or ACRC General Supply Order (GO) form
- Requests should include number of items and date needed
- Fax or mail to DCC

Clinical Centers will provide

- Blood collection supplies (needles, tourniquet, etc)
- Dry ice
- Scotch tape
- Koko spirometer and supplies (including noseclips)
- Methacholine and methacholine test supplies not provided by the DCC and safety supplies
- Aerocrine NIOX MINO and supplies
- FedEx mailing labels
- FedEx envelopes for SD cards and HRCT disks
- Packing material (bubble wrap, “peanuts,” or crumpled newspaper)
- Study forms and questionnaires (downloaded from CPAP website <http://www.jhcct.org/Secure/CPAP/CPAPHome.asp>)
- Pregnancy test kits
- Insulated gloves for handling dry ice

Forms (abbreviation)

- CPAP Supply Order (CO) form
- ACRC General Supply Order (GO) form
- Methapharm Provocholine Order (LP) form
- Peak Flow Meter Order (PO) form

3.5. Participant Binders

Purpose

- Provide participants a collection of forms and materials for home use.

When

- V1 (Screening)

Supplies

- 1" binder with CPAP cover
- Labels, ML-1000

Instructions and materials included

- Information label – Place on front of inside pocket of the binder. Use ML-1000 labels provided by DCC or similar labels from your clinic.
 - For each ACRC Clinical Center (primary or satellite), print the study coordinator name, study physician name, clinic daytime and after hours phone numbers and the mailing address on the label.

- Schedule of Visits (SOV) - Fill in the day, date, and time of scheduled appointments for that participant.
- Instructions for Measuring Peak Flow (IPF) - Place copy of the instruction sheet in binder.
- Instructions for CPAP Diary Cards (IDC) - Place copy of the instruction sheet in binder.
- Participant Instructions for Methacholine Challenge Test (IMC)- Place copy of the instruction sheet in binder
- CPAP Diary Cards (DC) - Fill out CPAP Diary Cards (DC) to cover entire enrollment, treatment and washout period (total study period is approximately 16 weeks). Refer to Section 8.2.1, for complete instructions on filling out the CPAP Diary Cards (DC).
- Asthma Action Plan Card (AAP).
- General Asthma Educational materials.

Forms and instruction sheets (abbreviation)

- Asthma Action Plan Card (AAP)
- CPAP Diary Card (DC)
- Instructions for CPAP Diary Cards (IDC)
- Instructions for Measuring Peak Flow (IPF)
- Schedule of Visits (SOV)

3.6. Communication prototypes

The following are templates to use when creating necessary correspondence. The final versions you create will require the approval of your institution's IRB. The prototypes included are:

- Primary physician introduction letter
- Participant release to share results to asthma care provider (may not need if covered by consent form)
- Physician exit letter
- Participant exit letter

3.6.1. Prototype: primary physician introduction letter

Dear Dr. _____:

Your patient, _____, was recently enrolled in the clinical trial, Effect of Positive Airway Pressure on Reducing Airway Reactivity in Patients with Asthma (CPAP). This study is designed to assess the effect of nocturnal CPAP on airway reactivity in patients with asthma and to determine the durability and tolerability of the effect over 12 weeks. We plan to enroll 192 participants and randomly assign each participant to receive a CPAP device with a fixed level of airway pressure to use every night. CPAP devices will be provided by ResMed. The three treatment arms will receive warm, humidified, filtered air via nocturnal CPAP at the following levels:

- Low, less than 1 cmH₂O
- Medium, 5 cmH₂O
- High, 10 cmH₂O

This randomized, sham controlled trial involves 18 clinical centers in the United States and will enroll approximately 192 participants with asthma.

Additional goals of the study are to:

- Determine whether there is a dose response effect by evaluating 2 levels of CPAP (10 cmH₂O, 5 cmH₂O) and Sham (less than 1 cmH₂O).
- Assess the impact of CPAP on asthma control and symptoms.
- Determine adherence and tolerability of CPAP.

The primary outcome measure will be change in PC₂₀. Eligibility will be determined by tests and questionnaires, including a methacholine challenge test. Participants must have a PC₂₀ less than or equal to 8 mg/ml for FEV₁ to be eligible for the study. Questionnaires will be used to rule out participants who are at risk of having sleep apnea.

Treatment will last approximately 12 weeks, followed by a 2 week washout. Participants will have six clinic visits and one follow-up phone call. The trial will collect information concerning demographics, medical history, lung function, as well as asthma. Participants will be given a Peak Flow Meter, and asked to record their best PEF daily. An Asthma Action Plan Card (AAP) outlining how to respond to asthma symptoms will be distributed to all participants.

Your patient should continue to use you as their primary asthma care physician.

- A small number of participants (48 participants) will be asked to volunteer to participate in a mechanistic substudy that will use HRCT scans to determine whether chronic nocturnal CPAP alters airway-parenchymal interdependence and maximal airway caliber. HRCT scans will be taken prior to use of CPAP and after 10 to 12 weeks of CPAP use.

At the end of the study participants will learn which study treatment they received, and will be given a copy of the results from their last methacholine challenge test. We will advise your patient to schedule an appointment with you to review this information. Your patient will be counseled to follow the guidelines on his/her Asthma Action Plan Card (AAP) and told that he/she may contact our clinic for emergencies, if necessary. Please feel free to contact our clinic (xxx-xxx-xxxx) or me personally if you have any questions.

Sincerely,
Principal Investigator
Institution

3.6.2. Prototype: participant release to share results to asthma care provider

Prototype: Participant release to send methacholine results to asthma care providers

PARENT/GUARDIAN CONSENT TO RELEASE
RESEARCH SUBJECT BREATHING TEST RESULTS FORM

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

Protocol No.: IRB Name Protocol # XXXXX

Sponsor: The American Lung Association (ALA)
 Funding Source: NIH, NHLBI
 Investigator: Michael Busk, MD; Janet Holbrook, PhD
 Site(s): Johns Hopkins University Bloomberg School of Public Health
 ACRC Coordinating Center
 Johns Hopkins Center for Clinical Trials
 615 North Wolfe Street, W5010
 Baltimore, Maryland 21205
 United States

STUDY-RELATED

PHONE NUMBER(S): Research study questions

Principal Investigator

Phone number

Research-related injury

Robert Wise, M.D.

410-550-0545

443-287-5791 (24-hours)

SUBINVESTIGATOR(S): Robert Wise, MD

Permission to Notify Physician (for participants ages 18 and older):

I give permission for study personnel to fax/send my breathing test results to my asthma care physician.

Printed Name of Participant

Signature of Participant

Date

Permission to Notify Physician (for participants ages 15-17):

I give permission for study personnel to fax/send my child's breathing test results to his/her asthma care physician.

Printed Name of Participant

CONSENT SIGNATURE

Printed Name of Participant's Parent or Legally
Authorized Representative

Signature of Participant's Parent or Legally
Authorized Representative

Date

Authority of Participant's Legally Authorized Representative

or Relationship to Participant

CLINIC SIGNATURE(S)

Signature of Person Conducting Informed Consent
Discussion

Date

Signature of Investigator (if different from above)

Date

3.6.3. **Prototype: Physician exit letter**

Dear Dr. _____:

Your patient, _____, recently completed participation in the clinical trial, Effect of Positive Airway Pressure on Reducing Airway Reactivity in Patients with Asthma (CPAP). This study is designed to assess the effect of nocturnal CPAP on airways reactivity in patients with asthma and to determine the durability and tolerability of the effect over 12 weeks. The study plan is to enroll 192 participants and randomly assign each participant to receive a CPAP device with a fixed level of airway pressure to use every night. CPAP devices will be provided by ResMed. The three treatment arms will receive warm, humidified, filtered air via nocturnal CPAP at the following levels:

- Low, less than 1 cmH₂O
- Medium, 5 cmH₂O
- High, 10 cmH₂O

Treatment on blinded CPAP lasted approximately 12 weeks and included 6 clinic visits and 1 follow-up phone call.

Your patient has now completed all study visits and has received an envelope indicating the assigned study treatment and the results from his/her last methacholine challenge test. We have counseled your patient to visit you within 3 weeks to review current asthma treatment and to show you the treatment assignment and the results of his/her final methacholine challenge test. Your patient was instructed to follow the guidelines on his/her Asthma Action Plan Card (AAP) and told that he/she may contact our clinic for emergencies, if necessary.

We hope participation in this clinical trial was beneficial to your patient. Please contact our clinic (xxx xxx-xxxx) or me personally with any questions.

Sincerely,

Principal Investigator
Institution Name

3.6.4. Prototype participant exit letter

Dear _____,

Thank you for participating in the clinical trial Effect of Positive Airway Pressure on Reducing Airway Reactivity in Patients with Asthma (CPAP). This purpose of the study was to assess the effect of nocturnal CPAP on airways reactivity in patients with asthma and to determine the durability and tolerability of the effect over 12 weeks. The CPAP devices are supplied by ResMed. All participants receive warm, humidified, filtered air via nocturnal CPAP. The trial compares the effects of CPAP at two levels of pressure (5 and 10 cmH₂O) to very low pressure (less than 1 cmH₂O). In addition the trial hopes to determine:

- If the response to CPAP relates to the amount of pressure (the 3 levels)
- The impact of CPAP on asthma control and symptoms, and
- How well participants tolerate CPAP and how consistently they use it

The treatment to which you were assigned is listed in the enclosed, sealed envelope. We have also enclosed the results of your final methacholine challenge test. You should arrange to see your regular asthma care provider within the next three weeks. We recommend that you show your asthma care provider your treatment assignment and results of your final methacholine challenge test. Be sure to follow the guidelines on your Asthma Action Plan Card (AAP). If you have problems with your asthma medication before you see your asthma care provider, you can call our clinic at: XXX-XXX-XXX.

There are other participants in the study, enrolled after you, who are still being treated and followed. It is important that you do not inform me, the other study personnel, or other study participants what treatment you were assigned because the study is still collecting information on these people. We make it a point not to know what treatment participants are assigned during the study so that knowledge of the treatment assignment does not influence the data we are collecting.

Again, thank you for your participation in CPAP.

Sincerely,
Principal Investigator
Institution Name

Enclosures:
Treatment assignment envelope
Results of final methacholine challenge test

4. Procedures

4.1. Spirometry

4.1.1. Spirometry procedures

Purpose

- Measure FEV₁ (the amount of air expired in the first second during a forced expiratory maneuver and FVC (forced vital capacity).

When

- As part of methacholine challenge tests at V1, V5, V6 and V7

Standardization of equipment

- Equipment and procedures are based on the ATS recommendations for accuracy and precision
- For CPAP all personnel performing spirometry as part of a methacholine challenge test will have to be CPAP certified for Methacholine Challenge Testing. See Section 4.2.4.
- All sites will use KoKo spirometry software version 4.11 (During the study, the new version 4.15 will be sent out to clinics along with a PPM and instructions to download)
- Spirometers must be calibrated before performing spirometry on the day spirometry is to be performed. Calibration can be done once in the morning for multiple visits on the same day.

Predicted values

The predicted values are calculated according to the published predicted values (Hankinson et al).

Use values listed in the table in Section 4.1.2 or calculate online using the CPAP pulmonary function calculator. To access the online calculator

- Go to the CPAP website: <http://www.jhcct.org/Secure/CPAP/CPAPHome.asp> and follow the link to the calculator under the CPAP data system header
- OR
- Manually calculate using predicted FEV₁ value per Hankinson (formula in the table under Section 4.1.2) and the following formula:

$$\text{Percent predicted} = \text{FEV}_1 / \text{predicted FEV}_1 \times 100$$

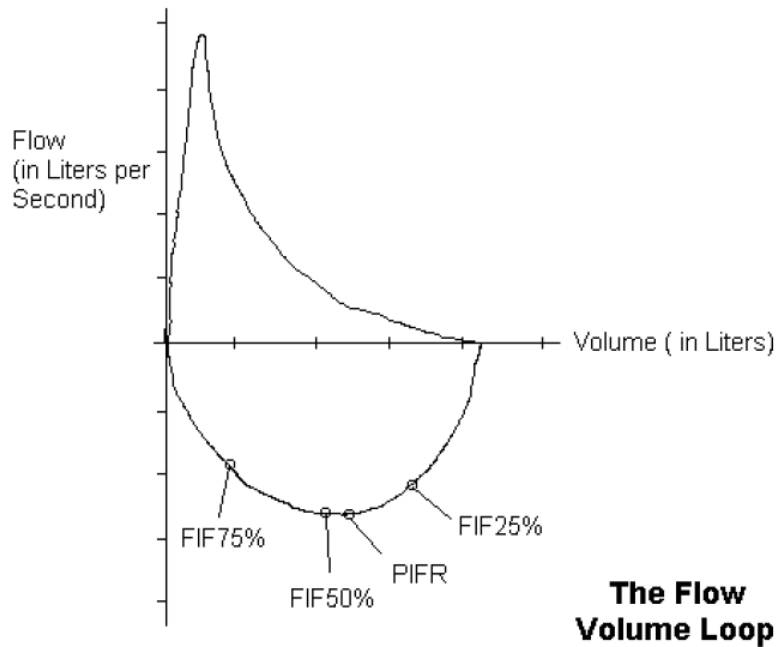
Note: Even if your spirometry system can be programmed to use the Hankinson (NHANES III) predicted values, note that your reports may print numbers for the predicted and percent predicted values that are not the same as the official ACRC values due to differences in rounding and calculation. ACRC clinics must use the exact values as reported by the online calculator. If your spirometry system can be programmed and verified to give exactly the same values as the online calculator, it will not be necessary to use the online calculator for each participant visit.

Participant preparation

Since spirometry is performed as part of the methacholine challenge test, participant preparations match those of the methacholine challenge test (Section 4.2)

Testing procedure

- Height and weight should be measured prior to each methacholine challenge test.
- Avoid having participant sit on a chair with wheels when conducting test
- Instruct participant and demonstrate procedure
 - Lips should be sealed around the mouthpiece
 - Emphasize the necessity for deep and full inspiration, a hard and forceful expiratory “blast”, a complete expiration for at least 6 seconds, and finally a forceful inspiration following the expiration. (It is acceptable to do forced inspiration before the forced expiration if equipment requires, but forced inspiration should follow forced expiration whenever possible.)
 - Perform test until acceptability and reproducibility criteria are met
- Acceptability criteria
 - **Test start:** The peak flow should be sharp on FV curve. Participants may need coaching to get this right (e.g. BLAST it out)
 - **Cough:** This can cause flow irregularities. Reject test when cough is within the first one second (FEV_1 will not be accurate). Cough in the later part of the VC is not a reason per se to reject the effort. Often cough can be reduced by asking the participant to exhale SLIGHTLY less forcefully
 - **End of expiration:** When the expiratory effort lasts at least 6 seconds. Participants with severe obstructive lung disease may continue to exhale for 10 or more seconds. Occasionally, premature glottis closure causes abrupt test end. Participants may need to relax and try again with slightly less than maximum effort
 - **Forced inspiration:** Maximum inspiratory effort following the end of expiration as shown on flow-volume curves
- Reproducibility criteria
 - **Definition:** Using the two criteria of FVC and FEV_1 to determine how well each acceptable effort compares with the largest acceptable effort
 - **FVC:** The second largest FVC should be within .15 L of the largest acceptable FVC
 - **FEV_1 :** The second largest FEV_1 should be within .15 L of the largest acceptable FEV_1
- At least 3 acceptable and 2 reproducible efforts should be obtained. If this cannot be obtained after approximately 8 attempts, then the testing should be halted at V1
- The largest acceptable FEV_1 and FVC should be recorded on the Methacholine Challenge Testing (MC) form. These do not have to be taken from the same maneuver
- Inspiration may or may not be required but is shown in following figure.



- Print out the individual curves, if the equipment allows. Otherwise, whatever quality assurance values are obtained should be noted (this depends on equipment)
- Note quality assurance values: time to peak flow, back extrapolation volume, and total expiratory time to help assess the quality of each maneuver and overall test session
- Calculate FEV₁ percent predicted value as explained above.

Troubleshooting

Online troubleshooting for issues with KoKo is located on the ACRC website.

<http://www.jhcct.org/Help/ACRCHelp.asp>

Forms (abbreviation)

- Methacholine Challenge Testing (MC)

4.1.2. Table of pulmonary function predicted values

The general form of the prediction equations is: $PFT = Z + A(\text{Age}) + B(\text{Age}^2) + C(\text{Height}^2)$

| PFT | Race/Ethnicity | Gender | Z | A | B | C | |
|--------------------------|--------------------------|-------------------|---------|---------|----------|-----------|-----------|
| FVC | Caucasian adults* | Male | -.1933 | .00064 | -.000269 | .00018642 | |
| | | Female | -.3560 | .01870 | -.000382 | .00014815 | |
| | African-American adults* | Male | -.1517 | -.01821 | ----- | .00016643 | |
| | | Female | -.3039 | .00536 | -.000265 | .00013606 | |
| | Mexican-American Adults* | Male | .2376 | -.00891 | -.000182 | .00017823 | |
| | | Female | .1210 | .00307 | -.000237 | .00014246 | |
| | Caucasian child | Male | -.2584 | -.20415 | .010133 | .00018642 | |
| | | Female | -1.2082 | .05916 | ----- | .00014815 | |
| | African-American child | Male | -.4971 | -.15497 | .007701 | .00016643 | |
| | | Female | -.6166 | -.04687 | .003602 | .00013606 | |
| | Mexican-American child | Male | -.7571 | -.09520 | .006619 | .00017823 | |
| | | Female | -1.2507 | .07501 | ----- | .00014246 | |
| | FEV ₁ | Caucasian adults* | Male | .5536 | -.01303 | -.000172 | .00014098 |
| | | | Female | .4333 | -.00361 | -.000194 | .00011496 |
| African-American adults* | | Male | .3411 | -.02309 | ----- | .00013194 | |
| | | Female | .3433 | -.01283 | -.000097 | .00010846 | |
| Mexican-American adults* | | Male | .6306 | -.02928 | ----- | .00015104 | |
| | | Female | .4529 | -.01178 | -.000113 | .00012154 | |
| Caucasian child | | Male | -.7453 | -.04106 | .004477 | .00014098 | |
| | | Female | -.8710 | .06537 | ----- | .00011496 | |
| African-American child | | Male | -.7048 | -.05711 | .004316 | .00013194 | |
| | | Female | -.9630 | .05799 | ----- | .00010846 | |
| Mexican-American child | | Male | -.8218 | -.04248 | .004291 | .00015104 | |
| | | Female | -.9641 | -.06490 | ----- | .00012154 | |

- Age is in years at last birthday
- Height is standing height in cm
- PFT predicted values are in liters
- Predicted values for Latinos will be as for Mexican-Americans
- Predicted values for other race/ethnic groups will be as for Caucasians
- Participant's race/ethnic identity is self-defined

**Adult is greater than or equal to 20 years old for males and greater than or equal to 18 years old for females*

Participant specific predicted values may be obtained from the data system following the initial screening spirometry and printed as appropriate for the participant's chart or file or to be shared with participant's healthcare provider.

4.2. Methacholine challenge test – 11-Step

4.2.1. Overview

Methacholine bronchial challenge assesses the presence and degree of airway hyper-responsiveness to methacholine, a non-specific acetylcholine agonist. Airway responsiveness is described by the provocative concentration of methacholine causing a decrease in FEV₁ by 20% from post-diluent (PC₂₀).

- The hypothesis for this trial is that twelve weeks of treatment with nocturnal CPAP will decrease airways reactivity to methacholine.
- PC₂₀ of the methacholine challenge testing **is the primary outcome** for the CPAP trial

4.2.2. Purpose and schedule

Purpose

- To measure airway reactivity to establish eligibility
- Primary outcome measure is change in PC₂₀


When

- V1: For Eligibility
- V5 and V6: Measure treatment effect
- V7: Follow-up measurement after 2 week washout

Methacholine is preferably to be performed in the mornings, at the same time of the day every time. Participant should be reminded to use their CPAP device the night before methacholine.

Rescheduling

- If a participant does not hold medications –reschedule participant as long as the scheduling is in the visit time window
- If a participant cannot perform methacholine due to a low FEV₁, reschedule the challenge **once**. Complete a Methacholine Challenge Testing (MC) form for each visit. If participant cannot perform methacholine within the time window in any of the two visits, record on MC form and move on to the next visit.
- **Do NOT** re-schedule the methacholine more than once per visit for a participant with a low FEV₁.
- Both Methacholine Challenge Testing (MC) forms are to be data entered in the system
- Guidelines on waiting times to reschedule:
 - Low FEV₁:
 - At V1: participant is ineligible, wait 4 weeks and rescreen participant
 - At follow up visits: it is recommended that a rescheduled challenge should be performed no earlier than 2 weeks from the first challenge
 - Failing to achieve acceptability and reproducibility at V1: rescheduled challenge should be performed no earlier than 1 week from the first challenge

 **Note:** If V6 methacholine is to be rescheduled, the CPAP device must be kept with the participant, and the participant should use the device until their methacholine challenge is performed. The Treatment

Termination (TT) form and the Study Evaluation (EV) form should be completed after the participant returns the CPAP device and masks (end of treatment).

4.2.3. Definitions

- **Baseline FEV₁** – for a methacholine challenge test this refers to the **pre-diluent FEV₁** measurement
- **% predicted** – Reference value, refers to the average or mean value observed from many healthy persons of the same age, gender, height and race as the person being tested. For CPAP we will use the Hankinson (NHANES III) predicted values, note that your reports may print numbers for the predicted and percent predicted values that are not the same as the official ACRC values due to differences in rounding and calculation. ACRC clinics must use the exact values as reported by the online calculator.
- **Target FEV₁**–is the FEV₁ value that is a 20% drop in FEV₁ from post-diluent for the participant, and is the stopping point for methacholine dosing during the methacholine challenge test. To calculate the target FEV₁, take 80% of the post-diluent (0.8 x post-diluent FEV₁). The Target FEV₁ is used to calculate the PC₂₀.
- **Recovery FEV₁** –is equal to **90% of the pre-diluent FEV₁**, and a participant is considered recovered from the methacholine challenge test when his/her FEV₁ has returned to this value.
- **Acceptable spirometry effort** – refer to MOP 4.1.1, acceptability criteria
- **Reproducible spirometry effort** – refer to MOP 4.1.1, reproducibility criteria

4.2.4. Requirements for personnel administering the methacholine challenge

The methacholine challenge administered by an ACRC clinic will be performed according to the 11-step methacholine procedure as outlined in Section 4.2.12 of the MOP and posted on the CPAP website (<http://www.jhcct.org/Secure/CPAP/CPAPHome.asp>). The CPAP methacholine procedure is based on ATS recommendations. The test is to be conducted either by:

1. ACRC staff with experience conducting methacholine challenge tests at clinical center facility, or
2. Non-ACRC staff at a pulmonary testing lab in the clinical center's facility or institution, or
3. Non-ACRC staff at an outside pulmonary testing lab that has been identified by clinical center staff.

For quality control and safety assurance, the following requirements must be met before any ACRC clinic methacholine challenge tests are conducted. These requirements apply to both methacholine challenges conducted at the clinical center as well as those conducted at an associated or outside pulmonary function testing lab:

- All centers must use the KoKo spirometer, the external KoKo dosimeter, and characterized nebulizer cups. The nebulizer cups are supplied by the DCC.
- The Principal Investigator must complete the Methacholine Challenge Test Assurance Statement (MA). Refer to Certification requirements Section 3
- All methacholine challenge testers for the ACRC (clinic staff and affiliated or outside lab technicians) must complete certification requirements approved by the DCC before they may conduct methacholine challenge tests. Refer to Certification Requirements (Section 3).

Methacholine safety conditions

All clinic sites should adhere to the following for the CPAP trial

2. Conduct the methacholine test according to the clinic and institutional guidelines
3. Conduct the methacholine challenge testing according to the CPAP protocol and Manual of Procedures, with the Principal Investigator signing off a CPAP Methacholine Challenge Test Assurance (MA) Statement
4. Provide assurances that the required equipment and resuscitation kits at the clinics are available and up-to-date (component of clinic certification process)
5. Personnel who will be conducting the methacholine challenge test must be certified by the Data Coordinating Center by performing a methacholine challenge on a volunteer and submitting all forms and reports for approval and quality assurance prior to enrollment
6. At least one coordinator from each clinic site was required to attend the ACRC training meeting in February 2012 which covered methacholine challenge testing procedures in detail.
7. Adhere to the recommendations of the ATS and AARC with respect to the necessary expertise and physician availability.

The American Association of Respiratory Care (AARC) guidelines¹ indicate the following:

“10.2.2 During the testing procedure, a physician knowledgeable in provocation testing procedures and trained to treat acute bronchospasm and use resuscitation equipment must be close enough to respond in an emergency.”

We do not define physician availability specifically for methacholine test supervision, but a useful definition has been provided by CMS (Centers for Medicare & Medicaid Services) in their April 23, 2010 bulletin addressing the issue of supervision of procedures and clarifying what they mean by “on campus”.

“Is a physician or non-physician practitioner considered immediately available as long as they are on the hospital campus?” Section 42 CFR 410.27(f) sets up a two-pronged requirement for direct supervision of therapeutic services in the hospital or CAH (Critical Access Hospital): the physician or non-physician practitioner must be present on the same campus of the hospital and must be immediately available, meaning physically present. For the purposes of supervision of hospital outpatient therapeutic services, we recognize the 413.65(a)(2) definition of campus as “the physical area immediately adjacent to the provider's main buildings, other areas and structures that are not strictly contiguous to the main buildings but are located within 250 yards of the main buildings, and any other areas determined on an individual basis, by the CMS regional office, to be part of the provider's campus.”²

1 AARC Clinical Practice Guideline. Methacholine Challenge Testing: 2001 Revision & Update. Available at: http://www.aarc.org/daz/rcjournal/rcjournal/x.RCJOURNAL.COM%2002.21.07/online_resources/cpgs/mctcpg-update.html. Accessed May 3, 2012

2 Common questions about supervision requirements for Medicare payment of hospital outpatient services. Available at: <http://www.cms.gov/Medicare/Medicare-Fee-for-Service->

Hence, the definition of available in the CPAP trial indicates that a physician must be close enough and respond within a few minutes when contacted by phone or by pager if needed, in the same manner for an emergency.

4.2.5. Contraindications

Absolute contraindications

For safety purposes, do not conduct the methacholine challenge test if the participant has any of the following conditions:

- FEV₁:
 - V1: an FEV₁ less than 75% predicted or less than 1 L (using Hankinson predicted equations, or using the CPAP online calculator).
 - V5, V6 and V7: an FEV₁ less than 70% predicted or less than 1 L (using Hankinson predicted equations, or using the CPAP online calculator).
- Myocardial infarction or stroke within last 3 months
- Known aortic aneurysm
- Uncontrolled hypertension (ie, SBP > 200, DBP > 100)
- Positive pregnancy test or breastfeeding (for women of child-bearing potential a negative pregnancy test is required before every methacholine challenge)
- Current use of a beta-blocker

Relative contraindications

- Per precautions listed on Provocholine® package insert, a physician must determine whether the methacholine challenge may be conducted if the participant has any of the following conditions:
 - Epilepsy
 - Bradycardia
 - Vagotonia
 - Peptic ulcer disease
 - Thyroid disease
 - Urinary tract obstruction
 - Current use of a cholinesterase-inhibitor medication

In addition, the physician must review the following before proceeding with the test:

- Other serious illness in the last 4 weeks
- Wheezing or showing other signs of asthma

General contraindications

- An acceptable methacholine test depends on the ability of a participant to perform acceptable spirometric maneuvers. If a participant is unable to perform reproducible (2 efforts) and acceptable (3 efforts) pre-spirometry tests at each of the pre- diluent and post-diluent sessions, the methacholine challenge test should not be conducted at V1

4.2.6. Medication holds prior to methacholine challenge

The following medication hold periods must be observed prior to methacholine challenge:

| | |
|-----------------------------------------------|------------------|
| Short-acting β -agonists | at least 6 hours |
| Medium-acting β -agonists | 24 hrs |
| Long-acting β -agonists | 24 hrs |
| Ultra-long acting bronchodilator (tiotropium) | 48 hrs |
| Anticholinergics | 48 hrs |
| Theophylline (oral) | 48 hrs |
| Cromolyn | 8 hrs |
| Nedocromil | 24 hrs |
| Leukotriene modifiers | 24 hrs |
| Antihistamines | 48 hours |
| Inhaled steroids | no hold period |

4.2.7. Other confounders

The results of the methacholine challenge could be confounded by the following:

- Caffeine, cola drinks, energy drinks and chocolate on the day of the test
- Exercise or smoking within past 6 hours
- Upper respiratory infection within past 4 weeks
- Known allergen exposures within past week

If any of these confounders are present, they should be noted on the Methacholine Challenge Testing (MC) form, but the methacholine challenge test can proceed as scheduled.

Due to diurnal differences in lung function participants should have their methacholine challenge visits at about the same time of day each time, preferably in the morning (V1, V5, V6 and V7).

4.2.8. Participant instructions

Two to three days before the test, remind participant:

- To hold medications as detailed in Section 4.2.6
- To abstain from caffeine, cola drinks, and chocolate on the day of the test
- To abstain from exercise and smoking for 6 hours before his/her methacholine challenge appointment

Instructions prior to initiating the challenge test:

- Keep explanation of the test as neutral as possible.
- Tell participant that they will inhale a mist of medication that could make them feel better, worse, or cause no change.
- Practice breathing instructions with participant
- Ask participant if he/she would like to use the bathroom before the test (stress incontinence could be precipitated).

4.2.9. Participant assessment

Participants should be assessed prior to testing:

- General physical condition and ability to perform the test
- Appropriate withholding of medications
- Other potentially confounding issues (as stated above)
- Pregnancy, test is to be done before each methacholine challenge test if the female participant is of child bearing potential
- Blood pressure
- Height and weight (to be measured before each test; updated measurements to be used for test)

4.2.10. Equipment and supplies

Make sure the following are available for each methacholine test:

- Concentrations of methacholine solution (described in MOP Section 4.2.11)
- KoKo External Dosimeter
- Step down adapter*
- T-pieces*
- Characterized nebulizer(s)* (*other nebulizers not acceptable*)
- Mouth pieces for nebulizer cups*
- KoKo Spirometer (with nose clip, mouthpiece)
- Timer
- Oxygen
- Stethoscope, sphygmomanometer, pulse oximeter
- Resuscitation equipment
- Emergency medications including albuterol (MDI and for nebulization) and atropine or equivalent anticholinergic medication (e.g., Ipratropium)
- Expiratory filters for T-piece*
- Compressed air tank

- Syringe for methacholine solutions
- Syringe filters for transferring methacholine solution to nebulizer*
 - Methacholine testing supplies and equipment not noted as supplied by DCC (those with *) are the responsibility of the clinical center staff or pulmonary testing lab.
 - Methacholine (Provocholine®) may be ordered using the Methapharm Provocholine Order Form (LP)

4.2.11. Preparation of methacholine solutions for 11-step methacholine challenge test

Methacholine must be compounded by a qualified individual (e.g., pharmacist) who has read and understands the protocol. The scheme recommended by the ATS, with one additional dose, will be used: 0.03125 mg/mL, 0.0625 mg/mL, 0.1250 mg/mL, 0.25 mg/mL, 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 4 mg/mL, 8 mg/mL, 16 mg/mL and 32 mg/mL.

Solutions are prepared using **Provocholine® 100mg in 20mL**, two vials will be required. Dilutions are as follows:

| Diluent will be 0.9% Normal Saline containing 0.4% phenol for preservative | | |
|-----------------------------------------------------------------------------------|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Vial A | 32 mg/mL | With first 100mg in 10 mL vial , add 3.125 mL of diluent to the first vial containing 100 mg of Provocholine®. This makes a solution of 32 mg/mL (total vol = 3.125mL) |
| Vial B | 16 mg/mL | With the second 100mg vial , add 6.25 mL of diluent to the vial containing 100 mg of Provocholine®. This makes a solution of 16 mg/mL (total vol = 6.25 mL) |
| Vial C | 8 mg/mL | remove 3 mL from vial B, transfer to another vial and add 3 mL of diluent. This makes a solution of 8 mg/mL (total vol = 6 mL) |
| Vial D | 4 mg/mL | remove 3 mL from vial C, transfer to another vial and add 3 mL of diluent. This makes a solution of 4 mg/mL (total vol = 6 mL) |
| Vial E | 2 mg/mL | remove 3 mL from vial D, transfer to another vial and add 3 mL of diluent. This makes a solution of 2 mg/mL (total vol = 6 mL) |
| Vial F | 1 mg/mL | remove 3 mL from vial E, transfer to another vial and add 3 mL of diluent. This makes a solution of 1 mg/mL (total vol = 6 mL) |
| Vial G | 0.5 mg/mL | remove 3 mL from vial F, transfer to another vial and add 3 mL of diluent. This makes a solution of 0.5 mg/mL (total vol = 6 mL) |
| Vial H | 0.25 mg/mL | remove 3 mL from vial G, transfer to another vial and add 3 mL of diluent. This makes a solution of 0.25 mg/mL (total vol = 6 mL) |
| Vial I | 0.125 mg/mL | remove 3 mL from vial H, transfer to another vial and add 3 mL of diluent. This makes a solution of 0.125 mg/mL (total vol = 6 mL) |
| Vial J | 0.0625 mg/mL | remove 3 mL from vial I, transfer to another vial and add 3 mL of diluent. This makes a solution of 0.0625 mg/mL (total vol = 6 mL) |
| Vial K | 0.03125 mg/mL | remove 3 mL from vial J, transfer to another vial and add 3 mL of diluent. This makes a solution of 0.03125 mg/mL (total vol = 6 mL) |

The vials will be used in reverse order, starting from the lowest concentration (i.e., Vial K will be used first followed by Vial J, Vial I, Vial H, Vial G, Vial F, Vial E, Vial D, Vial C, Vial B, and Vial A, in this order)

Transfer of solutions

- A syringe filter (sterile bacterial-retentive filter, porosity 0.22 µm) should be used when transferring the solutions from the vial to the nebulizer cup. Use one syringe for each MeCh testing session

Storage of solutions

Refrigerated storage:

- Solutions A-I may be stored up to 2 weeks in the refrigerator.
- Solutions J and K, the lowest concentrations, may be stored in the refrigerator but for no more than 24 hours.

Frozen storage:

- Solutions A-K may be stored frozen in unit-dose syringes for up to 6 months.
- After thawing, unused solutions should be discarded

Reference

Amus MJ, Vaughan LM, Hill MR, Chesrow SE, Hendeles L. Stability of frozen methacholine solutions in unit-dose syringes for bronchoprevention. *Chest* 121:1634-1637, May 2002.

4.2.12. Administration of 11-step methacholine challenge

1. All CPAP methacholine challenge tests will be performed using the following equipment:
 - KoKo spirometer running software version 4.14
 - An external KoKo dosimeter (not the Digi-doser)
 - Characterized nebulizer cups supplied by the DCC (other nebulizers not acceptable)
2. Allow methacholine solutions to come to room temperature for 30 minutes
3. Place methacholine solutions out of view of participant so that they will not know which dose they receive
4. Explain procedure to participant.

Pre-diluent lung function

5. Record **pre-diluent** spirometry
 - At V1:
 - If acceptability and reproducibility requirements are not met, do not proceed
 - Must obtain 3 acceptable and 2 reproducible efforts
 - Minimum of 3 efforts and maximum of 8 efforts
 - At V5, V6, and V7
 - If acceptability and reproducibility are not met after performing 8 maneuvers, select the highest FEV₁ from an acceptable maneuver (or the highest if none are acceptable) and proceed with the next step of the challenge
6. Minimum acceptable FEV₁ % predicted needed to proceed with challenge
 - V1 - FEV₁ greater than or equal to 75% predicted and equal to at least 1.0 L
 - V5, V6, V7 - FEV₁ greater than or equal to 70% predicted and equal to at least 1.0 L

Administration of diluent

8. Begin challenge, starting with 2 mL of diluent:
 - Add 2 mL of diluent to nebulizer using a syringe with a sterile filter (sterile bacterial-retentive filter, porosity 0.22 µm) when transferring the solutions from the vial to the nebulizer cup.
 - Check to be sure that the jet/baffle is in place; make sure the vents are left open
 - Attach compressed air to dosimeter box
 - Set dosimeter as follows:
 - dose duration of 0.6 sec
 - compressed air source at 35-60 psi
 - dose control in "Normal" mode
 - start duration of 0.5 seconds
 - Make sure dosimeter is on; attach tube from dosimeter to bottom of nebulizer
 - Actuate dosimeter 2 times to prime nebulizer and ensure visual production of aerosol
 - Have participant place one end of the nebulizer in mouth and put on noseclips
 - Have participant exhale to Functional Residual Capacity (FRC), followed by a deep, slow inspiration lasting about five seconds; at the beginning of the inspiration the dosimeter should actuate to administer the solution; it is important that the participant continue inhaling while the dose is being delivered. Have participant hold breath for about five seconds after reaching Total Lung Capacity (TLC)
 - Repeat actual administration of solution four more times at each level keeping careful count of number of doses given
 - After completing the 5th breath allow 30 seconds before beginning spirometry
 - Spirometry criteria:

Post-diluent

- Spirometry timing:
 - Initial effort is about 30 seconds after 5th breath (inhalation) of diluent and
 - Next effort is about 90 seconds following completion of the 5th breath
 - If additional efforts are needed to achieve repeatability, wait about 1 minute between efforts for participant to recover

Results

- At V1:
 - Must obtain 3 acceptable and 2 reproducible efforts
 - Minimum of 3 efforts and maximum of 8 efforts
 - Record the highest acceptable FEV₁ as post-diluent FEV₁ on Methacholine Challenge Testing (MC) form
 - If acceptability and reproducibility requirements are not met, do not proceed
 -
 - At V5, V6, and V7:
 - Minimum of 3 efforts and maximum of 8 efforts
 - Record the highest acceptable FEV₁ as post-diluent FEV₁ on Methacholine Challenge Testing (MC) form
 - Record the highest acceptable FEV₁ as post-diluent FEV₁ on Methacholine Challenge Testing (MC) form
 - If acceptability and reproducibility are not met after performing 8 maneuvers, select the highest FEV₁ from an acceptable maneuver (or the highest if none are acceptable) and proceed with the next step of the challenge
9. Assess response:
- If post-diluent FEV₁ remains greater than or equal to 80% of the pre-diluent FEV₁, proceed to the first methacholine dose
 - If post diluent FEV₁ is less than 80% of pre-diluent FEV₁, terminate challenge

Note: The post-diluent FEV₁ will be used to determine the Target FEV₁ (end of test) and the PC₂₀

$$\text{Target FEV}_1 = 0.8 * \text{post diluent FEV}_1$$

Administration of Methacholine concentrations

10. Prepare methacholine dose:
- Empty nebulizer by shaking excess fluid into sink.
 - Trigger the dosimeter once to dry the nebulizer nozzle.
 - Withdraw 2 mL of first methacholine dose and place in same nebulizer
11. Follow procedure as outlined in #7 above, after every methacholine concentration
- Assess response (FEV₁) to determine whether to proceed to next dose:
 - If the highest post-methacholine FEV₁ is greater than **the target FEV₁**, proceed to the next dose (step #7 above) until a post-methacholine FEV₁ is less than the Target or the 11th dose of methacholine (Vial A) has been administered

- If the highest post methacholine FEV₁ is less than or equal 80% of the post diluent FEV₁, terminate the challenge. This concentration will be used to calculate the PC₂₀

Note: Always base decision to proceed or terminate on highest FEV₁ for that dose, even if one of the FEV₁ measurements is less than 80% of post diluent FEV₁, the decision to proceed will be based on whether the highest FEV₁ is equal to or greater than the Target

At V1: If PC₂₀ is greater than 8 mg/mL for FEV₁, participant is not eligible; terminate the challenge after the 16mg/mL concentration and continue with the recovery phase.

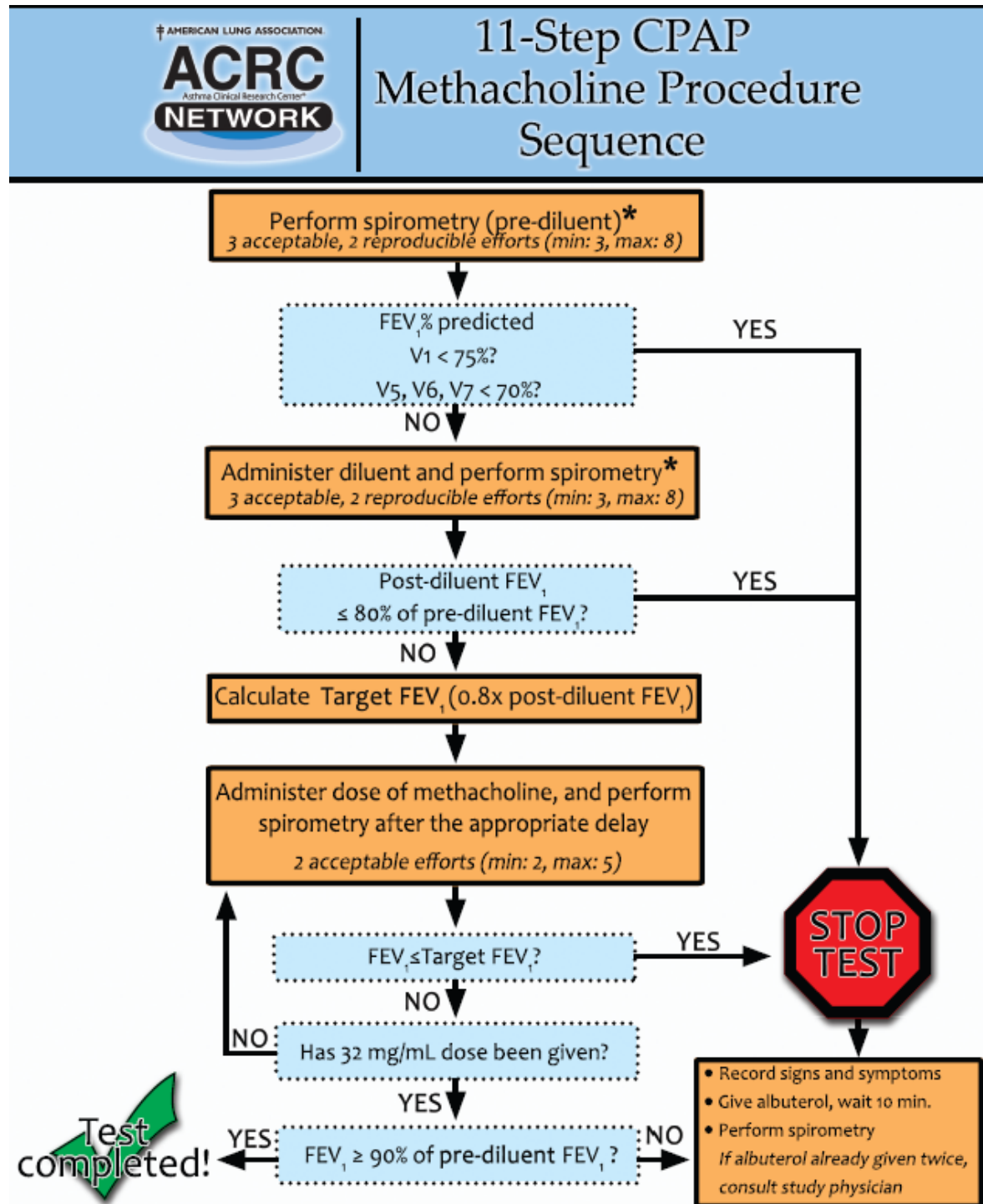
Administration of bronchodilator

12. Recovery:

- If the highest FEV₁ from any dose is less than or equal to 80% of pre-diluent FEV₁(as found in Step #5) when the test is terminated or completed,
 - Administer 2 puffs bronchodilator (albuterol) by MDI according to manufacturer's instructions.
 - Wait 10 minutes and repeat spirometry.
 - If the post bronchodilator FEV₁ is 90% or more of pre-diluent, the participant is finished and may leave the laboratory.
 - If the post bronchodilator FEV₁ is less than 90% of pre-diluent,
 - administer 2 more puffs of albuterol,
 - wait 10 minutes, and repeat spirometry
- If FEV₁ falls to less than **90% of pre-diluent FEV₁** (as found in Step #5) when the test is terminated or completed,
 - Administer 2 puffs bronchodilator (albuterol) by MDI according to manufacturer's instructions.
 - Wait 10 minutes and repeat spirometry.
 - If the post-bronchodilator FEV₁ is less than 90% of pre-diluent,
 - administer 2 more puffs of albuterol,
 - wait 10 minutes and repeat spirometry

Note: Notify physician if post bronchodilator FEV₁ remains less than 90% of pre-diluent after administering bronchodilator twice

4.2.13. CPAP methacholine challenge testing sequence

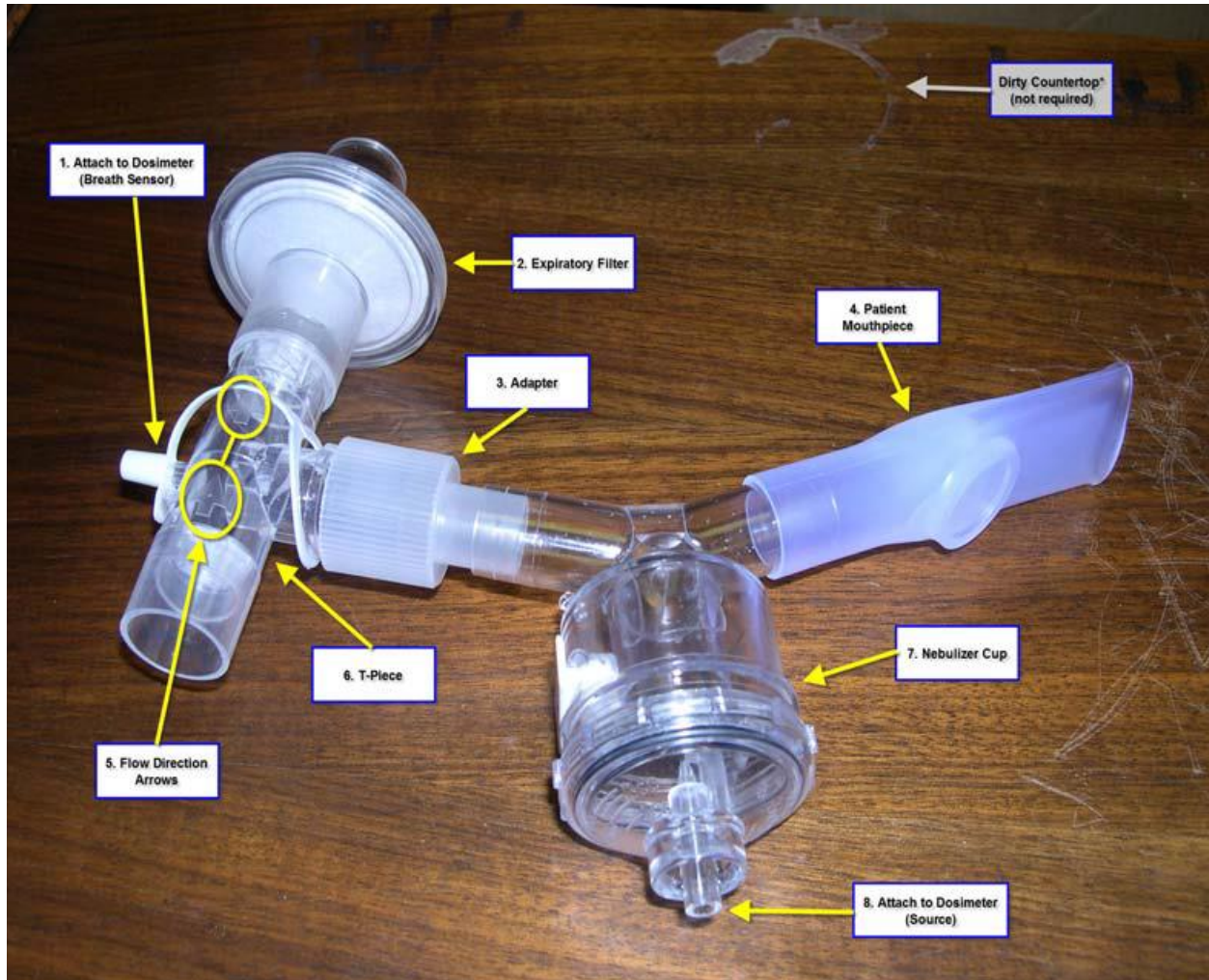


* V1: If none of the 8 efforts meet acceptability and reproducibility criteria for pre or post diluent, do not conduct methacholine challenge test.

V5, V6, V7: If none of the 8 efforts meet acceptability and reproducibility criteria for pre or post diluent, select the highest FEV1 from an acceptable maneuver (or the highest if none are acceptable) and proceed with the next step.

4.2.14. Pictorial of equipment setup

Methacholine Challenge Nebulizer Setup



1. Port to attach breath sensor tubing (remove white cap from t-piece)
2. Filter to capture exhaled methacholine
3. Adapter (“step-down adapter) to connect t-piece to nebulizer
4. Mouthpiece through which the participant breathes in and out
5. Arrows showing flow direction (both point toward expiratory filter)
6. The hard plastic “t-piece” with contained one-way valves
7. Methacholine solutions are placed here to be nebulized
8. Port to attach compressed gas source from dosimeter

Forms

- Methapharm Provocholine Order (LP) form
- Methacholine Challenge Testing (MC)
- Methacholine Challenge Worksheet – 11-Step (MW)

4.3. Exhaled Nitric Oxide (NIOX MINO)

Purpose

- Measure the fractional concentration of NO in exhaled breath (eNO) using the NIOX MINO®, Aerocrine, Inc.

When

- V2, V6 and V7
- Measurement to be taken before or one hour after spirometry (should be done prior to methacholine challenge, or one hour after return to baseline lung function as documented by last spirometry effort)






Overview

- Exhaled NO will be measured with a portable eNO device, the NIOX MINO®. The NIOX MINO® measures eNO at an exhalation pressure range of 10 to 20cm H₂O and an exhalation flow rate of 50±5 mL/s
- A NIOX MINO® is supplied by the DCC
- Sites are responsible for replenishment of patient filters, sensors and scrubbers

Equipment and supplies for testing

Please monitor the following expiration times (use information menu):

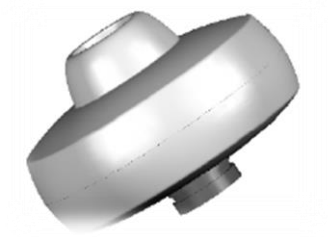
- Lifetime of the MINO instrument is 3 years or 3,000 tests, whichever comes first
- MINO Sensor maximum life is 12 months when mounted in MINO or as stated on the sensor, in addition it is only good for its specified number of tests (e.g., 50, 100)
- NIOX MINO scrubber is good for 12 months or 1,000 tests, whichever comes first
- An electronic version of the manual is provided and a training video have been provided. It is important that these be used for the set-up, use and eventual disposal of the machine.

| NIOX MINO® unit | The NIOX MINO® test supply kit | | NIOX MINO® scrubber | NIOX MINO® QC plug |
|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| | NIOX® patient filter | NIOX MINO® sensor | | |
|  |  |  |  |  |

4.3.1. External quality control (QC)

Equipment for external quality control procedure

- NIOX MINO® QC plug
- Patient filter



Objective

The external quality control is one of the procedures done to ensure the unit is operating within its specifications. It assures that the QC tester's eNO falls within range and that the NO scrubber is removing enough NO to get a reading of <5ppb.

Overview

The external QC consists of two parts:

- One positive control from a qualified staff member with a stable eNO value providing a normal biological eNO sample, and
- A negative control consisting of a NO free gas sample, generated from ambient air

Quality Control requirements for the NIOX MINO®:

“Daily” is a misnomer; a daily QC is required only on days the NIOX MINO® is to be used for participant testing.

FDA regulations mandate daily QC for clinical measurements (results being used for clinical care).

However, if the ‘daily QC’ has not been performed or has failed for a positive control (tester), it is still acceptable to measure the participant's eNO (results not being used in clinical care).

Note: QC should be done as soon as possible after the visit to assure the machine is in good working order.

Selection of Normal Control Testers for QC

Identify staff members (minimum of 2) who will serve as the Biologic Controls (Normal Control Testers) and who fulfill the following criteria:

- Over 18 years of age
- No ongoing respiratory or sinus infection or known airway disease
- Non-smoker
- Expected stable eNO values between 5 and 40 ppb
- Preferably no chronic allergies, sinonasal disease or asthma


“Qualification” of Normal Control Tester

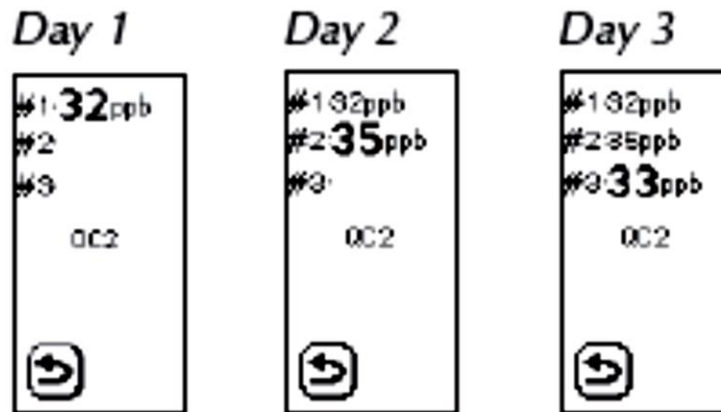
- Each Normal Control Tester is assigned a different individual number
- A mean value is calculated from the first three measurements, and the following tests must be within ± 10 ppb from the tester's mean (these are the individual tester's limits) and the scrubber result must be < 5ppb
- Each tester must perform a QC procedure at least once every 30 days to maintain his/her qualification status
- For tester to obtain reliable results, the tester should:
 - Avoid nitrate rich food within 3 hours of measurement
 - Avoid strenuous exercise at least one hour before the measurement
 - Not perform QC measurement if he/she has an ongoing cold or acute allergies

Note: During the first 20 days of instrument start-up, a maximum of four QC testers can be qualified without impact to the number of remaining tests on the Sensor

Performing the QC tests:

Note: A Normal Control Tester should not perform a measurement in case of ongoing respiratory infection or acute seasonal allergies

- Prior to first test allow a Sensor to be connected for 2 hours
- Prior to any QC measurement, the Normal Control Tester should:
 - Avoid nitrate rich food for 3 hrs
 - Avoid any strenuous exercise at least 1 hour
- Select QC mode
- Select QC tester number
- Perform a normal eNO measurement (standard NIOX disposable patient filter)
- Remove the patient filter
- Immediately attach the QC plug
- Select Forward icon on the display 
- Wait for the analysis to be completed and the test result to be displayed (about 5 minutes)
- QC results will be displayed
 - a. Day 1 - #ppb for tester
 - b. Day 2 - #ppb for tester on both Day 1 and Day 2
 - c. Day 3 - #ppb for tester on Day 1, Day 2, and Day 3



- d. Subsequent QC results for tester
 - i. Tester's current result (ppb) and limits (positive control)
 - ii. QC tester number
 - iii. Negative control (should be <5ppb)
- Remove QC plug

QC failure

- Repeat the QC procedure if the positive control (tester) or negative control test fails
- If the failure is due to the Normal Control Tester's eNO value being out of his/her range it is recommended that the test be repeated with another Normal Control Tester
 - Remember that any respiratory infection or allergies can influence the tester's eNO
 - A new patient filter is to be used for the repeat test
- If the QC failure persists, contact Aerocrine Inc. Technical Support at 1-866-275-6469 ext. 116

Note: tests performed with the NIOX MINO® unit during the QC procedures will not affect the number of remaining tests on the NIOX MINO® sensor

4.3.2. Measurement of eNO

Participant preparation:

Test results can be affected by many things. Testing should be done so that:

- Participant has not had any food or drink for one hour prior to eNO testing
- Participant has not done any strenuous exercise or smoking for one hour prior to eNO testing
- Participant has not used bronchodilator for 2 hours prior to eNO testing
 - eNO measurement should be done before spirometry

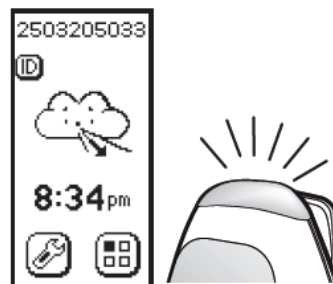
The Nitric Oxide (NO) form is to be completed at the time of the procedure so exceptions to these circumstances are accurately documented.

Supplies:

- MINO
- Patient filter
- Computer and USB cord if using visual incentive screen

Test procedures:

1. Assess the MINO machine:
 - A twinkling asterisk on the screen indicates the external QC procedure is activated, and QC should be performed by one staff member
 - New/unused NIOX MINO® patient filter in place
 - # tests remaining for sensor sufficient
 - If machine was recently plugged in, be sure it is ready for measurement

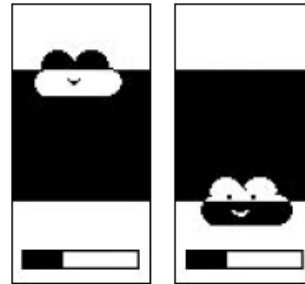


2. Participant ID is to be entered for each participant:
 - Select ID button on the main screen

- Input using the number buttons
 - Select ok to accept the ID
 - Record ID for participant's future tests
3. Participant preparation:
 - Participant should be seated
 - Review procedure with participant, using the demonstration mode
 - Participant is to empty lungs
 4. Place mouth on filter and inhale deeply through the filter to total lung capacity (should maintain tight seal)
 5. Exhale with steady pressure through the filter until the top light and sounds turn off
 - If breath is sufficient strength the result is continuous sound and top is lit
 - If breath is too soft/weak result is low frequency sound and slow flickering light
 - If breath is too hard/blast result is high frequency sound and fast flickering light



Correct exhalation display



Exhalation too hard (left) or too low (right)

6. Machine indicates end of necessary effort; the sound ceases with a click, the top light turns off and 2 clouds appear
7. Wait for result (1:40min.) to be displayed on the screen.
8. Record the result on the Nitric Oxide (NO) form.

Important: If the result for participant is " <5 ppb", record as "000" ppb on NO form
9. Repeat the test procedure and record results from second test on NO form
10. If unable to get results indicate issue on NO form
11. Discard used filter (mouthpiece) after testing

Forms (abbreviation)

- Nitric Oxide (NO) form

4.3.3. eNO Troubleshooting

Purpose

- Ensure that only under rare circumstances eNO measurements are not obtained during participant visits.

Resources

- User Manual (Aerocrine)
- Aerocrine Technical Support: 1-866-275-6469 ext. 116
- Common problems and solutions listed below

Common problems, potential issue and proposed solutions

| Problem | Potential issue | Solution |
|--------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|
| QC Fail – negative control | Failure to insert QC plug | Attach QC plug when instructed |
| QC Fail – positive control | Delay in inserting the CQ plug | Replace faster |
| | Normal control tester too high | Use a different normal control tester |
| Machine won't calibrate/or stay calibrated (spinning arrows) | High ambient NO (>300ppb), room temperature or humidity | New location |
| | Interference from equipment (this includes all nearby devices, e.g., participant's mobile devices, staff mobile devices) | Move all mobile phones, cordless phones, and other mobile devices that may interfere away from the MINO |
| Participant can't do the procedure | Participant stops too soon, | Encourage participant to keep blowing until you tell them to stop, count up to 10 out loud and slowly |
| | Participant blowing too hard or too soft | Demonstrate effort needed, use optional incentives* on computer screen |
| | Participant tired | Allow time between tests. |

**Instructions for the set-up of visual incentives are located in the User Manual*

The NIOX MIO® User manual has a comprehensive list of other problems, error codes and solutions. Keep the manual with your machine for quick and easy reference.

4.4. Specimen collection

Purpose

- To collect specimens for inflammatory biomarkers, eosinophil, and DNA (optional)

When

- Randomization (V2), V6 and V7

Pregnancy test for women of childbearing potential is to be done for eligibility for enrollment and prior to each methacholine challenge (V1, same day as methacholine for eligibility), V5, V6, and V7)

4.4.1. Overview of specimen collection schedule

| Specimen | DNA | Serum | Eosinophil |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Collection Tube | 10 mL lavender top Vacutainer (EDTA) | 10 mL clot activator (tiger top) Vacutainer tube | 6 mL lavender top Vacutainer (EDTA) |
| Label | Designated Barcode label from Label Sheet | Designated barcode label from Label Sheet | Per institutions guidelines, and Designated Barcode label from Label Sheet |
| Processing | <ul style="list-style-type: none"> Invert vacutainer 10 times to distribute anticoagulant May store at 4° C for up to 30 minutes before processing Centrifuge for 7 min at 2000g, 4° C Immediately remove plasma from Vacutainer tube and aliquot into 2mL cryovials. Label cryovials with participant ID. Firmly replace HemoGuard closure on the Vacutainer Freeze Vacutainer and cryovials at -70° C | <ul style="list-style-type: none"> Allow sample to clot for about 30 minutes at room temp. Centrifuge at 1300g (2500 rpm) for 15 minutes Place a minimum of 0.5mL of serum into each 2mL cryovial Sample to be divided between 2 cryovials (unless there is less than 1 mL of serum) Store in freezer, between -20 to -80°C | <ul style="list-style-type: none"> Invert vacutainer 10 times to distribute anticoagulant. Follow local lab requirements for CBC |
| Shipping | <ul style="list-style-type: none"> Batch ship both plasma and packed cells together on dry ice (frozen) priority overnight to: Pharmacogenetics Center c/o Ed Mougey Research, 9th floor Nemours Children's Clinic 807 Children's Way Jacksonville, FL 32207 Upon shipment, send email to: emougey@nemours.org | <ul style="list-style-type: none"> Batch ship serum on dry ice (frozen) priority overnight to: Pharmacogenetics Center c/o Ed Mougey Research, 9th floor Nemours Children's Clinic 807 Children's Way Jacksonville, FL 32207 Upon shipment, send email to: emougey@nemours.org | <p>Local lab</p> <p>Results recorded on: Clinic Visit (CV) form</p> |

4.4.2. Supplies for collection and processing

Supplied by DCC

- 10 mL EDTA vacutainer tubes (lavender top) V2 only for genetic testing
- 6 mL EDTA vacutainer tubes (lavender top) for eosinophil count
- 10 mL clot activator (tiger top) vacutainer tubes for collection of serum
- 2 mL cryovials (orange top)
- Transfer pipettes
- Barcode Label Sheets per participant that include labels for vacutainer tubes and cryovials
- Cardboard boxes and dividers for specimen storage (8"x8')
- Biohazard specimen bags (8"x8')

Supplied by DCC upon request

- Cryovial markers

Supplied by clinic

- Needle (appropriate gauge for age of participant)
- Needle holder
- Gloves
- Swabs for cleaning blood draw site
- Band-Aids
- Scotch tape
- Emergency supplies readily available

4.4.3. Collecting blood for samples

4.4.3.1. General requirements

- Gloves must be worn at all times when handling specimens. This includes during removal of the rubber stopper from the blood tubes, centrifugation, pipetting, disposal of contaminated tubes, and clean-up of any spills.
- Tubes, needles, and pipets must be properly disposed of in biohazard containers, in accordance with institutional requirements.
- Universal precautions and OSHA (Occupational Safety and Health Administration) and institutional requirements (<http://www.osha.gov/SLTC/biologicalagents/index.html>) should be followed, including gloves, eye protection or working in a biosafety cabinet for blood processing
- Use the appropriate barcode labels from the Label Sheet for each participant sample collected and processed. Fill in Name Code (Code) using marking pen. Print legibly. Cover with clear tape.
- If DNA sample is collected, wrap the barcode vacutainer label for Packed-cells onto lavender/EDTA vacutainer. Place Scotch tape on vial to cover label so that the tape completely covers the label and adheres to the tube on either side.

4.4.3.2. Blood draw for DNA and plasma

Purpose


- To collect blood specimens for pharmacogenetics testing and future studies related to asthma.


When

- Randomization visit (V2)

Draw blood:

- Verify participant consented for DNA analysis
 - Collect at least 8mL into labeled 10 mL EDTA (lavender top) vacutainer
 - Gently invert EDTA tube 10 times after collecting
 - Sample to be processed promptly, may store at 4° C for up to 30 minutes
 - Processing of blood in EDTA (lavender top) tube – plasma/ DNA
1. Centrifuge at 2000g for 7 minutes at 4° C
 2. Transfer plasma (upper layer) into 2 labeled 2mL orange top cryovials. Do not fill beyond 1.8mL line.
 3. Replace vacutainer top (lavender HemoGuard closure) and keep packed cell pellet
 4. Immediately place cryovials and vacutainer in -70° C freezer and hold specimens for batch shipment at a later date. If -70° C freezer is unavailable samples may be stored at -20°C for up to one week.

 **Note:** Lay vacutainer tube horizontal in freezer for 20 minutes prior to storing upright, otherwise expansion of ice crystals may crack the tube

 **Note:** If DNA cannot be drawn at V2, draw blood at a following clinic visit and use spare labels to label form and specimens. Record as a protocol deviation.

4.4.3.3. Blood draw for Inflammatory Profile

Purpose

- To collect blood specimens for inflammatory biomarkers and future studies related to asthma.

When

- V2, V6 and V7

Draw blood

- Collect 10 mL of blood in labeled 10 mL clot activator (tiger top) vacutainer
- Allow sample to clot for 30 minutes at room temperature

Processing of blood in clot activator (tiger top) tube – Inflammatory profile

- Centrifuge at 1300g (2500 rpm) for 15 minutes
- Place a minimum of 0.5mL of serum into each labeled 2mL cryovial, do not fill beyond 1.8 mL fill line
 - Sample to be divided between 2 labeled cryovials (unless there is less than 1 mL of serum)
- Store in freezer, between -20 to -80°C

Note: If blood cannot be drawn at a certain visit, draw blood at a following clinic visit (V4) and use spare labels to label form and specimens. Record as a protocol deviation.

4.4.3.4. Eosinophil count

Purpose

- To collect blood specimens for eosinophil count.

When

- V2, V6 and V7

Draw blood

- Collect blood in labeled 6 mL EDTA (lavender top) vacutainer
- Invert vacutainer 10 times to distribute anticoagulant.

Processing of blood in EDTA (lavender top) tube – Eosinophil count

- Sample is to be processed at the local lab for the ACRC clinical site. Sample is to be processed according to institution's guidelines.
- Result is to be recorded on the Clinic Visit (CV) form

Analysis arrangements

- Make arrangements for local analysis, at local CLIA – approved laboratory
- Use whatever method used at the laboratory for eosinophil count (cells per μL). Both flow cytometry and manual counting are acceptable methods. Eosinophil counting must be reported as cells/ μL , NOT as percentage.
- To convert % eosinophil to cells/ μL :
 - Multiply % eosinophil by number of white blood cells
 - Typical count for white blood cells is 4,000 - 10,000 cells/ μL

Example:

1% eosinophils x 5,000 white blood cells/ μ L = 50 eosinophil cells/ μ L

- Obtain collection and processing/storage instructions from lab

Form

- Clinic Visit (CV)

4.4.4. Specimen labeling

Purpose

- To label cryovials and vacutainers for specimen shipping and tracking

When

- V2, V6, and V7

Overview

- Each sheet of labels corresponds to one participant ID.
- Specimen labels are printed in identical pairs: one for the specimen (e.g., cryovial) and a matching one for the CV form.
- Labels are arranged in separate columns, each column corresponds to a visit and a specimen type. Each column has the two identical labels
- The barcode labels are pre-printed to include:
 - Participant ID
 - Space for the name code (to be hand written)
 - Visit ID
 - Specimen type (DNA-plasma, DNA-packed cells, serum or eosinophil), and
 - Aliquot number

Visit ID & Column number

Participant ID, Visit ID, and type of specimen with aliquot number

One of the paired labels for a specific specimen, which includes

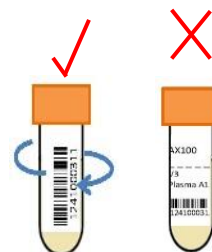
- Participant ID
- _____ for hand entry of Name Code
- Visit ID
- Specimen type (plasma, packed cells or serum) and aliquot number (A1 or A2)
- Barcode
- Barcode number

The 2nd label for the matched pair

Tasks

Labeling cryovials and vacutainers

- Check the Participant ID, Visit ID, and Specimen type on the paired labels.
- Place one label of the pair on the appropriate sample (e.g., cryovial or vacutainer), wrap it around as indicated for barcode to scan successfully, and wrap clear tape around the label.
- Fill in the 5-letter Name Code of the participant on the paired labels.
- Always make sure the labels are used as a pair.



Pre-printed labels for CV form


- Place the other label of the pair on the CV form in the appropriate space below item 41, 43, or 44.
- Make sure the label on the sample and the corresponding one on the CV form have the same aliquot number.
- Add a clear tape on the CV form label as well

41. DNA specimens processed and available for shipping

a. Plasma aliquot 1: Yes (1) No (2)

PX100
AEXRM
V2 Plasma A1
2241000211


↔



b. Plasma aliquot 2: Yes (1) No (2)

PX100
AEXRM
V2 Plasma A2
2241000212


↔



c. Packed cells vacutainer: Yes (1) No (2)

PX100
AEXRM
V2 P-Cells A1
2241000221

↔



42. Was serum for inflammatory biomarkers collected (expected at V2, V6, V7):

Yes (1) No (2)


44. ————

43. Serum processed and available for shipping

a. Serum aliquot 1: Yes (1) No (2)

PX100
AEXRM
V2 Serum A1
2241000231

↔



b. Serum aliquot 2: Yes (1) No (2)

*Serum Aliquot 2
barcode here*

Do NOT attach barcode for a specimen that is not available

44. Eosinophil count (*expected at V2, V6, V7*)


a. Eosinophil blood specimen collected:

Yes (✓₁) No ()₂

45. ————

PX100
AEXRM
V2
Eosino A1
2241000241

←————→



b. Record results of eosinophil analysis:

1 0 0 0
—————
cells/μL

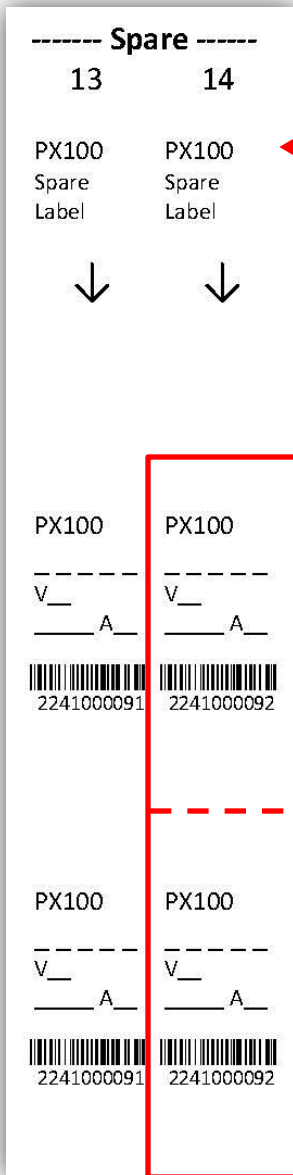
Spare labels

- Spare sets of labels are provided on each label sheet. These are to be used if the pre-printed labels are damaged or unusable.
- Make sure the spare labels are used as a pair.
- Fill in name code, visit ID, specimen type, and aliquot number.
- Place one label of the pair on the appropriate sample (i.e., cryovial or vacutainer), wrap it in the same way as the pre-printed label, and wrap clear tape around the label.
- Place the other label of the pair on the CV form in the appropriate space below item 41, 43, or 44.
- Make sure the label on the sample and the corresponding one on the CV form have the same aliquot number.
- Activate the new barcode number in the data system before shipping.

Note: Each clinic will receive 2 spare labels per participant ID. If clinic uses both spare pairs, contact the DCC to receive more spare labels by completing a CPAP Supply Order form (CO) and specifying Participant ID sheet requested.

Important Note: If specimens are collected on a different visit than expected, please use the spare labels for the specimens.

It is extremely important when you enroll new participants that you make sure to use a participant ID for which you have a corresponding sheet of barcode labels. If labels are not available, notify the DCC immediately to acquire labels before randomization.



Participant ID

One of the paired labels for a specific specimen, which includes

- **Participant ID**
- _____ for hand entry of name code
- **V__** for hand entry of visit ID
- _____ **A__** for hand entry of specimen type (Plasma, Serum, or P-cells) and aliquot number (1 or 2)
- **Barcode**
- **Barcode number**

The 2nd label for the matched pair

4.4.5. Specimen shipping

When

- After completion of V7 for a participants every 3 months

General overview

- When a number of specimens are ready for shipping, the process is to log them in the CPAP data system to generate a shipping log.
- After entering clinical identification information, you will be prompted to enter the barcodes from each specimen into a web application.
- Scan each specimen vial with your provided barcode reader and make sure the number entered on the screen matches the number printed beneath the barcode on the label.
- If your barcode scanner is malfunctioning or you are having difficulty scanning the barcodes, please make sure that:
 - There is no condensation over the label,
 - Your barcode scanner is plugged in and recognized by your computer. Individual labels that are difficult to scan may be entered by hand.
 - If you believe your scanner is malfunctioning, contact the DCC to request a replacement.
- Once you have finished entering all the barcodes for one shipment container, the system will generate a shipping log identifying all the specimens in your shipment box. Please look over the log to make sure all specimens match those that are being shipped.
- Print a copy of the log to place in the shipment container, and retain another copy at the clinic.

Shipping supplies include

- Supplied by DCC
 - Styrofoam box with outer cardboard box (shipper)
 - Plastic biohazard specimen bag (8"x8")
 - Absorbent sheet
 - Dry ice label (UN1845)
 - UN3373 label
 - Cardboard box with divider for specimen storage (8"x8')
- Supplied by clinic
 - FedEx air bill
 - Dry ice

Planning your shipment

1. Be certain the lab will be available to receive specimens
 - Only ship Monday through Wednesday
 - Do not ship within 3 days of a holiday (labs may close for different holidays)
 - Assess that weather should not be a factor (no pending hurricane or snow storm) at your site, the receiving site or transfer (check FedEx for any warnings they may have posted)
2. Set aside sufficient time to complete the process; specimens are sensitive to changes in temperature; the process of scanning/packaging/shipping should not be interrupted
3. Have the following ready
 - ALL specimens to be shipped
 - Shipping box/container with dry ice
 - Computer access to ALA-ACRC site, printer and barcode scanner

4. Remember the limit is one shipment (one shipper box) per day
5. Each shipper box should contain no more than 2 participant samples

How to scan study specimens and prepare the Specimen Shipment Record

1. Go to the appropriate study website and select specimen shipping. Accessing the shipping page will require you to log in.

Note: Note: Currently the data entry page is viewable only in Internet Explorer version 9 and below. If you are using Internet Explorer 10, please enable Compatibility View and add “jhct.org” to the list of websites to be displayed in that mode.

2. Click on “Specimen Shipping and Receipt”
3. On the following screen, click on “Ship Specimens.” The screen for Specimen processing and tracking includes:
 - a. Simple instructions (at top of page)
 - b. Display of barcode(s) scanned for shipment as entered
 - c. A brief description of any specimen with issues, such as “specimen not found”

Note: The system will know to expect a sample barcode only if the CV form is entered into the data system.

4. With the cursor placed in the box next to “Scan specimen here”, scan the barcode on the sample to be shipped.
 - a. Verify that sample has been added to list of specimens for shipment
 - b. Confirm that the participant ID and visit ID correspond to the label on the specimen
 - c. Systematically scan all specimens for shipment
 - i. Keep the specimens at the appropriate temperature before and immediately after scanning specimens
 - ii. If there are errors or issues with scanning a specimen please refer to Section 1.7 Troubleshooting.

Tips and other important information

- Only scan one vial at a time. The laser used to scan the barcode is quite long, so attempting to scan vials in close proximity to each other may result in recording an incorrect barcode.
- If a barcode is unable to be scanned, it can also be typed in.

For other issues refer to Section 1.7, Troubleshooting or contact the DCC at ala-acrc@jhsph.edu.

5. Verify the total number of specimens scanned equals the number being shipped.
6. Click the “Done scanning, Continue” button
7. Click “OK” when prompted to “Save data and prepare shipment log”
8. Print out the Specimen Shipping Log that is displayed on the following page
 - a. Click “Print” button

Note: Note: if you are unable to print to a printer at the moment you can print to PDF (providing you have Adobe Acrobat installed on your computer).

- b. Print two copies of the Specimen Shipping Log
 - i. One copy to be included as the shipping record
 - ii. Additional copy to store for your records

General packaging and shipping tasks

- Ship frozen samples (serum, plasma and packed cells) when a participant completes V7
 1. Prepare shipper box:
 - a. Fill Styrofoam shipper with dry ice
 - Styrofoam shipper box is to be filled with **at least 10 pounds** of dry ice
 - b. Affix proper labels on outside of cardboard shipper box
 - UN3373 label (Biological Specimens)
 - UN1845 (Dry ice label) if applicable
 2. Specimens should be protected:
 - a. Specimens should remain frozen for NCC throughout the packaging and shipping process
 - b. Packed cells (in 10 mL lavender top vacutainer) should be placed in a bubble wrap sleeve after being scanned
 - c. Cryovials (orange tops) should be placed in specimen cardboard box with divider (8"x8'); and protected with an absorbent sheet
 3. Shipments are to be done by ACRC coordinator who is :
 - a. Familiar with the CPAP ACRC specimen shipment protocol (including watching the specimen training presentation on the CPAP website)
 - b. CPAP DSO certified
 - c. IATA certified.
 4. Clinic should have an ACRC Specimen Assurance Statement signed by the PI and Lead Coordinator of the main ACRC site
 - a. This ensures specimen shipping is conducted in accordance with ALA-ACRC shipping guidelines

Note: If specimens are to be packed and or shipped by a non-ACRC staff member, it is the responsibility of the Lead Coordinator to train and verify the shipment is performed per ACRC requirements.

Instructions for the specific specimens

CPAP specimens to be shipped to Nemours:

Per participant

- EDTA tube (DNA/packed cells),
 - 2 cryovials (plasma; aliquots 1 & 2) from V2
 - 6 cryovials (serum; aliquots 1 & 2) from V2, V6, V7
1. Place all 8 cryovials for one participant in the cardboard box with divider for specimen storage (8"x8') as seen in the picture below
 2. Place the EDTA tube with DNA packed cells in a bubble wrap and lay tube inside the box.
 3. Close the cardboard box and wrap it with two rubber bands to hold the lid on
 4. Place the cardboard box in a biohazard ziplock bag
 5. Place an absorbent sheet in the bag

Note: Shipment of specimens is limited to specimens for 2 participants per shipper and to one shipment per day

Participant PX000



Participant PX001

6. Place the biohazard bag with cardboard box in a Styrofoam shipping container that has dry ice placed in the bottom
7. Cover box with the remaining dry ice
 - There should be little room for air in the container, extra moisture resistant packing material can be used to fill the container or eliminate more air space
 - Dry ice should be above and below the samples
8. Place Styrofoam cover on the container
9. Place signed shipping record (print out of scanned specimens) in a sealed bag on top (outside) of the Styrofoam lid
10. Seal cardboard shipper with packing tape
11. Prepare FedEx Airbill:
 - CPAP FedEx account to charge is: 3053-6089-9
 - Item 4a: Express Package Service check FedEx Priority Overnight
 - Item 5: Packaging – select other
 - Item 6: Special Handling
 - Indicate “Yes. Shipper’s Declaration not required.”
 - check "Dry Ice" and fill in weight of dry ice in kilograms (10 lbs. = 4.4 kg)
 - Verify same day pick-up
 - Verify that Biological Specimen and Dry Ice labels are attached to shipper
 - Item 3: Recipient to ship to :
 - Pharmacogenetics Center
 - c/o Ed Mougey
 - Research, 9th floor
 - Nemours Children’s Clinic
 - 807 Children’s Way
 - Jacksonville, FL 32207
 - (904) 697-3781
 - Affix FedEx label to shipper
 - Verify shipment is for same day pick up

12. Immediately upon shipment notify lab by sending email to emougey@nemours.org and copy Shawn.Sweeten@nemours.org

Note: Include FedEx tracking number in email

13. Shipment is not considered complete until you have verified that it arrived at the lab by:
- email from lab or
 - FedEx confirmation (with tracking number)

Note: FedEx has option for you to receive automatic confirmation of delivery, see Section 1.6.

Note: Each shipper should must include a single cardboard box

Note: If sending multiple shipments, do not send them all on the same day

Tracking specimen shipments with FedEx

You can indicate to obtain proof of delivery for a shipment or use FedEx Desktop

On the ACRC Investigators website is a video that explains how to utilize FedEx tracking notifications when shipping specimens for a study. The link to the video can be found below:

[https://www.jhcct.org/Secure/investigators/Meetings/RG%20\(Feb13\)/DCC%20FedEx%20Shipping%20Video.wmv](https://www.jhcct.org/Secure/investigators/Meetings/RG%20(Feb13)/DCC%20FedEx%20Shipping%20Video.wmv)

To track a shipment on FedE.com, click the following link:

https://www.fedex.com/fedextrack/?cntry_code=us&tab=1&tracknums=&clienttype=wtrk

Troubleshooting for specimen shipments

The table below includes suggestions for solving and preventing problems with specimen shipment. If you have an issue that is not addressed below you can submit a data feedback form or call the DCC. Since the system will not save information if it times out, you may find it preferable to not ship a “problem” specimen with a later shipment.

Note: At this time specimens without barcodes and specimens with barcodes that cannot be read (e.g. rubbed off in part or in full) cannot be shipped, but should be kept in appropriate storage conditions until system can accommodate them.

| Issue | Solution (s) | Prevention |
|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| Scans (can see the light, hear the beep) but number does not show up on screen | <ol style="list-style-type: none"> 1. Be certain cursor is in the box for the value to go in. 2. Be sure that scanner is securely attached to the computer. 3. Barcode number can be typed in if scanner not working. | |
| Specimen has a spare label | Scan the same as for other barcode labels. Spare label | Before using labels always |

| | | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| on it | is participant and specimen specific. | verify: Right participant Right specimen Right visit |
| The label is for the correct participant , but the wrong specimen type | <ol style="list-style-type: none"> 1. Complete a spare label for the correct participant and specimen type 2. Dry off tube. 3. Apply new label and apply clear tape over label 4. Attach 2nd spare label to the CV form 5. Amend data entry of CV form with new barcode; include notation regarding event 6. Notify DCC | Always verify: Right participant Right specimen Right visit Right place (one on specimen one on CV) |
| The label is for the wrong participant, but with 100% certainty the correct participant ID is known | <p>Re-label with extreme care:</p> <ol style="list-style-type: none"> 1. Complete the correct label (if available) or complete spare labels 2. Dry outside of tube or cryovial 3. Apply new label and apply clear tape over label 4. Attach matched 2nd label to the CV form 5. Amend data entry of CV form with new barcode 6. Complete a UE form | Always verify: Right participant Right specimen Right visit Right place (one on specimen one on CV) |
| <p>System gives message that specimen has not been collected. If it is because:</p> <ol style="list-style-type: none"> 1. CV form not data entered 2. CV barcode entry does not match barcode on specimen tube 3. Barcode not in system because specimen labels applied incorrectly (applied duplicate labels to specimens and CV resulting in specimens having one set of matched labels and the CV having the other matched set). | <p>Message indicates only that barcode data from CV is not in the system. Solutions:</p> <ol style="list-style-type: none"> 1. Verify whether the CV form has not been entered. Manually verify that barcode labels match and ship. 2. Compare specimen label to CV form label. Remember the specimen ID must be identical before specimen can be shipped. Correct CV entry if necessary. Note: This is more likely to happen if barcode information is typed in. 3. Requires re-labeling: <ul style="list-style-type: none"> - Carefully complete spare label sets - Dry outside of tube or cryovial - Apply new label(s) and apply clear tape over the label on specimen(s) - Attach matched 2nd label(s) to the CV form - Amend data entry of CV form with new barcode information - Complete a UE form | <ul style="list-style-type: none"> - Enter CV data within 10 days of visit and - Use barcode scanner to enter barcode in data system - Always verify labels are applied one to specimen and one to CV form |
| How do I know what specimens I need to ship | Access the Specimen Status page to see status of all specimens | |
| Will the data system save a partially entered shipment | If the page times out the data entered will be lost. <i>Note: Page times out after about 15 minutes.</i> | Set aside enough time to scan, package and ship |

| | | |
|-------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|
| | | specimens as one continuous process. |
| What if I can't print the shipping log/manifest | If the page cannot be printed to paper the following are suggested: 1. Print to PDF and save to your computer 2. Use print screen function and save as a file Remember this log is for your records and to be included in the shipping container. Do not ship specimens without it. | Always have printer access when entering shipment. |

4.5. Peak flow measures

Purpose

- Measure peak flow to determine change in morning peak expiratory flow rate (PEFR) as a study outcome and as a method of self-monitoring for participants

When

- Daily throughout the study
 - Morning peak flow at least 6 hours after last dose of asthma medications and before morning dose of asthma medications
- At V1 to calculate Asthma Action Plan Card (AAP) zones

Equipment

- Mini-Wright Peak Flow Meter (ordered from Bayview Medical Inc.)

Testing procedure

- Instruct participant to:
 - Stand up and relax. Always measure peak flow in the same position
 - Slide the red indicator to zero and insert the mouthpiece. Be sure your fingers do not obstruct the slot in which the pointer slides or the end where the air comes out
 - Take a deep breath
 - While holding breath, place the Peak Flow Meter in mouth – on tongue – then close lips around the mouth piece
 - Blow out as hard and as fast as possible. One second is long enough to blow out. Do not puff air out with cheeks, use lungs to force the air out
 - Write down the number read off the meter
 - Repeat measurements 2 to 5 more times. The goal is to match the two highest blows within 40 LPM; that is, the two highest numbers should be within 40 above or below each other
 - Reset indicator to zero before you repeat the measurement
 - Report the highest number measured on the appropriate form
 - Participant records daily on CPAP Diary Card (DC)

- At V1, record participant's three efforts on the Screening (SC) form the personal best on the Asthma Action Plan Card (AAP)

Note: Personal best for Asthma Action Plan Card (AAP) is the highest peak flow of three efforts from V1

Note: Disposable one way valve mouthpieces can be used for peak flow at V1

Forms (abbreviation)

- CPAP Diary Card (DC)
- Screening (SC) form

Information sheets (abbreviation)

- Asthma Action Plan Card (AAP)*
- Instructions for Measuring Peak Flow (IPF)*

**Not entered into database*

5. Study treatment

5.1. Study device

5.1.1. Device description

Device

A continuous positive airway pressure (CPAP) device delivers air to a user via a flow generator and mask system. The CPAP devices used in this trial are made by ResMed Inc., a medical device company based in Australia, which specializes in respiratory therapy. Below is an arrangement of the CPAP device and its associated humidifier.

CPAP unit (left) + humidifier (right) = CPAP device



Treatment groups

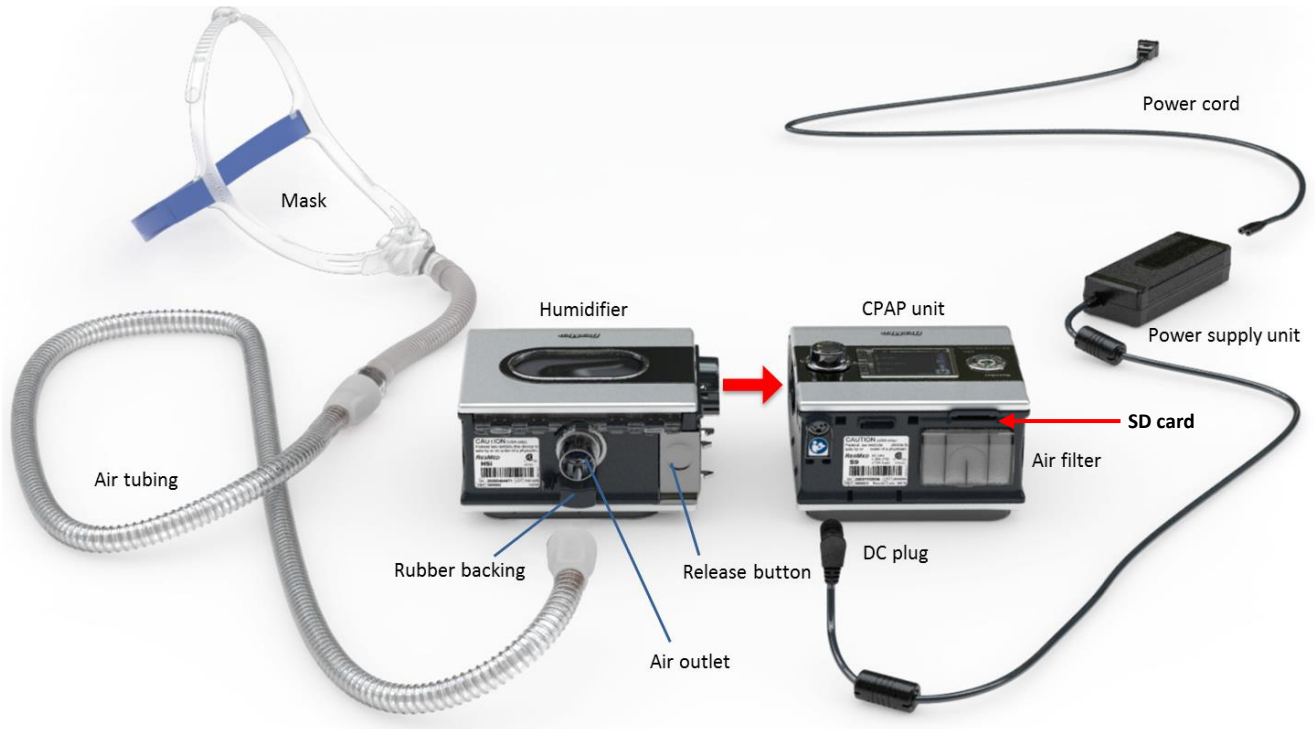
All arms of the trial will receive warm, filtered, humidified air at pressures of

- 10 cmH₂O (high), or
- 5 cmH₂O (medium), or
- Less than 1 cmH₂O (low)

5.1.2. Device setup

How to connect the CPAP device

The CPAP device and associated components will come in a travel bag that carries the unit and all its accessories (shown in the figure below)



1. Align your **humidifier** with your **CPAP unit** and push them together until they click into place. To separate the study device units, push the **release button** and pull them apart. The CPAP unit and humidifier are designed to be connected together as one unit.
2. Connect the **DC plug** of the **power supply unit** to the back of the **CPAP unit** and connect the **power cord** to the **power supply unit**. Make sure the DC plug is oriented correctly when inserting.
3. Plug the other end of the **power cord** into a grounded outlet or surge protector.
4. Remove the **rubber backing** adjacent to the **air outlet**.
5. Connect the end of the **air tubing** with the orange tab to the **air outlet**. Turn clockwise to lock.
6. Connect the other end of the **air tubing** labeled "ClimateLine" to the assembled **mask**.

There is no reason to detach the CPAP unit and humidifier unless traveling, or if instructed by the coordinator.

Filters and water tubs should be spot checked during follow up visits for cleanliness and should only be replaced if they are severely clogged or damaged.

The **air filter** is located on the back of the study device and is important for clean filtered air flow. The participant should not remove the filter from the device at any time.

The **SD card** is located in a slot above the filter. It is used to record participant compliance and should not be taken out by the participant.

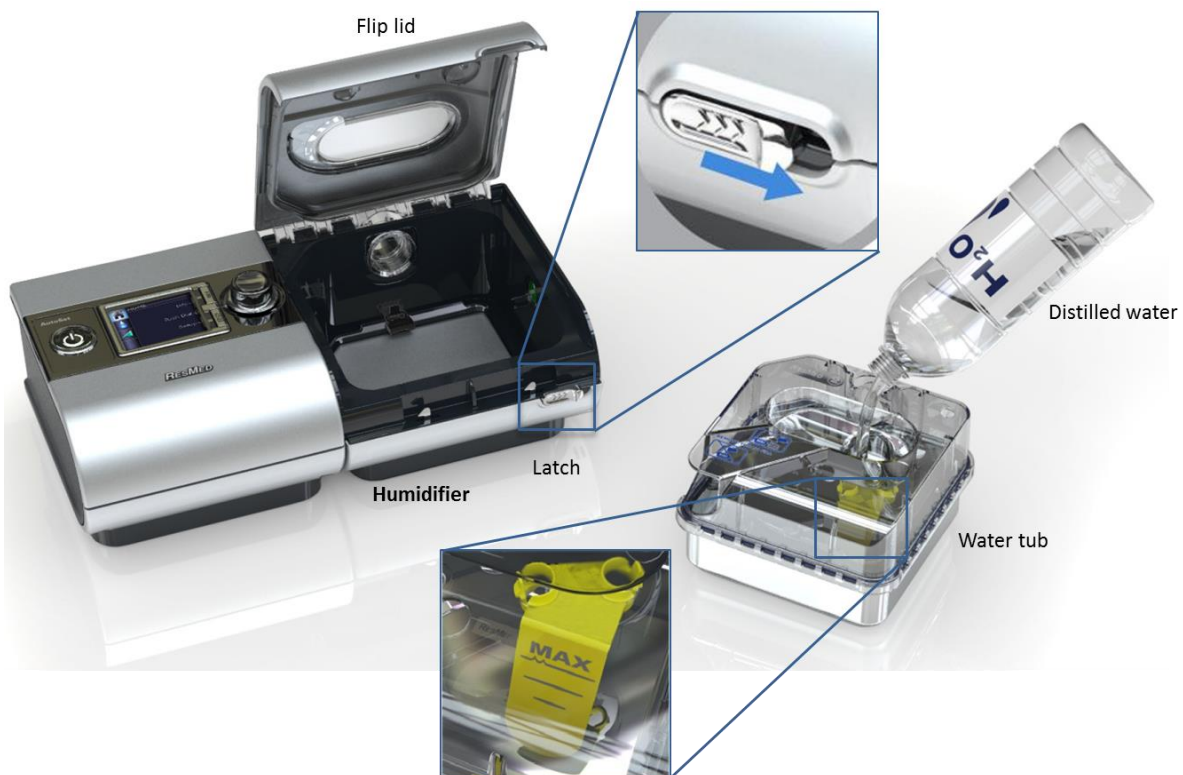
Air tubing

Each CPAP unit will come with a 6 foot length of Climate Line air tubing that connects from the humidifier to the mask system. This air tubing provides extra heating to incoming air flow in order to avoid any condensation that might otherwise form within the tube.



How to prepare the humidifier for use

1. Slide the **latch** and lift open the **flip lid**. Remove the **water tub**.
2. Fill the **water tub** (through the center hole) with distilled water up to the maximum water level mark.
3. Return the water tub to the humidifier. Close the flip lid ensuring that it clinics into place.



If distilled water is not available, bottled water or tap water can be used. If tap water is used, it should be boiled for **10 minutes** and be cooled before it is used.



Participants should fill the humidifier with fresh water before each use.



Make sure the water tub is **empty** before moving your CPAP device.



Always remove the water tub from the humidifier to refill it.



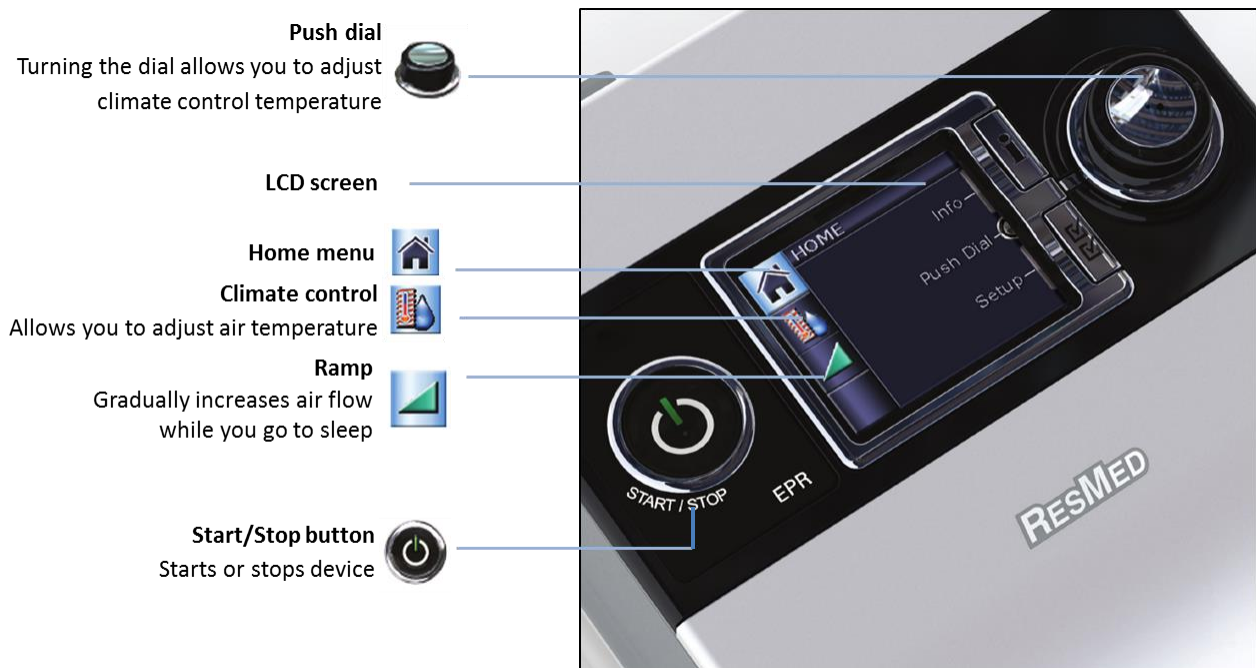
Take care when handling the humidifier as the water/water tub may be hot.

The CPAP device display/key pad

The display of the CPAP device has three main elements:

1. The **start/stop button** is used to begin or end the therapy air flow.
2. The **push dial** allows the user to navigate menus and select items. Turn the dial right or left to cycle through menu elements and push down the dial to select an option.
3. The **LCD screen** on the CPAP unit displays information related to the functioning of CPAP.

You may note two additional buttons on the device face marked with an “i” symbol and a checkbox ✓ symbol. These buttons will show information that has been made meaningless for the study.



In the figure above, the device is displaying the **Home screen** which is the screen most often seen when the participant is interacting with the device. The small house icon on the left hand side indicates that the device is on the home screen. When all device accessories are connected, the home screen will appear as shown above.

When the device is in use, the lights on the LCD screen will dim after a few seconds. To illuminate the display, press the push dial.

Below the home screen icon is the icon for **climate control** menu. The temperature of incoming air can be adjusted in the climate control menu.

To access the climate control menu, simply turn the dial **clockwise**. Pressing the “i” button at any time will return the user to the Home screen or the Climate Control menu. If you are returned to the climate control menu, simply turn the dial clockwise to reach the Home menu.

Adjusting air temperature on the device

The Climate Control function allows the participant to select a comfortable temperature for their therapy. When the device is in use, you may simply turn the dial to increase or decrease the temperature. It is recommended that the device be set to **80°F**.



From the **Home** screen, turn the **push dial** until **Climate Ctrl** screen is displayed in blue.



Press the **push dial**. The selection is highlighted orange.



Turn the **push dial** until desired temperature is displayed.



Press the **push dial** to confirm your choice.

When adjusting temperature, it is recommended to increase or decrease temperature in **increments of 2**.



Ramp setting

The ramp icon is located beneath the Climate Control icon, as shown in the figure above. The ramp feature gradually increases the air flow over a set interval while the participant goes to sleep. The ramp will be preset for 15 minutes and it assists participants in adjusting to the CPAP therapy, hence improving their adherence to treatment.

Temperature can be adjusted when the air flow is turned off, or on to start therapy.

5.1.3. Device cleaning and maintenance

CPAP unit

The participant should wipe the exterior of the CPAP unit and humidifier with a damp cloth and the provided soap on a weekly basis.

Water tub

It is recommended that the water tub be rinsed every morning after use. For weekly cleaning, the participant must rinse the water tub with warm water and the provided soap until it is free of bubbles. Let the tub air dry afterwards, but it does not have to be completely dry before reuse. The figure below illustrates steps of cleaning the water tub

The DCC will supply Ivory hand soap, which is recommended for cleaning the device, water tub, and masks.



Remove the air tubing by pulling on the finger grips on the cuff. Hang it in a clean, dry place until next use.



Slide the humidifier latch.



Lift open the flip lid and remove the water tub.



Wash the water tub in warm water using mild unscented hand soap.



Rinse thoroughly in clean water and allow it to dry away from direct sunlight.

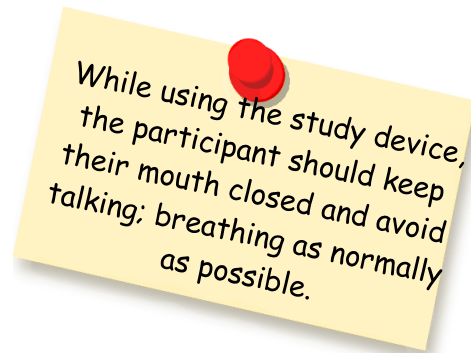
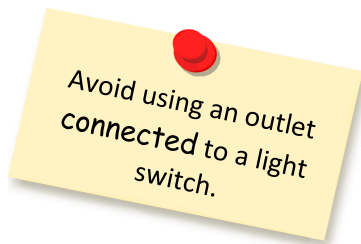


Before next use, fill the water tub, return it to the humidifier and close the flip lid.

5.1.4. Preparations to use the CPAP device

Before using the study device

- The study device should be placed on a **sturdy level surface**, preferably at head level or just below; a nightstand is ideal.
- Plug the device into a grounded outlet whenever possible. If a grounded outlet is not available, a surge protector may be used instead.
- All air tubing should be kept away from pets.



1. Make sure the power is connected and adjust the temperature (80°F is recommended).
2. Fill the humidifier with distilled water and connect it to the CPAP device.
3. Fit the mask as described by the coordinator and in the instructions packet.
4. Connect one end of the air tubing to the device and connect the other end to the mask.
5. To start therapy, simply press the **Start/Stop** button. The LCD screen on your CPAP will dim after a few moments but the device will continue to blow.
6. Lie down and arrange the air tubing so that it is free to move if you turn in your sleep.
7. To stop treatment at any time, remove the mask and press the **Start/Stop** button.

Participant should record the time they used the CPAP device on their Diary Cards every morning.

Note: The on/off button is yellow when the device is on standby (hooked up to an outlet but the air pressure is off) and blue when the pressure is on.

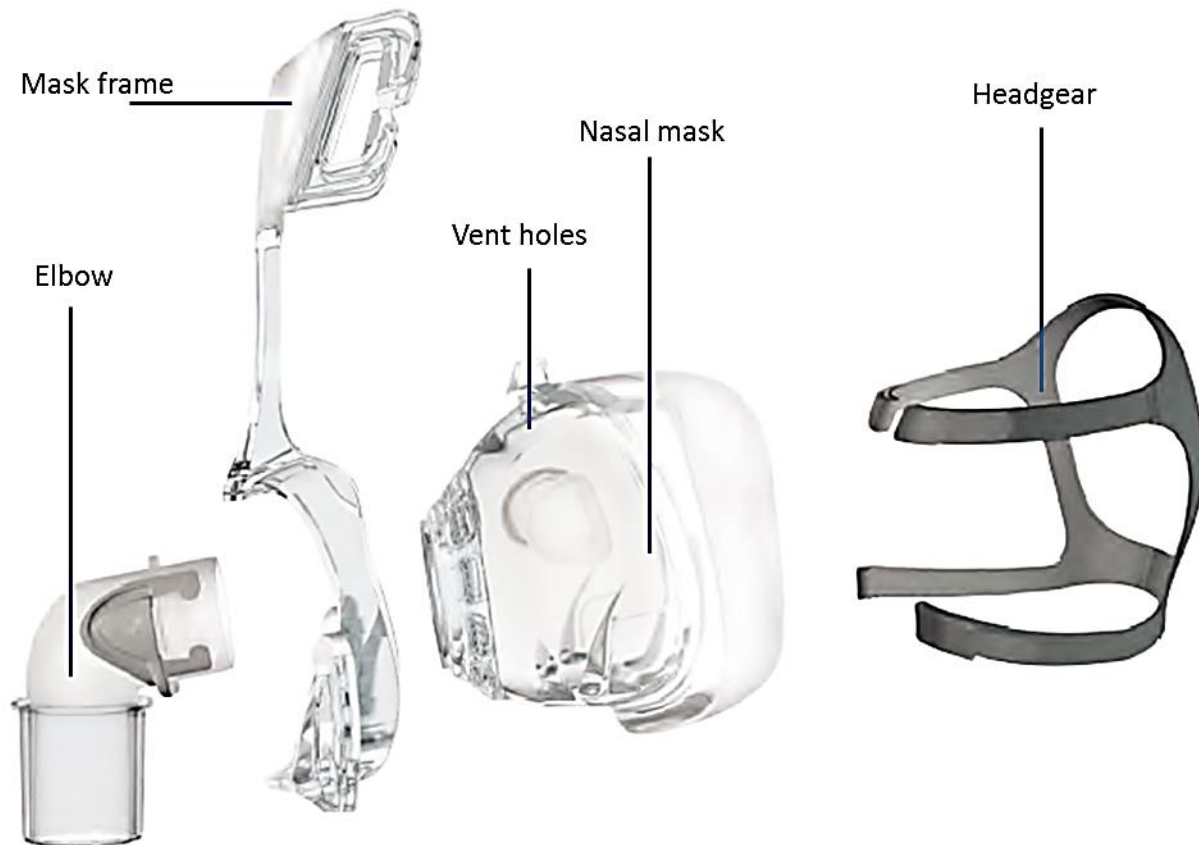
5.2. Study masks

5.2.1. Mirage FX

5.2.1.1. Parts and assembly

The Mirage FX is a **nasal mask** which completely encloses the participant's nose. The mask system is comprised of a detachable elbow, mask frame, nasal mask, and headgear.

The nasal mask comes in two sizes: standard and wide.



Disassembly of nasal mask



1 Unhook the upper headgear straps from the mask frame; there is no need to undo the Velcro.



2 Remove the elbow and air tubing from the mask by pressing the side-tabs and pulling away from the mask. Then separate the elbow from the air tubing.



3 Gently separate the cushion from the mask frame.

Reassembly of nasal mask



1 Align the top cushion tab with the indentation in the top of the mask.



2 Gently pull the cushion through the front of the mask frame until the cushion locks into the mask frame. The tabs on either side of the cushion should be sitting against the mask frame. Make sure the cushion is not twisted or distorted.



3 Attach the top headgear straps to the mask frame by looping onto each of the upper headgear hooks.



4 Replace the elbow into the air tubing and attach the other end of the mask by pressing the side-tabs and pushing.

5.2.1.2. Fitting

The general rule for fitting the masks is for the mask to be snug, not tight. To test for a snug fit while fitting the mask, you should be able to fit two fingers under the headgear comfortably. This is called **the 2-finger rule**.



Prior to fitting the mask, remove the elbow from the mask by pressing the squeeze-tabs. The squeeze-tabs allow the mask to be quickly detached from the tubing if the participant gets up in the middle of the night to use the bathroom.



Connect the elbow to the device air tubing. To remove the elbow from the tubing, hold the tubing in one fist and the elbow in the other, and bend the two in a breaking motion.



With both lower headgear straps released, hold the mask against the face and pull the headgear over the head.



Bringing the lower straps below the ears, loop the headgear into the lower hooks on the mask frame. Once the lower straps are positioned correctly, remove them from the mask system by pulling the loop off the frame rather than removing the Velcro. For easy removal during use, simply pull off one loop off the mask system and then remove the rest with your other hand.



Unfasten the straps, pull the upper headgear straps evenly until they are comfortable and firm, and reattach the straps. Repeat with lower straps.



Attach the combined elbow assembly and air tubing to the mask by pressing the squeeze-tabs and pushing into the mask frame. Turn on the airflow device.

To ensure a proper mask fit, it is recommended that the participant lie down and test the mask with the machine on:

- While participant is lying down, check mask for comfort and leaks and adjust headgear straps if necessary.
- Feel the exchange of air from the vent holes.
- Turn participant head side to side, up and down. Check for leaks and adjust accordingly.
- Tell participant to concentrate on breathing in and out

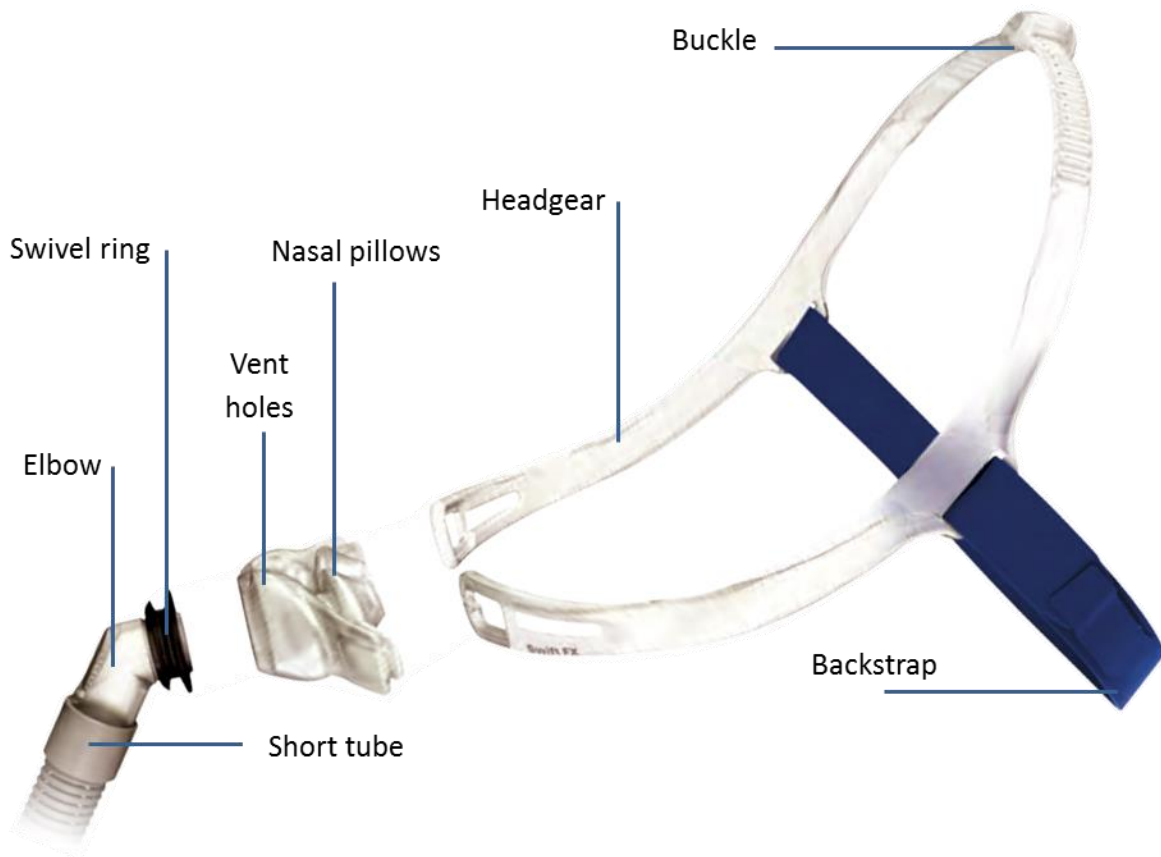
Since coordinators will assist participants in fitting the masks at the randomization visit (V2), there should be no need for the participant to readjust the mask after leaving the clinic.

5.2.2. Swift FX

5.2.2.1. Parts and assembly

The Swift FX is a **nasal pillow** set which sits just in the nostrils of a participant. The mask system is comprised of a detachable short tube, nasal pillow, and headgear.

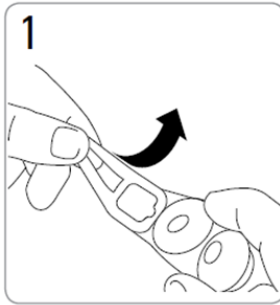
The nasal pillows come in three sizes: small, medium, and large.



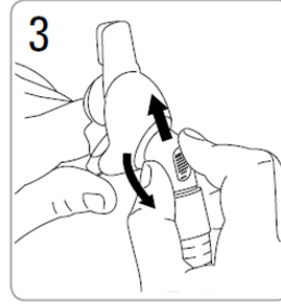
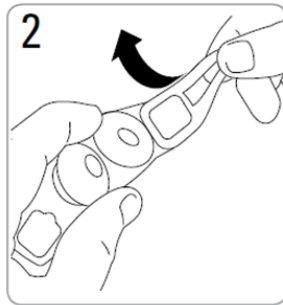
Sleeves are also included with the nasal pillows and can be placed on the headgear for more comfort during use and for minimizing red marks that can occur on cheeks.



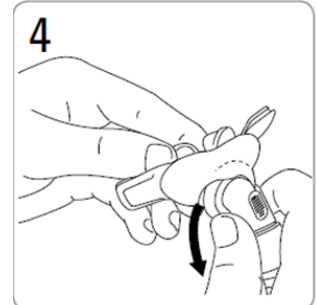
Disassembly of nasal pillows



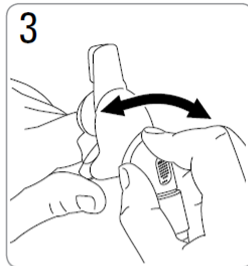
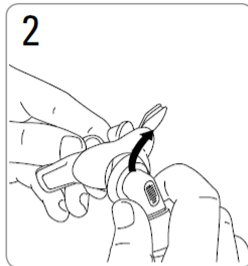
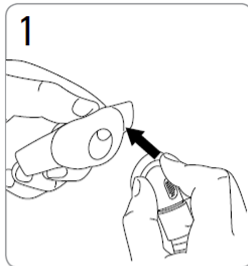
Unhook the straps.



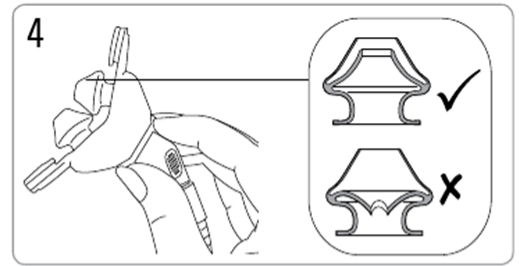
Remove elbow from the mask



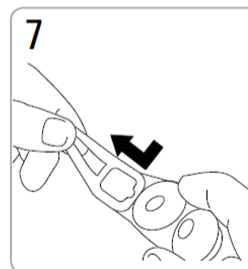
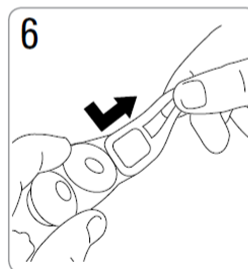
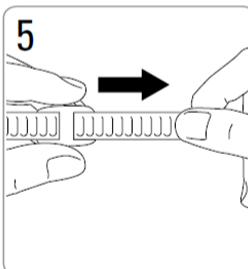
Reassembly of nasal pillows



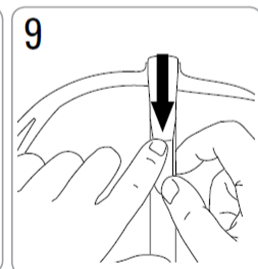
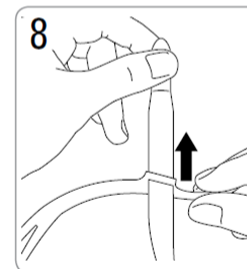
Attach the elbow to the pillows



Make sure the pillows are properly aligned



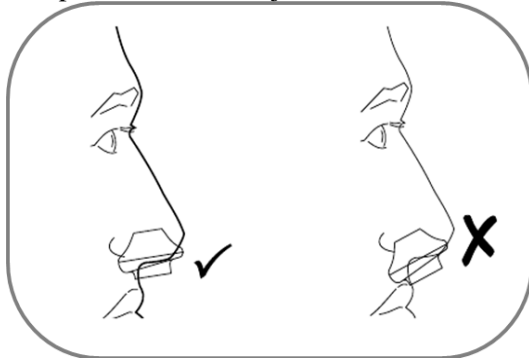
Rehook the straps to the pillows. Make sure that there is a ResMed logo next to the pillow size and that all logos are upright and readable.



Adjust straps for comfort

5.2.2.2. Fitting

The pillows should sit just inside the nostrils in a position that is snug but not tight.



Always remember the **two-finger rule** to test for a snug mask fit.

Follow the steps below to properly fit a participant with nasal pillows.



1 Holding the pillows at your nose, pull the headgear over your head. Headgear should sit midway between the ears and eyes.



2 Adjust the top strap first. Pull the strap through the buckle one notch at a time. Don't over tighten.



3 Adjust the backstrap if needed, but don't over tighten. The backstrap can be positioned over or under the hair. Be sure you are able to place two fingers underneath the backstrap for a good fit.



4 Adjust pillows to the most comfortable angle in the nose.

To ensure a proper mask fit, it is recommended that the participant lie down and test the mask with the machine on:

- While participant is lying down, check mask for comfort and leaks and adjust headgear straps if necessary.
- Feel the exchange of air from the vent holes.
- Turn participant head side to side, up and down. Check for leaks and adjust accordingly.
- Tell participant to concentrate on breathing in and out

Since coordinators will assist participants in fitting the masks at the randomization visit (V2), there should be no need for the participant to readjust the mask after leaving the clinic.

5.3. Selecting a mask

Selecting a mask type

The key to this trial is participant adherence to CPAP therapy. Ensuring that the participant is comfortable with their mask is the priority. Sizing the participants for both types of masks is important because a participant might need to switch the type of mask they are using if they feel any discomfort.

At the Randomization visit (V2) you will be fitting the participant with both types of masks, but you will send them home with only one type of mask. It is preferable to start the fitting with the Swift FX pillows because it is the least confining interface and most participants are attracted to that. However, prior to fitting it is helpful for you to know which mask might fit best for the participant. This may help to limit the number of mask discomfort calls you might receive. Ask the participant the following questions prior to mask selection:

Do you have any of the following?

- Nose bleeds
- Sinus problems
- Allergies
- Prone to skin irritation
- Deviated septum or previous broken nose

If a participant answers yes to any of the above, be sure to recommend they use a **nasal mask (Mirage FX)**.

Also ask the participant if they have claustrophobic tendencies. If so, be sure to recommend that they use the **nasal pillows (Swift FX)**.

The participant may choose either mask based on what best suits their comfort and will support their adherence. The participant should go home with **one type** of mask after trying both masks at the randomization visit (V2). If participant wants to exchange the mask they initially chose with the other type, schedule a clinic visit and fit them with the other mask.

Headgear size

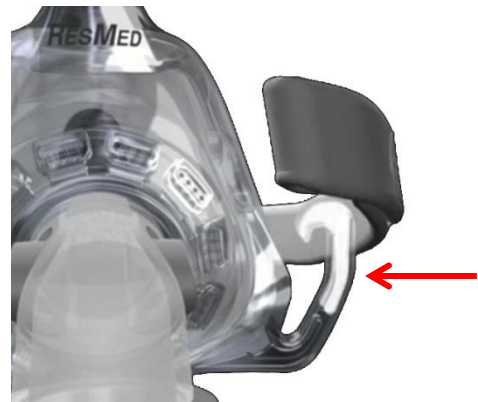
Some participants may be turned off by the size of the headgear on the Mirage FX in which case the fewer straps and optimal positioning of the Swift FX will be more appealing.



Removing the Mirage FX

If the participant prefers the feel of the Mirage FX mask over the Swift FX pillows, but they are concerned about the difficulty in removing the headgear, instruct the participant to unloop only one of the lower straps when taking off and putting on the mask system.

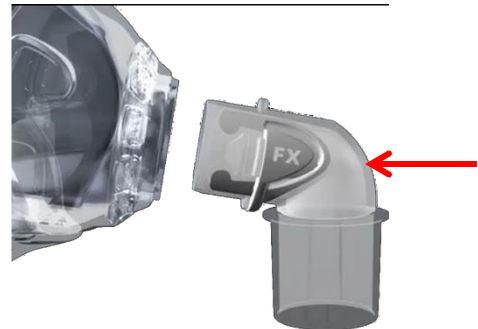
Both masks have a swivel at the elbow that rotates 360 degrees to give more freedom of movement at night. Alternately, participants can detach the mask using the elbow as shown below.



Using restroom at night

For those participants concerned about waking during the night to use the restroom, the Mirage FX is equipped with a quickly detachable elbow tube. To remove the elbow tube, press the squeeze tabs indicated.

For those participants using the Swift FX, they can detach the short tube of the mask from the air tubing.



Sizing the participant

Each mask offers varying sizes to accommodate a variety of nose and facial shapes.

Mirage FX comes in standard and wide sizes. Standard size will generally fit 90% of participants. Mirage Wide fits people who have shorter and wider noses.



Standard



Wide

Swift FX nasal pillows come in small, medium, and large sizes. The pillow sizes refer to the size of the participants nostrils.



The **chin strap** is provided for all participants in their assigned kit. Chin straps are used to help participants who are mouth breathers to breath from their nose instead of their mouth to get the maximum treatment benefit.



5.4. Mask cleaning and maintenance

Recommended mask and air tube cleaning

It is recommended that the participant clean the mask, air tubing, and headgear on a weekly basis. Note that participants should never use solutions containing vinegar, bleach, chlorine, alcohol, aromatics, moisturizers, antibacterial agents or scented oils to clean any part of the system or air tubing as they may damage and reduce the life of the product. No part of the system or tubing should be exposed to direct sunlight as it may deteriorate the product. For all mask components, ask participants to:

1. Gently and thoroughly bathe the components (mask and air tubing) in warm water using mild soap.
2. Rinse all components well with drinking quality water and allow to air dry out of direct sunlight.
3. When all components are dry, reassemble the mask according to the instructions.

5.5. Practice kits

Each main clinic will be supplied with one practice kit that will remain at the clinic to help coordinators learn about the device and for the purposes of displaying it to participants during the screening visit (V1). The practice kit contains every item that will be placed in study kits:

- CPAP unit,
- Humidifier and water tub,
- CPAP Device User Instructions (ICD),
- Air tubing,
- SD card,
- Power unit and power supply,
- Swift FX mask (2 sets for demonstration purposes),
- Mirage masks - standard and wide (2 sets for demonstration purposes), and
- Chin strap

The practice masks are **sample masks** that should be used at the screening visit (V1) for participants to demonstrate what is expected of them during the study.

Do NOT hook up the mask to the sample device. Assess the participant's readiness and confidence to use CPAP every night for 12 weeks.

DO NOT start treatment on the device while the participant is trying the sample masks on

If the participant does not feel comfortable wearing the mask at the screening visit, or is not willing to use it for the next 12 weeks, it might be better not to enroll the participant in the study at this time.

5.5.1. Disinfecting/sterilizing sample masks

Sample masks must be sterilized or disinfected between participant uses as per local hospital/clinic/health facility disinfection requirements. The DCC recommends the manufacturer's guidelines for disinfection:

Disinfecting/Sterilizing the Mask or Nasal Pillows System between participants

The following are the recommended and validated procedures for cleaning, disinfection and sterilization of the mask. We advise that each healthcare facility consult its own procedures before carrying out the following instructions.

Warnings and cautions

- ResMed cannot give any assurances that deviations from the procedures listed below, and their effect on the performance of the product, will be acceptable.
- The mask components should not be subjected to autoclave or ethylene-oxide gas sterilization.
- When using detergents, disinfectants or sterilization agents, always follow the manufacturer's instructions.

Note

- The headgear does not require disinfection or sterilization. However, it is necessary to thoroughly wash the headgear before using between participants.
- The mask must be disassembled and cleaned prior to disinfection or sterilization. The mask must also be inspected after disinfection/sterilization. See the section "Inspection after Disinfection/Sterilization" for inspection details.

After disassembly, thoroughly disinfect or sterilize the mask components by following the procedure for one of these methods:

- Chemical Disinfection
- Thermal Disinfection
- STERRAD Sterilization

OPTION 1 – Chemical Disinfection**Pre-disinfection**

4. Disassemble the mask.
5. Clean the individual parts of the mask with a soft bristle brush for one minute while soaking them in detergent (eg, Aniosyme™ DDI or Alconox™). Pay particular attention to all crevices and cavities.
6. Rinse the components twice by agitating them vigorously in drinking quality water (5 liters per mask) and allow them to air dry out of direct sunlight.

ResMed has tested the detergents Aniosyme DDI (diluted at 0.5% for 15 minutes) and Alconox (diluted at 1%).

Disinfection

7. Soak the disinfectable mask components in a commercially available solution of peracetic acid 0.15% (eg, Anioxyde™ 1000), ortho-phthalaldehyde 0.55% (eg, CIDEX™ OPA) or glutaraldehyde 3.4% (eg, CIDEX Plus™).
8. Rinse the mask components in drinking quality water (5 liters per mask) and allow them to air dry out of direct sunlight.

Testing by ResMed has shown that the mask components can withstand 15 cycles using solutions of peracetic acid (0.15% Anioxyde 1000 for 30 minutes), ortho-phthalaldehyde (0.55% CIDEX OPA for 20 minutes) or glutaraldehyde (3.4% CIDEX Plus for 20 minutes).

Note: If using the detergents and disinfectants listed above, the following combinations should be followed:

- Detergent Aniosyme DDI with Anioxyde 1000 as the disinfectant
OR
- Detergent Alconox with disinfectant CIDEX OPA or CIDEX Plus.

OPTION 2 – Thermal Disinfection**Pre-disinfection**

9. Disassemble the mask.
10. Clean the individual parts of the mask with a soft bristle brush for one minute while soaking them in detergent (eg, Neodisher™ Medizyme or Alconox). Pay particular attention to all crevices and cavities.
11. Rinse the components twice by agitating them vigorously in drinking quality water and allow them to air dry out of direct sunlight.

ResMed has tested the detergents Neodisher Medizyme (concentration at 2% for 30 minutes) and Alconox (diluted at 1%).

Disinfection

Using a certified hot water disinfection system, soak the disinfectable mask components using one of the temperature-time combinations listed in the following sections.

European Standards

Based on prEN ISO 15883-1, the mask has been tested at the following temperature-time combinations:

- 70°C for 100 minutes
- 75°C for 30 minutes
- 80°C for 10 minutes
- 90°C for 1 minute.

Regional Requirements

Due to specific regional requirements, the mask has also been tested for disinfection at the following temperature-time combination:

- 93°C for 10 minutes.

Testing by ResMed has shown that the mask components can withstand 15 cycles of thermal disinfection using the above temperature-time combinations. The device used for testing was Branson™ LTH 1828-24 hot water bath.

OPTION 3 – STERRAD Sterilization System

Pre-sterilization


12. Disassemble the mask.
13. Clean the individual parts of the mask with a soft bristle brush for one minute while soaking them in detergent (eg, Alconox). Pay particular attention to all crevices and cavities.
14. Rinse the components twice by agitating them vigorously in drinking quality water and allow them to air dry out of direct sunlight.

ResMed has tested the detergent Alconox (diluted at 1%).

Sterilization


Sterilize the sterilizable mask components as described in the manufacturer's instructions for the STERRAD Sterilization System (eg, Sterrad 100S or Sterrad NX).

Testing by ResMed has shown that the mask components can withstand 15 cycles of the STERRAD 100S Sterilization System, when using the tray method.

 **Note:** *The use of pouches is not recommended.*

Inspection after Disinfection/Sterilization

Perform a visual inspection of each mask component. If any visible deterioration of a mask component is apparent (cracking, crazing, tears, etc), the mask component should be discarded and replaced. Slight discoloration of the silicone components may occur and is acceptable.

 **Note:** *If a healthcare facility requires an additional disinfection or sterilization process after reassembly, the number of validated cycles is halved.*

5.6. Safety warnings

The following are recommendations that the coordinator should communicate to the participants to ensure the safety and effectiveness of the device.

Good Practices

- **Use these devices only as directed by your coordinator.**
- **The vent holes on masks must be kept clear.**
- **Always disconnect the humidifier from the CPAP unit before moving the device.**
- **Make sure air tubing is secure before sleeping; the tubing may twist around the head or neck.**
- **Do not cover mask with blankets while sleeping. This will cause you to re-breathe CO₂ and may also cause the device to overheat and shutoff.**
- **Keep your mouth closed, avoid talking, and breathe normally when using your device.**
- Clean the chamber daily to prevent mold growth. Use distilled water, which will prevent mineral build-up in the chamber.
- If you put the device on the floor, make sure the area is free from dust and clear of bedding, clothes or other objects that could block the air inlet or cover the power supply unit.
- Keep the power cord away from hot surfaces.
- Make sure the area around the device and tubing is dry, clean, and clear of objects or pets.
- Explosion hazard—do not use near flammable substances.
- Do not share device with others.

Device

- **Do not immerse the CPAP unit, humidifier, power supply, or power cord in water. Ensure the device is dry before plugging it in.**
- **A mask should not be worn when connected to the CPAP device unless the machine blower is turned on and operating properly.**
- In the event of a power failure or machine malfunction, remove the mask.
- Place the unit on a level surface such as a bedside table or on the floor. Do not place the unit above the user's head in order to prevent mask and tubing from filling with water.
- If you notice any changes in device performance, if it is making unusual sounds, if the device or the power supply are dropped or mishandled, if water is spilled into the CPAP unit, if the enclosure is broken, or if you see signs of any damage, discontinue use and contact your coordinator.
- Do not attempt to open the CPAP device or the water tub.
- Blocking the air tubing and/or air inlet of the CPAP device while in operation could lead to overheating of the device.

Humidifier

- **Do not overfill the water tub as water may enter the device and air tubing.**
- **Take care when handling your humidifier as the water/water tub may be hot. Allow 10 minutes for the heater plate and any excess water to cool.**
- Connection of other delivery tubes or accessories could result in injury or damage to the device.
- If liquids are spilled into or on the humidifier, unplug the device from the power outlet. Disconnect the humidifier from the CPAP device and allow the docking station to drain and dry before re-using.

Air tubing

- Before attaching tubing, check to make sure that rubber backing on the humidifier is removed.
- Do not wash the air tubing in a washing machine or dishwasher.
- Do not hang the air tubing in direct sunlight as it may harden over time and eventually crack.
- Do not drop or insert any object into any tubing or opening.

5.7. Common side effects of CPAP

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.

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:

- Mask allergies skin or eye irritations
- Dry mouth or throat
- Congestion, runny nose, sneezing, sinusitis
- Nosebleeds
- Ear discomfort
- Stomach bloating and discomfort

5.8. Adherence factors

Factors that improve adherence to treatment include:

1. Technical interventions*a. Heated humidifier*

The humidifier adds warm moisture to the air, preventing airways from drying out and decreasing irritation.

b. Ramp feature

The ramp feature allows the pressure to start low and increase gradually to its pre-set pressure in 15 minutes to provide a more comfortable treatment to participant

2. Participant education*a. Understanding of CPAP use, maintenance, and cleaning*

It is important to take the time to educate the participant on how to use the device, fit the mask, and clean and maintain the mask.

b. Allow time for adjustment for treatment- acclimation – motivational enhancement

Usually, the initial exposure to CPAP treatment can be difficult; however after adjusting for the treatment the participant will get used to the device and will understand how it works, and how they should use the device.

It will also take some time to get used to wearing the mask at night. Participants are expected to feel strange at first, just as eyeglasses do. However participants will be able to get used to it after a short time.

c. *Mask fit*

Mask discomfort is the most common bothersome effect from using CPAP due to poor fitting. If the mask does not fit well, the participant will not use it. This is why there are a variety of masks for each participant.

Participants will have the chance to see and fit the masks at the screening visit (V1). This will give them an idea of what is expected from them in the study.

With having multiple sizes for the participant to choose from, as well as proper mask fitting when initiating therapy make the participant more willing to use the device.

3. Initial follow-up

Staying in contact with the participant is the most important means to get better adherence to treatment. During the participant's first week of CPAP use, if coordinator follows up on a regular basis, the participant is more likely to be compliant for the rest of the study period.

The initial follow-up phone call (V3) and the clinic visit after that (V4) are important to determine if the participant has used the device since they received it, and that they understand how to use the device, fit the mask properly, and maintain device and mask. If the participant requires additional assistance, participant should go to the clinic and have the coordinator help them refit the mask, or use another type or size mask.

4. Follow-up and monitoring adherence

At the follow up visits, it is crucial that coordinators provide personal feedback on how to use the CPAP and solve potential problems with the use of the device and mask. The troubleshooting tables provided in this MOP can be used as references (Section 5.9.3).

In addition, the DCC will review the SD Cards shipped and provide a CPAP compliance report showing device usage as well as recommendations for improving adherence. The DCC reviews the adherence based on:

- **Consistency:** the number of nights the participant uses the device in the specified period
- **Continuousness:** the number of hours the participant uses the device every night

Compare the CPAP compliance reports for each participant to the adherence flowcharts and review the usage with the participant at their next Clinic visit

Call DCC for any additional questions or concerns.

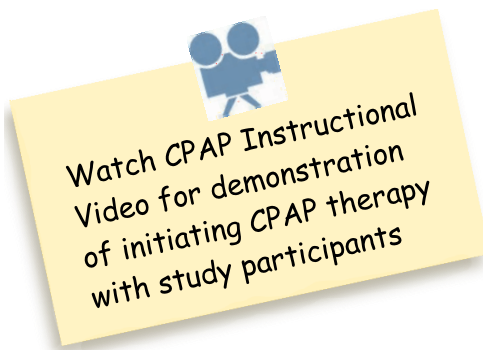
5.9. Participant education

5.9.1. Initiating CPAP therapy

Overview

Initiating CPAP therapy should be performed after the participant is assigned a randomization study kit at their randomization visit (V2), unless participant is participating in HRCT substudy.

YOU TOUCH IT, YOU TEACH IT is a useful concept in CPAP, in which educating the participant on the device setup and mask fitting by showing them at their clinic visit is crucial for their adherence and confidence using the CPAP device.



HRCT

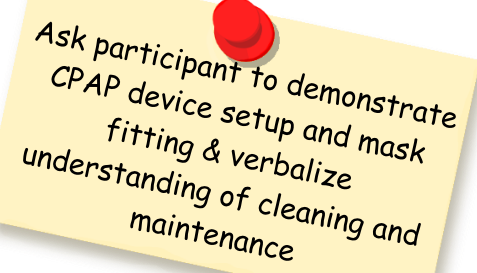
CPAP therapy is initiated after participant's first HRCT S1. See Section 7

To initiate CPAP therapy with the participant:

1. Prepare yourself by reviewing the instructions to set up device, fit the masks, and safety warnings from MOP Section 5.1, 5.2, 5.3, 5.4, and 5.6
2. Use your CPAP randomization task checklist (VC2) to guide you through topics to cover with the participant
3. Review/explain purpose of study with participant and assess participant's verbal understanding of the study
4. Retrieve study kit with assigned Kit ID
5. Open the study kit and verify all components are present and labeled with the same Kit ID (components listed in Section 6.1.1)
6. Use hand sanitizer in front of participant
7. Explain that the CPAP Device User Instructions (ICD) that comes with the device has all the information they need to know regarding device set-up, mask fitting, and troubleshooting.
8. Instruct participant on his/her CPAP device:
 - a. Placement of CPAP unit and humidifier – show the release button
 - i. Once CPAP unit and humidifier are put together, they stay together as one device, unless participant is traveling and needs to repackage the CPAP unit and humidifier in the travel bag
 - ii. Device should be placed on a sturdy surface, always at or below head level
 - b. Start from the back of the device
 - i. Power cord connection - plug device directly to a wall outlet, if possible

- ii. Filter – part of the CPAP therapy is to breath clean filtered air
 - 1. No need for participant to remove filter
 - iii. SD card – monitors device usage
 - 1. No need for participant to remove it, but make participant aware that device records of their use
 - iv. Air tubing – warms the humidified air for more comfort
 - 1. Show air tubing connection to humidifier
 - 2. Rubber backing stays attached to the humidifier
9. Turn device around and explain device function
- a. Humidification system – humidifies air to prevent nose dryness
 - i. Show water tub and how to fill through hole in top; tub does not need to be opened
 - ii. Recommend using distilled water, filtered, or bottled water. If using tap water, it is recommended boil water for 10 minutes and cool before use.
 - iii. Always fill the water tub when it is outside the device
 - iv. Always fill water to the max line
 - v. Empty water tub every day and refill with fresh water
 - b. How device works
 - i. Air comes from atmosphere through device and flows through mask into nose at one of 3 pressures
 - ii. Air is filtered and humidified
 - c. Key pad and LCD
 - i. Screen turns on when device is plugged in wall outlet
 - ii. Lights of screen dim out after a couple of minutes
 - iii. Show push dial and start/stop button
 - iv. To illuminate screen, use push dial
 - v. Main screen is home screen
 - vi. Temperature adjustment (80 F is recommended)
 - 1. To make adjustments, screen turns orange (unlocked). To confirm adjustments, screen turns blue (locked)
 - vii. Increase/decrease temperature by increments of 2
 - viii. Ramp feature – builds up pressure with time to help participant fall asleep
 - ix. Info button – ignore as this feature is inactivated for this study and information shown is inaccurate.
 - x. To start machine, press start/stop button
 - d. For safety warnings. Refer to the CPAP Device User Instructions (ICD)
 - e. For cleaning and maintenance of device and air tubing. Refer to the CPAP Device User Instructions (ICD)
 - f. For troubleshooting of device and air tubing, see CPAP Device User Instructions (ICD)

10. Fit participant with masks
 - a. Fit both types of masks (Swift FX (appropriate pillow size) and Mirage FX (appropriate size)) during the randomization visit (V2) so that the participant can choose which one they prefer to use. It will also give them a better idea of how both masks feel in case they want to switch to a different type of mask later in the study. Refer to Section 5.3 for more information about selecting the proper mask.
 - b. Properly fit participant with mask.
 - i. Have the participant lay down if possible to make adjustments
 - ii. Make participant aware that the mask has holes to release CO₂
 - iii. Ensure participant that if power goes out, holes in mask prevent participant from suffocating
 - iv. Goal is a snug fit, not tight (two-finger rule)
 - c. Connect mask to air tubing and to device
 - d. Instruct participant to turn device on when they feel ready
 - e. Check for leakage and participant comfort with therapy
 - f. Have participant feel flow of air coming out of the mask holes and assure participant that they should feel this flow (not a leak)
 - g. Have participant turn their head side to side to ensure no leakage and good mask fit
 - h. Provide chin strap for participant if they are mouth breathers
 - i. Review troubleshooting techniques for mask. Refer to Section 5.9.3.
 - j. Provide chin strap, if needed
 - k. For Swift FX, give participant the sleeves that can be attached to straps
11. Allow participant to test CPAP therapy for several minutes
12. Participant removes CPAP
13. Review cleaning and maintenance of masks and device parts
14. Listen and respond to any questions / concerns the participant may have
15. Re-package equipment and supplies in the travel bag
16. Use hand sanitizer when set up is complete
17. Review Device User Instructions (ICD) with participant to ensure they understand where to find more information if needed
18. Give participant CPAP device and accessories, preferred type of mask (send them home with only one mask/size, e.g., Swift FX with Small pillows), and soap.
19. Encourage participant to call you if he/she needs to refit the mask or if having trouble adjusting to the CPAP therapy.



Ask participant to demonstrate CPAP device setup and mask fitting & verbalize understanding of cleaning and maintenance

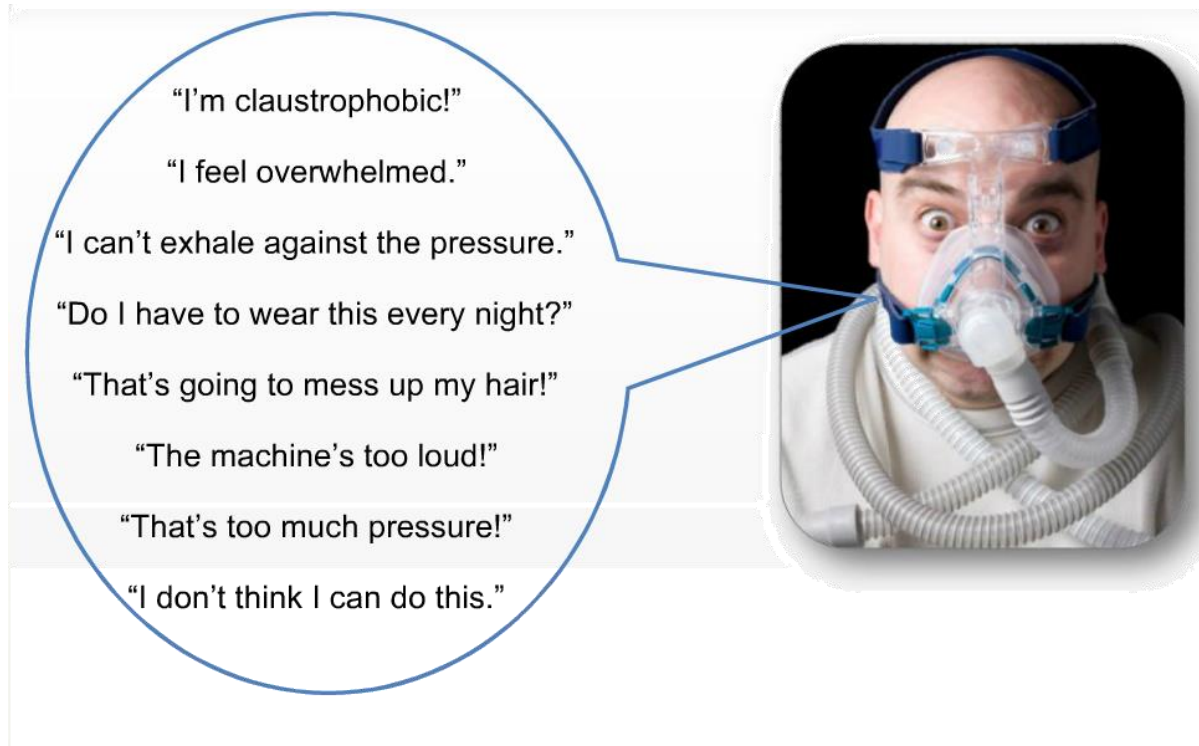
5.9.2. CPAP Acclimation Process

Some participants may experience trouble adjusting to CPAP therapy. They may feel claustrophobic and/or have difficulty breathing. These participants may need acclimation to CPAP therapy.

1. Have the participant sit in a chair, without connecting to the air tubing or device; have the participant hold the mask over their nose. Have the participant breathe normally, in and out through the mask. If they feel uncomfortable, remove the mask. Continue this procedure until the participant is comfortable.
2. Again while sitting, have the participant connect the air tubing to the mask (no headgear), and turn on the device. Encourage them to watch TV or listen to music. If at any time they feel uncomfortable, remove the mask. Continue this process until the participant feels comfortable. The participant should breathe for a minimum of 5 to 10 minutes every evening without falling asleep. Once successful, proceed to step 4.
3. Again while sitting, have the participant connect the air tubing and headgear to the mask, and turn on the device. If at any time they feel uncomfortable, remove the mask. Once they are comfortable with this phase, have them lie down and close their eyes. Continue this process until the participant feels comfortable.
4. Encourage the participant to gradually increase their time lying down, until they are wearing the device at least four hours per night.
5. Participants can also stop the CPAP therapy and then restart it so that the ramp feature can assist them in acclimating to the CPAP pressure gradually at night

5.9.3. Troubleshooting

The success of the CPAP trial depends on the participants using their CPAP machine. During the course of the study, you might get complaints from participants regarding adjusting to treatment, mask fit, or device problems.



5.9.3.1. Device FAQs and troubleshooting

The lights on my machine dims out. Does that mean my machine is shutting off during my therapy?

- Remind the participant that one of the features of the machine is that the backlights dim out 30 seconds after therapy is initiated or if the machine is not in use. If you are unsure if the machine is still on, place a hand near the mask and feel for the flow of air.

My machine is plugged in, but will not turn on.

- Ask the participant if the machine is plugged into an outlet connected to a wall switch or ask them to make sure it is plugged in firmly at the outlet and the back of the machine.
- Try another outlet if it is plugged into an outlet connected to a wall switch.

The display is blank after I plug it in

- Make sure that the device and humidifier are connected correctly and the power plug is securely attached

Error messages on the machine display, e.g. high leak

- If you receive any, re-plugging the machine should clear most messages.

What is the SD card used for?

- The SD card is used to record the participant’s usage of the machine. Tell participant it is there, but don’t touch.

Participant states “I removed the filter and/or SD card. Is the machine broken?”

- Tell the participant that the machine is not broken, but remind them that they should not remove the filter cover and filter or the SD card. Also instruct them how to reinsert the SD card by plugging it in with the arrow pointing in towards the slot and up so they can see it. Contact DCC if the SD card or the filter is damaged and needs replacement.

What if there is a blackout, will I suffocate?

- Tell participant will not suffocate because of the vent holes in the mask.

It feels like it’s too much air pressure

- Restart the machine this will allow ramp feature to start with lower pressure that gradually increases
- Close mouth, avoid talking with the mask on, and concentrate on breathing with the machine.

I go to the bathroom several times throughout the night and it’s too much trouble to keep adjusting the mask

- Disconnect the hose from the mask and leave the nasal interface on the face. Turn off the machine and then use the bathroom.
- Reattach the tubing to nasal interface.

I’m having problems adjusting to my CPAP therapy

- Try acclimation process training placing the mask on the face without the air flow.
- Practice wearing the mask with airflow while awake.

Do I have to wear this every night

- The purpose of this study is to assess if asthma will improve in participants when using the device every night.
- The air breathed in will be filtered and humidified clean air.
- It might be a little strange to wear the mask at first, but participant will get used to it after a short time.

I feel overwhelmed

- Try the acclimation process. This takes the participant in slower steps to get adjusted to the new treatment. It may help to start by practicing wearing just the CPAP mask for short periods of time while you're awake, for example while watching TV. Then try wearing the mask and hose with the air pressure on, still during the daytime, while you're awake. Once you become accustomed to how that feels, shift to using the CPAP device every time you sleep — at night and during naps. Inconsistently wearing the CPAP device may delay getting used to it. Stick with it for several weeks or more to see if the mask and pressure settings you have will work for you.

I can’t exhale against the pressure

- Try to breathe with the device instead of against the device.
- Use the device in the supine position. This makes the air flow go in more smoothly than sitting upright.

5.9.3.2. CPAP humidifier troubleshooting

Common concerns from participants and possible solutions:

Do I have to open the water tub to fill or clean it?

- Remind the participant that they do not need to open the water tub to clean it or fill it. If they did open it, it is not broken. Simply replace the lid and snap tabs on each side while you listen for snapping sound on the phone.

Do I need to replace the water in the humidifier each night?

- The humidifier provides warm moist air to relieve side effects, e.g. dryness. It is recommended that you replace the water each night. You can also adjust the air temperature for your comfort.

The humidifier is “not working”

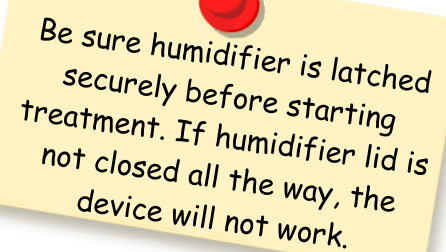
- The humidifier hot plate is designed to cool rapidly and so if the participant feels the hot plate just after use, it will still feel cool. To test the heating function of the hot plate, while on the climate control menu, push the dial for 3 seconds to quickly warm and cool the hot plate. If this is felt, the humidifier is working correctly.

Water is leaking from the humidifier unit or from the water tub

- Check that the water level is below the maximum level mark.
- Water tub may need to be replaced

When I wake up in the morning, my humidifier is still full of water. What’s going on?

- Ask the participant how frequently they need to refill their water tubs. If they wake up in the morning and it is still full that can be a sign of a low temperature setting or a malfunctioning humidifier. Check the humidifier when they next bring it to the clinic. If they use up the water too quickly, that may indicate that the temperature setting is too high. Advise them to lower it first before further investigation of the humidifier.



Be sure humidifier is latched securely before starting treatment. If humidifier lid is not closed all the way, the device will not work.

5.9.3.3. Mask troubleshooting

Common concerns from participants and possible solutions:

My mask is too noisy

- Refit or reposition the mask. Adjust the headgear
- Remove the elbow from the mask and reassemble it according to the instructions

My mask is too big or too small

- Participant might need a different mask or size

My Swift nasal pillows won't seal properly, are uncomfortable, or cause red marks

- Check that the ResMed logo on top of the pillows is facing outwards
- Readjust headgear
- Squeeze pillow sides to release inner wall
- Fit participant with another pillow size
- Use the comfort sleeves provided

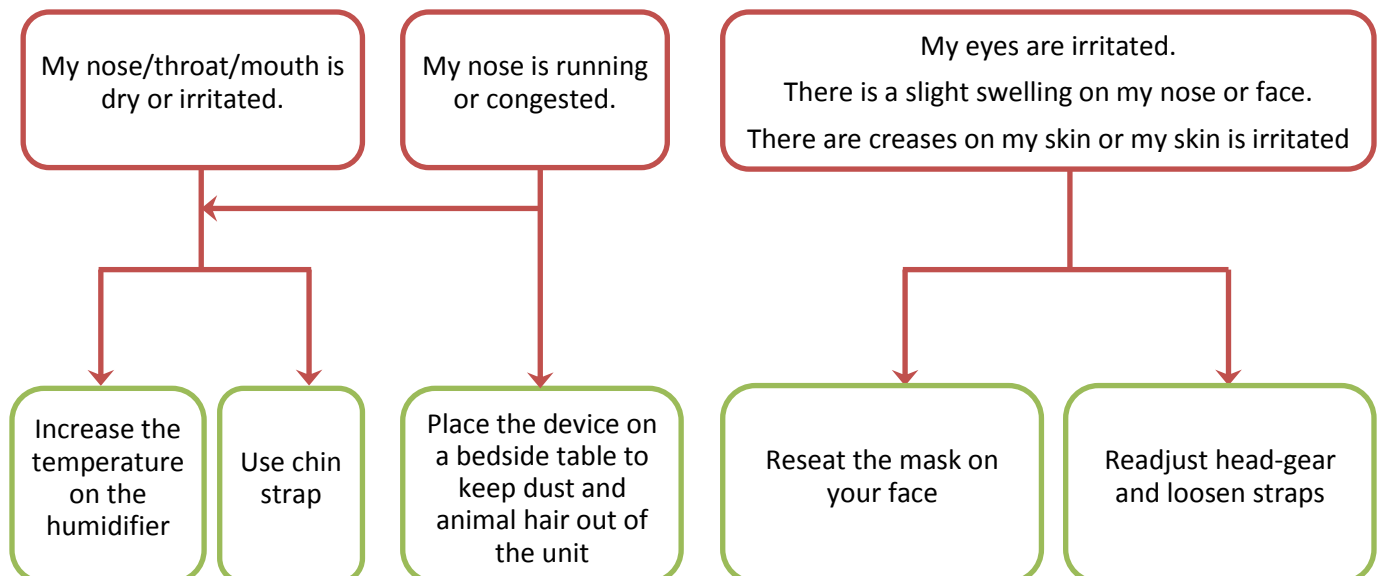
I'm claustrophobic; I can't wear the mask

- Try acclimation process with the mask
- Change mask style/type to nasal pillows

5.9.3.4. Troubleshooting side effects

Some side effects a participant might experience are mouth breathing, airway dryness, and nasal congestion. These problems are usually due to inadequate humidification and can be corrected by the participant adjusting the air temperature on their humidifier. If the problems persist, call the DCC.

Common concerns from participants and possible solutions:



Other solutions:**My nose feels congested since I've started using the CPAP device**

- Check the filter

The mask makes my eyes irritated

- Improper mask fit or size/change cushion size to Wide if using the Standard nasal mask

My skin gets irritated when I'm wearing my mask

- If the headgear straps are too tight, readjust and loosen headgear to allow a secure fit on the face
- Change mask type/style

Contact DCC for any questions regarding troubleshooting for side effects.

6. Study kit administration

6.1. Study kits: description, procurement, receipt and return

6.1.1. Overview

All study kits will be distributed from the CPAP Device Distribution Center.

Clinics should use the Device Dispensing and Return (DD) form to record dispensing and returning of study device, masks, and accessories. Receipt, issuance, and return of study kits should be recorded on the Study Kit Accountability Log (DA).

All kits are to be stored in a dry place.

Study treatment administration

The CPAP device with an appropriate mask is to be used every night from the time participant goes to bed until the time he/she wakes up.

Study device packaging

- Study devices and accessories are packaged in a box called a “kit”
- Each kit has its own unique Kit ID
- Study kit label that has Kit ID and serial number is covered by an orange sheet of paper
- Each participant is assigned to a Kit ID
- Each kit box contains the following:
 - CPAP travel bag
 - CPAP unit
 - Humidifier and water tub
 - 3 SD cards (SD Card A inside the device, SD Cards B & C in cases)
 - ClimateLine™ Air tubing
 - Chin strap
 - Power unit and power cord
 - Swift FX mask (3 pillows: Small, Medium, Large pillows)
 - Mirage FX standard mask
 - Mirage FX wide mask
 - CPAP Device User Instructions (ICD)
 - Unmasking envelope
- Study kits can be identified by the green tape on the box.
- Study kits should only be opened at V2 when it is assigned to a participant.
- Study kit’s original box should be kept at the clinics until end of V7, which, at that time, is to be shipped back to the Device Distribution Center



6.1.2. Kit procurement

Procurement of study kits

- Study kits are automatically supplied to clinics from the Device Distribution Center
- Upon clinic certification, the DCC will notify the CPAP Device Distribution Center to send the clinic an initial supply of one kit (clinics participating in the HRCT substudy will receive two kits)
- Data entry of a Randomization (RZ) form will automatically generate a notice to the CPAP Device Distribution Center to send another study kit to the clinic
- Study kits may be manually ordered by the clinic only for unusual circumstances; i.e., two or more randomizations expected within one week
- The study kit has all the items a participant will need for the 12 weeks of CPAP therapy
- **Do not** open the study kit until participant is randomized

To access the CPAP Device Distribution System for kit orders:

Note: To order study kits, a coordinator must be certified for data entry

1. Go to <http://www.jhcet.org/Secure/CPAP/CPAPHome.asp>
2. Under “Data System,” click on “Data entry programs”
3. Log-in using clinical center ID, coordinator PIN, and personal password (see MOP Section 3 for more details)
4. Click on “CPAP Device Distribution System”
5. To place an order for extra study kits to be used for randomization (for unusual circumstances e.g., two or more randomizations expected within one week)
 - a. Click on “Order Randomization Kit”
 - b. Follow instructions to place order as indicated and confirm
 - c. Contact the DCC with any problems or special requests

HRCT

If clinic or participant not participating in the HRCT, coordinator **MUST** indicate **‘No’** for HRCT participation when ordering study kit through the data system

Clinics generally will receive kit(s) 2-3 working days after receipt of order by the CPAP Device Distribution Center

Note: If clinic needs kits for a randomized participant or for upcoming randomization(s) immediately, clinic coordinator must contact the DCC and request overnight delivery

6.1.3. Kit Receipt and storage

Upon receipt of study kits

1. Sign packing slip and fax to CPAP Device Distribution Center
2. The kit label will be covered with an orange paper. Remove the orange paper from the label
3. Record receipt, dispensing, and transfer of study kits on Study Kit Accountability Log (DA)
 - b. Maintain one DA log for all kits
 - c. Satellite clinic should have a separate DA log
4. Store study kit:
 - i. In a secure, locked location with limited public access
 - ii. Store kits separately; e.g., store the kits on designated shelf
 - a. Store study kits in a secure, locked location with limited public access
 - b. Store kits separately; e.g., store kits on a designated shelf
 - c. Store kits in a dry place
 - d. **Do NOT** store a study mask or device returned by a participant separately from their study kit; always keep any used or unused items in the same study kit assigned.
 - e. Any part of a study kit dispensed to a participant cannot be returned and used by another participant. All used kits and their contents must be returned back to the CPAP Device Distribution Center.

Note: Unassigned kits should only be stored at main site for CPAP because it will not be known at which site the next participant will be randomized

Log/Administrative forms (abbreviation)

- Study Kit Accountability Log (DA)

Do NOT open study kit upon receipt. Only open study kit when assigned to a participant at V2.

6.1.4. Kit dispensing

Purpose

- Distribute assigned CPAP device and accessories to participant

When

- Randomization visit (V2)

Overview

- Participants are assigned a Kit ID at randomization (V2) which is provided by the online randomization system and corresponds to a study kit in stock at the clinic center
- Main clinic is responsible for shipping the study kit to the satellite clinic, if applicable, after a randomization occurs in that satellite clinic

HRCT

If participant is in HRCT substudy, distribute after the first HRCT scan (S1). Refer to MOP Section 7.

Tasks

Main clinical site

- Remove kit with assigned Kit ID from storage
- Record Kit ID as “assigned” to the participant or as distributed to a satellite on the Study Kit Accountability (DA) Log

Site that is randomizing

- Fill in Participant ID on label on the outside of the kit box (see Sections 6.1.1 and 6.1.11)
- Break seal and open kit box
- Make sure study kit with the unique kit ID includes the following items
 - CPAP travel bag
 - CPAP unit
 - Humidifier and water tub
 - 3 SD cards (SD Card A inside the device, SD Cards B & C in cases)
 - Air tubing
 - Chin strap
 - Power unit and Power cord
 - Swift FX mask (3 pillows: S, M, L)
 - Mirage FX standard mask
 - Mirage FX wide mask
 - CPAP Device User Instructions (ICD)
 - Unmasking envelope
- Fill in information on all labels including CPAP device label, SD cards, Swift FX , Mirage FX standard, and Mirage FX wide labels
- Fill in participant ID on the unmasking envelope that is found inside the study kit. Keep the unmasking envelope in the study kit until V7.
- Complete the Device Dispensing and Return (DD) form
 - Make sure Device and Mask IDs are identical to the Kit ID
 - Remove tear-off label attached to device and affix to DD form
- Instruct participant on
 - Initiating CPAP therapy. See Section 5.1
 - Contacting study personnel if side effects occur or if having problems using device
 - Bringing study device with the mask and all accessories to each clinic visit

Forms (abbreviations)

- Device Dispensing and Return (DD)
- Study Kit Accountability Log (DA)*

**Not entered into database*

6.1.5. Kit return and shipment

Purpose

- Returning study treatment from participant and shipping study kit back to the Device Distribution Center for recycling

When

- Kit return: end of treatment visit (V6)
- Kit shipment to the Device Distribution Center: after washout visit (V7)

Overview

- Clinics are responsible to ship the study kits back to the Device Distribution Center.
- Satellite clinics must ship study kits directly back to the Device Distribution Center, not to the main clinic.

Tasks

At end of treatment (V6)

- Make sure study kit returned includes the all the items that were originally dispensed from the kit (See list under Section 6.1.1)
- Complete the Device Dispensing and Return (DD) form. Make sure Device and Mask IDs are identical to the Kit ID
- If participant fails to return study kit at V6, make sure device is returned to clinic before or at V7
- Record the returning of study kits on Study Kit Accountability Log (DA)
- If device is not return by V7, complete a UE form

At final washout (V7)

- Ship device to the Device Distribution Center according to the instructions below in this section
- Record date of shipment on Study Kit Accountability Log (DA)

Shipping supplies provided by clinic

- FedEx air bill
- Original study kit
- Orange paper sheets to cover kit label

Shipping tasks

- DO NOT ship on a day before a national holiday
- Complete a Device Transmittal Sheet (CT)
- Use FedEx account number: 3053-6089-9
- Record FedEx tracking number on transmittal sheet
- Place device and its accessories in the CPAP travel bag
- Place travel bag inside the study kit box
- Place all masks inside the study kit (Swift FX with 3 sizes of pillows (S, M, and L), Mirage FX standard, and Mirage FX wide)
- Make sure the Device ID, Kit ID, and Mask IDs are identical.
- Use Styrofoam to make sure device bag does not shift when shipped
- Place a copy of the Device Transmittal Sheet (CT) in the kit.
- Cover the kit label with an orange sheet, similar to how the kit was received
- Ship study kit to the following address within 3 days of completing V7:

Data Coordinating Center

911 S. Ann St

Baltimore MD 21231

Phone: 443-287-3170

Fax: 775-871-4030

! Address changed to:
415 N Washington St.
2nd floor
Baltimore, MD 21231

- Immediately upon shipment, notify Device Distribution Center by emailing or faxing the CPAP Device Transmittal Sheet (CT) (email ryasin@jhsph.edu or fax to 775-871-4030)
- Record shipment on Study Kit Accountability Log (DA)

Important Notes

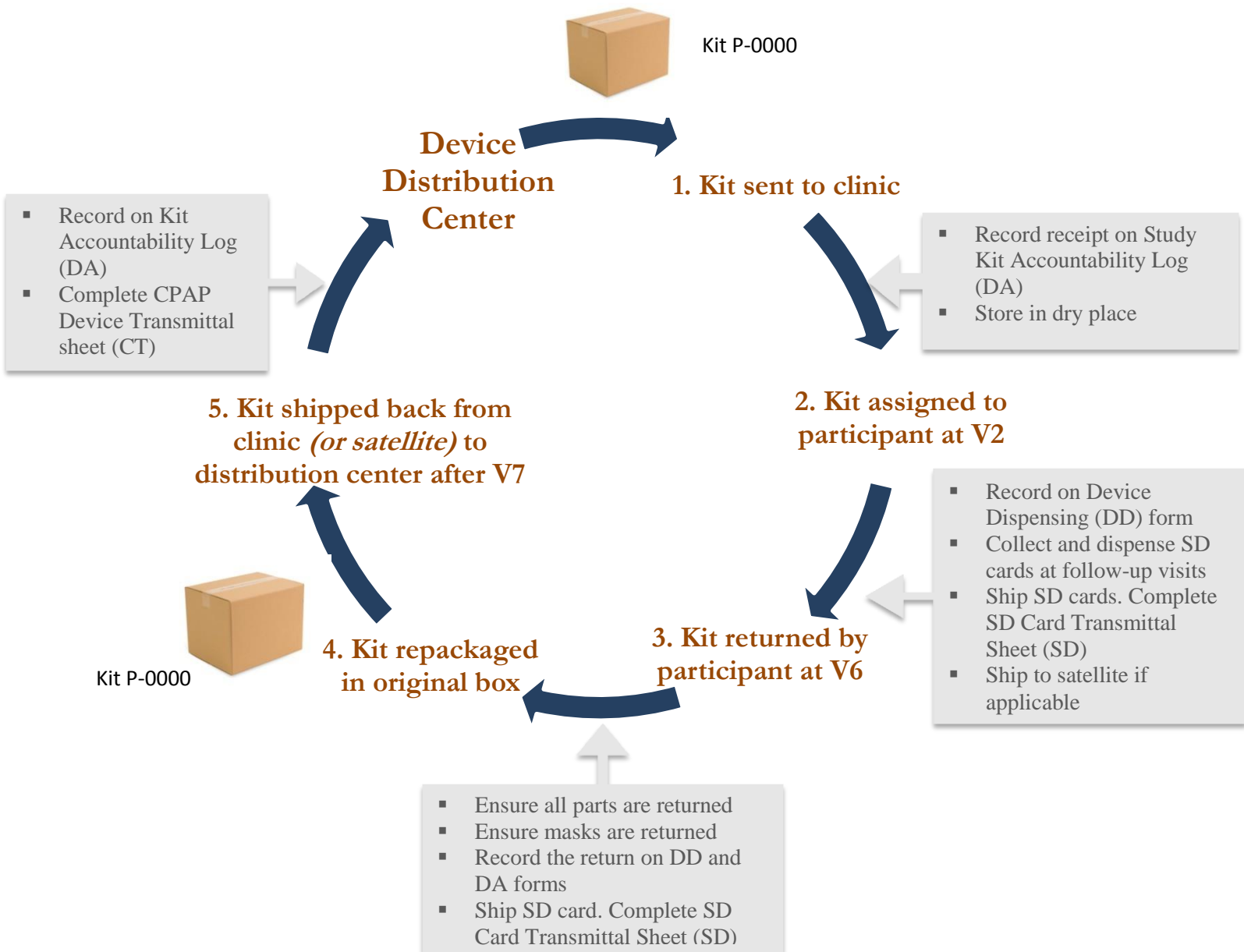
- Record all items returned in the original kit box on the CPAP Device Transmittal Sheet (CT).
- Required items to return by V7 (complete a UE form if not returned by V7)
 - CPAP Unit
 - CPAP humidifier
 - Air tubing
 - Power unit and power cord
 - Swift masks (S, M, L pillows)
 - Mirage FX standard
 - Mirage FX wide
- Items that need to be reported on the CT form (no need to report as UE)
 - Chin strap
 - Water tub
 - CPAP travel bag

Forms (abbreviation)

- Device Dispensing and Return (DD)
- Unusual Event (UE)
- CPAP Device Transmittal Sheet (CT)*

*Not entered into database

6.1.6. Kit recycling



Make sure IDs of device and mask are the same at V2 and whenever mask is replaced



If device need to be replaced, order a new kit (comes with new masks) and ship the old kit with old masks back



Make sure all required kit parts are returned at V6 (See Section 6.1.5)

6.1.7. SD card collection and shipping

Purpose

- SD cards will be used to monitor participant usage and adherence to treatment. Data is stored on the device and is saved on the SD card.

When

- V4, V5, V6

Tasks

V2 (Randomization)

- SD Card-A is inside the CPAP unit
- Remove card and record Participant ID on SD Card-A.
- Re-insert SD Card-A in the device and distribute to participant.
- Explain to the participant that the usage information is stored on the device and also on the SD card. This information will be used to monitor adherence.

V4

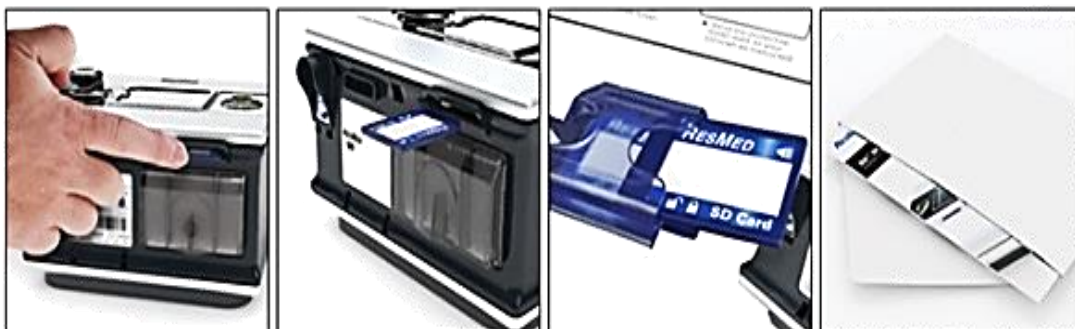
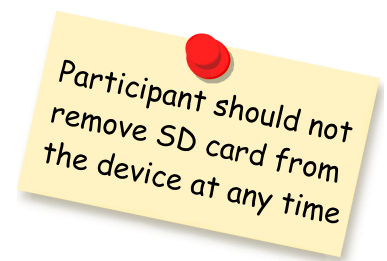
- Collect SD Card-A from the device
- Place SD Card-A in a card case and ship to the DCC according to the instructions below
- Record Participant ID on SD Card-B
- Insert SD Card-B in the device and distribute to participant

V5

- Collect SD Card-B from the device
- Place SD Card-B in a card case and ship to the DCC according to the instructions below
- Record Participant ID on SD Card-C
- Insert SD Card-C in the device and distribute to participant

V6 (end of treatment)

- Collect SD Card-C from the device
- Place SD Card-C in a card case and ship SD to the DCC according to the instructions below in this section



Shipping supplies provided by clinic

- FedEx air bill

Shipping tasks

- DO NOT ship on day before a national holiday
- Complete an SD Card Transmittal Sheet (SD)
- Use FedEx account number: 3053-6089-9
- Record FedEx tracking number on the SD Card Transmittal Sheet (SD)
- Place SD Card in its card case. Card cases are found in each study kit
- Place card case inside a FedEx Envelope
- Place a copy of the SD Card Transmittal Sheet (SD) in the envelope
- Ship envelope to the following address within 3 days of collection
CPAP Team
911 S Ann St
Baltimore, MD 21231
- Immediately upon shipment, notify DCC by emailing or faxing the SD Card Transmittal Sheet (SD) to DCC (ryasin@jhsph.edu; fax: 775-871-4030)

**! Address changed to:
415 N Washington St. -
2nd floor
Baltimore, MD 21231**

Important Notes:

- ▶ **If SD card is lost, destroyed, or not expected to be shipped to DCC, complete a UE form and send to DCC.** This will inform DCC not to expect the shipment.
- ▶ If participant loses the SD card between visits, instruct participant to bring study device to their next visit so you can replace the missing SD card in the device.
- ▶ If any cards were mistakenly removed from the device and not returned back by V6, make sure the participant returns them by V7 (washout visit)

Forms (abbreviation)

- SD Card Transmittal Sheet (SD)
- Unusual Event (UE) form

6.1.8. Equipment maintenance during follow-ups

Purpose:

- To ensure that the device and all other accessories are functional and in good condition, and to check if any replacement is needed for any of the parts

When:

- V4- V7

Tasks:

At each follow-up visit, make sure to check the following:

- Remove SD card from the device to be shipped to the DCC
- Place a new SD card in the device
- Ensure that the filter on the device is in place, in good condition, and check for any damage or malfunction

- Ensure that the water tub is in good condition, and check for any damage or malfunction
- Inspect the masks used by the participant for any damage or lost parts

6.1.9. Compliance monitoring



At all follow up clinic visits and phone contact

- Discuss compliance and CPAP use based on the CPAP SD card compliance reports provided by the DCC
- Show participant their CPAP compliance report and device usage
- Refer to the Device User Instructions (ICD) or CPAP Participant Instructional Video when participant needs assistance in setting up or fitting the mask
- Resolve any issues the participant might have with the mask or device. If participant shows low compliance, contact the DCC for any questions or concerns.
- Record compliance information on Phone Contact (PC) form or Clinic Visit (CV) form, as applicable
- Collect and replace SD cards at each follow up visit. See MOP Section 6.1.7
- Participants must bring the study device, mask, and all accessories to each clinic visit
- When the device and/or masks are exchanged or returned
 - Record on Device Dispensing and Return (DD) form, and on the Study Kit Accountability Log (DA), if applicable
 - Returned study device and masks should be shipped to the DCC upon end of V7 for each participant. See Section 6.1.5
- Always place a participant's device or mask back in the original study kit when not in use

Forms (abbreviation)

- Clinic Visit (CV)
- Phone Contact (PC)
- Device Dispensing and Return (DD)

Log/Administrative form (abbreviation)

- Study Kit Accountability Log (DA)*

**Not entered into database*

6.1.10. Kit replacements

Procurement of replacement kits

- The study kit initially assigned and distributed to participant is to be used by participant for 12 weeks
- Replacement kits can be ordered if a study device or humidifier are malfunctioning, damaged, lost, or destroyed
- To place an order for a replacement kit, contact the DCC (Razan Yasin [ryasin@jhsph.edu; 443-287-5796] or the main number at the DCC (443-287-3170))
- Replacements kits will contain all items needed by the participant to resume treatment
- Each replacement kit will have a new, unique Kit ID
- Replacement kits will arrive at the clinic with the participant ID already recorded on the kit label

- Return all parts of the original kit to the Device Distribution Center, and dispense the new kit with the new masks and accessories to the participant
- Complete one new Device Distribution and Return (DD) form to record the return of the old kit and the issuing of a new kit.
 - If the exchange occurs on the same day, please enter the ID of the **kit dispensed** on item 7 of the form
- Complete the Study Kit Accountability Log (DA)
- Report any return or replacement of device, mask, or other accessories due to damage or malfunction on an Unusual Event (UE) form and send to the DCC. (See below for other accessories). Include the reason for replacement of device.

6.1.10.1. Mask replacement

- If the study mask is lost or destroyed, and the participant is most comfortable with that specific mask, contact the DCC. Due to the limited supply of masks, issuing of masks will be determined on a case by case basis.
- Record the return and issuance of masks on the Device Dispensing and Return (DD) form
- Complete an Unusual Event (UE) form and record the reason for ordering a study mask

6.1.10.2. Other accessories replacement

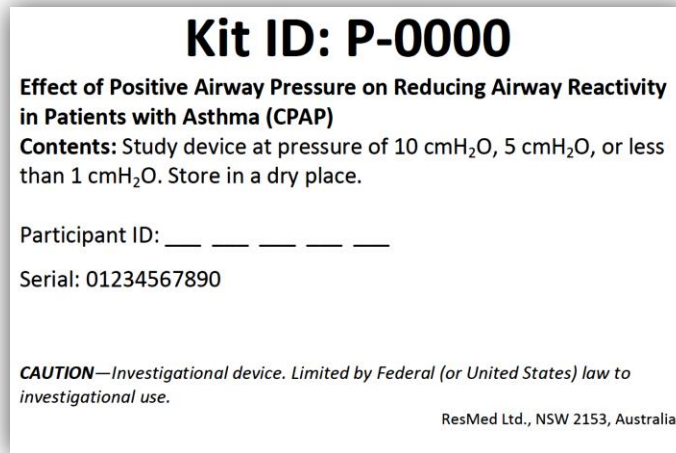
- If any of the following is lost or destroyed, notify the DCC by completing a CPAP Supply Order (CO) form and specifying the items needed under “other”
 - Air tubing
 - Power unit or power cord
 - CPAP Travel bag
 - Water tub
 - Filter
 - Chin strap
- Complete an Unusual Event (UE) form and record the reason for ordering air tubing, power units or power cords, water tubs, or filters.
- If any of the accessories need to be replaced, keep the older item in a zip lock bag and label it with Participant ID, Kit ID, and date. Keep the zip lock bag in the participant kit box and ship with the rest of the equipment after V7
- You do not have to complete a UE form to record lost chin straps or CPAP travel bags.

6.1.11. Study treatment labels

Each of the following items will be labeled for the CPAP trial. The labels will read “caution: investigational device. Limited by Federal (or United States) law of investigational use”

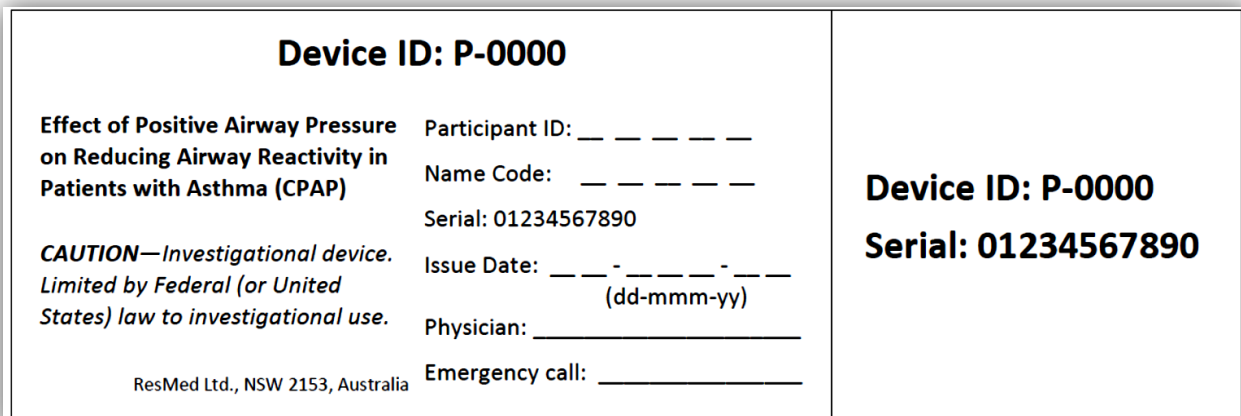
Kit label

- Each kit will have a label
- Label will be covered with an orange sheet upon receipt
- The Kit IDs will start with “P-” followed by 4 integers, e.g. P-1234
- The Device and Mask IDs will be identical to the Kit ID
- Participant ID is to be written on the kit label when the kit is assigned to a participant



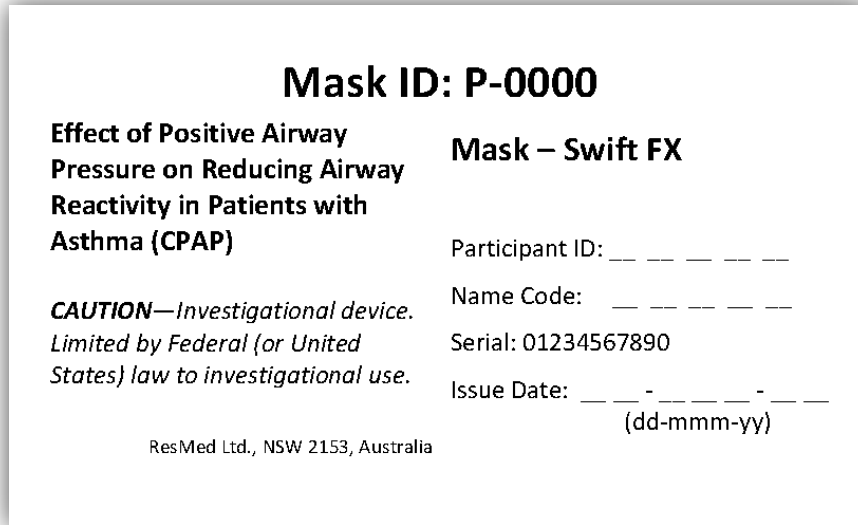
Study device label

- The Device ID will be on the left side of the device
- Participant ID and name code are to be written on the device label
- Other information to be written
 - Issue date
 - Name of CPAP physician (can be copied from the Asthma Action Plan Card (AAP))
 - Emergency phone number for the CPAP study physician (can be copied from the Asthma Action Plan Card (AAP))
- The label on the device has a tear-off section that is to be attached to the Device Dispensing and Return (DD) form when the device is dispensed to the participant



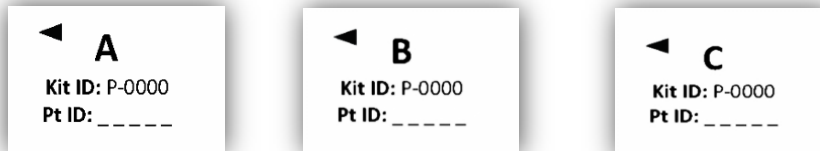
Mask labels

- The masks ID will be on the outer packaging of the masks
- Participant ID and name code are to be written on all mask labels
- Issue date is to be written on the mask that is dispensed to the participant. If participant exchanges the mask throughout the study, record issue date on the new mask given to participant



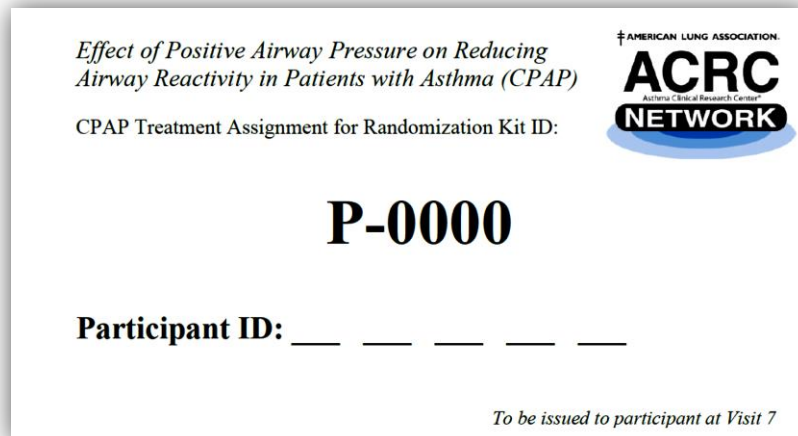
SD card labels

- The SD card ID is the participant ID, and has the letters A, B, or C
- Participant ID is to be written on all SD cards



Unmasking envelope labels

- Participant ID is to be written on the unmasking envelope at the time the study kit is assigned to the participant



6.2. Treatment accountability and termination

6.2.1. Accountability logs

- Each clinic must keep a Study Kit Accountability Log (separate logs for satellite clinics).
- Record the receipt, dispensing, returning, and shipping of the study kit. See examples below.
- Satellite clinics should ship study kits directly to the Device Distribution Center.

Main clinic (DA) example

| a. | | b. | | | c. | | | d. | e. |
|--------|--------|----------------|-------------|---------------|-----------------------------|-----------|------------------|--------------------|---------------------------------|
| Kit ID | | Received | | | Distributed (assigned/sent) | | | Returned to Clinic | Returned to Distribution Center |
| Entry | Kit ID | Specify Source | | | Specify Recipient | | | Date returned | Date shipped |
| | | Distr Ctr (✓) | Center name | Date received | Participant | | Satellite name | | |
| | | | | | ID | Name Code | Date Distributed | | |
| 1 | P-0000 | ✓ | | 30 Jul 12 | PZ000 | ABCDE | 31 Jul 12 | 23 Oct 12 | 6 Nov 12 |
| 2 | P-0001 | ✓ | | 1 Aug 12 | | | DCC-Satellite | 3 Aug 12 | |
| 3 | P-0011 | ✓ | | 10 Aug 12 | | | DCC-Satellite | 15 Aug 12 | |
| 4 | P-0002 | ✓ | | 20 Aug 12 | PZ003 | EBCDA | 22 Aug 12 | 14 Nov 12 | 28 Nov 12 |
| 5 | P-0003 | ✓ | | 30 Aug 12 | PZ004 | DECEA | 1 Sep 12 | 24 Nov 12 | 8 Dec 12 |
| 6 | P-0005 | ✓ | | 5 Sep 12 | PZ005 | DDFDA | 8 Sep 12 | 1 Dec 12 | 15 Dec 12 |
| 7 | P-0077 | ✓ | | 15 Sep 12 | | | DCC-Satellite | 17 Sep 12 | |

Satellite clinic (DA) example

| a. | | b. | | | c. | | | d. | e. |
|--------|--------|----------------|-------------|---------------|-----------------------------|-----------|------------------|--------------------|---------------------------------|
| Kit ID | | Received | | | Distributed (assigned/sent) | | | Returned to Clinic | Returned to Distribution Center |
| Entry | Kit ID | Specify Source | | | Specify Recipient | | | Date returned | Date shipped |
| | | Distr Ctr (✓) | Center name | Date received | Participant | | Satellite name | | |
| | | | | | ID | Name Code | Date Distributed | | |
| 1 | P-0001 | | DCC-main | 3 Aug 12 | PZ111 | ABBC | 3 Aug 12 | 26 Oct 12 | 13 Nov 12 |
| 2 | P-0011 | | DCC-main | 15 Aug 12 | PZ222 | CCBBA | 15 Aug 12 | 7 Nov 12 | 24 Nov 12 |
| 3 | P-0077 | | DCC-main | 17 Sep 12 | PZ333 | BACCA | 17 Sep 12 | 10 Dec 12 | 21 Dec 12 |
| 4 | | | | | | | | | |
| 5 | | | | | | | | | |
| 6 | | | | | | | | | |
| 7 | | | | | | | | | |

6.2.2. Temporary or permanent termination of study treatment

Purpose

- To set criteria for the temporary or permanent termination of study treatment administration

When

- Any time after completion of Randomization visit (V2) when study treatment is temporarily or permanently stopped due to adverse event, participant request, lost to follow-up, pregnancy, or other reason
- At end of 12 weeks of treatment use (completion of V6)

Tasks

- **Unscheduled temporary termination**
 - Record information relating to the hiatus in study treatment on the Clinic Visit (CV) form
 - Complete an Unusual Event (UE) form or Serious Adverse Event Report (SR) form as appropriate
- **Unscheduled permanent treatment termination before V6**
 - If participant experiences moderate or severe side effects
 - Study physician will evaluate severity of symptoms as rated by participant
 - Study physician will decide if side effects are suspected to be related to study treatment
 - Study physician will determine if study treatment should be terminated
 - If side effects fall into category of Serious Adverse Event, follow procedures outlined for reporting to Data Coordinating Center (see MOP Section 9)
 - Regardless of severity, all potential side effects should be recorded on Clinic Visit (CV) form
 - Complete Treatment Termination (TT) form
 - Collect all study kit parts: CPAP device and humidifier, masks, and other accessories from participant
 - Complete Device Dispensing and Counting (DD) form
 - Continue to follow participant for all study visits (i.e., continue all relevant study procedures) through V7
 - If early unmasking is necessary, refer to MOP Section 6.2.3
 - Ship device back to the Distribution Center. Refer to MOP Section 6.1.5
 - Record on the Study Kit Accountability Log (DA)
 - Ship SD cards to the DCC. Refer to MOP Section 6.1.7
 - It is recommended to encourage the participant to come for the follow up clinic visits even if they are not using the device. If the participant informs the clinic that they will not be coming back for the rest of the study visits, complete the exit tasks with the participant (Section 2.9)
- **Treatment termination at V6**
 - Complete Treatment Termination (TT) form
 - Collect all study kit parts: CPAP device and humidifier, masks, and other accessories from participant
 - Complete Device Dispensing and Return (DD) form

- Ship device back to the Distribution Center according to instructions detailed in MOP Section 6.1.5
- Record on the Study Kit Accountability Log (DA)
- Ship SD cards to the DCC according to instructions detailed in MOP section 6.1.7

Forms (abbreviation)

- Clinic Visit (CV)
- Device Dispensing and Return (DD)
- Treatment Termination (TT)
- Serious Adverse Event Report (SR)
- Unusual Event (UE)
- Study Kit Accountability Log (DA)*

**Not entered into database*

6.2.3. Unmasking

Purpose

- Reveal treatment assignment to participant after the participant completes the study (completion of V7)
 - In unusual circumstances, reveal treatment assignment to participant and treating physician before the participant completes the study

Conditions that may lead to unmasking

- Participant completes study
 - After completion of exit tasks and last study visit (V7)
- Early unmasking
 - An acute, severe reaction suspected to be related to the study device where knowledge of treatment assignment will help determine treatment
 - Request by physician or participant

Supplies

- Participant exit letter (see MOP Section 3.6)
- Sealed Treatment Assignment Envelope provided by DCC inside the study kit

Procedures for scheduled unmasking after exit tasks

- Give participant exit letter, Treatment Assignment Envelope, and final Methacholine testing results. Refer to MOP Section 2.9 for exit procedure details
- Complete Unmasking (UM) form

Note: Study personnel should not be unmasked until entire study is completed

Procedures for early unmasking

- In emergency situations
 - Call Data Coordinating Center if during business hours

Make sure study kit ID on unmasking envelope corresponds to Participant ID receiving envelope.

- If Data Coordinating Center staff cannot be reached,
- open the sealed Treatment Assignment Envelope. Report Study Kit ID on envelope to the DCC
- Complete Unmasking (UM) form

Note: It is preferable that the treatment assignment information be communicated directly to the treating physician and that study personnel remain masked. Only reveal treatment assignment to other study personnel if they need to know for medical reasons

- In non-emergency situations

Submit request to unmask the treatment assignment in writing, including the details of the situation to the Director of the Data Coordinating Center, Robert Wise

- Letters may be faxed to (775) 871-4030 or submitted by e-mail to ala-acrc@jhsph.edu
- Requests will be considered by the Director of the DCC and the ALA-ACRC Chair,
- William Bailey, in consultation with the ACRC Executive Committee as needed
- The DCC will communicate the decision and, if appropriate, reveal the treatment assignment to the designated clinic personnel or the treating physician

Forms (abbreviation)

- Unmasking (UM) form

6.3. Requirements for personnel initiating CPAP therapy and troubleshooting

Initiating CPAP therapy with the participants, educating them on the device set up and mask fitting, and device troubleshooting must all be performed according to the CPAP instructional procedures as outlined in this MOP and in the CPAP Coordinator Instructional Video. Participant CPAP education, mask fitting, and device troubleshooting is to be conducted either:

1. By ACRC staff at the clinical center facility who has been certified to be CPAP Clinic Coordinators
2. By non-ACRC staff at or outside the clinical center facility who has been identified by clinical center staff AND who has been certified to be CPAP Device Specialists

For quality control and safety assurance, the following requirements must be met before any CPAP Clinic Coordinator or Device Specialist dispenses educates participants on the use of CPAP devices and masks. These requirements apply any time prior to a participant being given a CPAP device or fitted for a mask for the study

- All centers must only use the sample devices and masks supplied by the DCC in the Practice Kits for demonstration purposes
- All centers must only use the device and masks that are provided in the assigned study kit for a participant
- All centers must verify the attendance by key study personnel at the February 2012 training meeting in Tucson, AZ
- To be certified to instruct participants on the use of the CPAP device and mask fitting, CPAP Clinic Coordinator and CPAP Device Specialists must complete the following:



- Watch the CPAP Coordinator Instructional Video
- Complete the CPAP Device Troubleshooting (DEV) assessment online. To access the CPAP troubleshooting assessment (DEV), go to CPAP website home page
 - Click on Certification; Knowledge Assessments (online quiz system)
 - You will need to log in using your PIN and password (at first log in, password is “changeme” at which time you will be prompted to choose your own password)
 - Follow instructions
 - 80% correct response is required to pass
 - When test is “passed,” print out results and submit to DCC along with other relevant certification materials
 - Can be repeated unlimited number of times and is open book

7. High Resolution Computed Tomography (HRCT) substudy

7.1. Design and outcome measures

Title

Effects of CPAP on Airway Size in Patients with Asthma (HRCT substudy)

Objective

The 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 airway hyper-responsiveness

Type of Study

- Substudy: HRCT performed on the subset of participants in the main CPAP study who are 18 years or older, enrolled at a center participating in the substudy, and volunteer to participate in the HRCT substudy
- Multicenter: *DUKE, NJC, NNEC, NYMC, OSU, STL, UMKC, UCSD, UAZ, STV*
- Fixed sample size: 48 (16 per CPAP treatment group)

Study Treatment

- HRCT images taken pre and post CPAP use at Total Lung Capacity (TLC) and Functional Residual Capacity (FRC)

Primary Outcome

- Changes in airway diameter and air trapping

Clinic preparation

- Clinic certification for HRCT substudy is required before any participants are enrolled in the substudy. See MOP Section 7.8

Substudy Principal Investigator

Dr. Robert Brown

7.2. Eligibility criteria

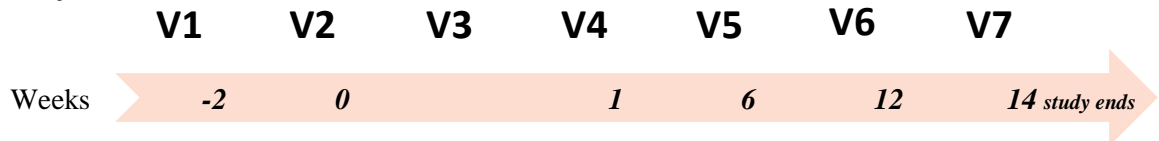
A total of 48 adult participants (16 per group), who are randomized in the main study, will be enrolled in the substudy. Participation in the HRCT substudy is voluntary; unwillingness to participate in the substudy does not affect the participant's eligibility for the main study.

Inclusion Criteria

- 18- 60 years of age at V1
- Randomized in the main CPAP study

7.3. Study visit time windows and data collection schedule

Main study



HRCT substudy

| | S1 | S2 |
|--------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Target | 0 | 12 |
| Visit window | 0 | 10-12 |
| | Performed after randomization in main study, but prior to initiation of CPAP | Performed on a different day or prior to methacholine challenge testing |

- At S1 and S2, two scans will be performed; one inspiratory scan at TLC and one expiratory scan at FRC
A pregnancy test will be administered to participants of child bearing potential at each visit before scans

7.4. Scheduling of visits

HRCT – S1

S1 HRCT scans should be performed after participant is randomized in the main study but before participant starts using the CPAP device.

- Ideally scans should be scheduled for the day the participant will be randomized
- If it is not possible to schedule scans to on the same day as randomization
 - Schedule scans as soon as possible but no longer than 1 week after randomization. Do not give participant the CPAP device to take home until the scans are done.
 - If scans cannot be scheduled within one week after randomization, contact the DCC with details of the event. Scheduling variances will be considered on a case by case basis.

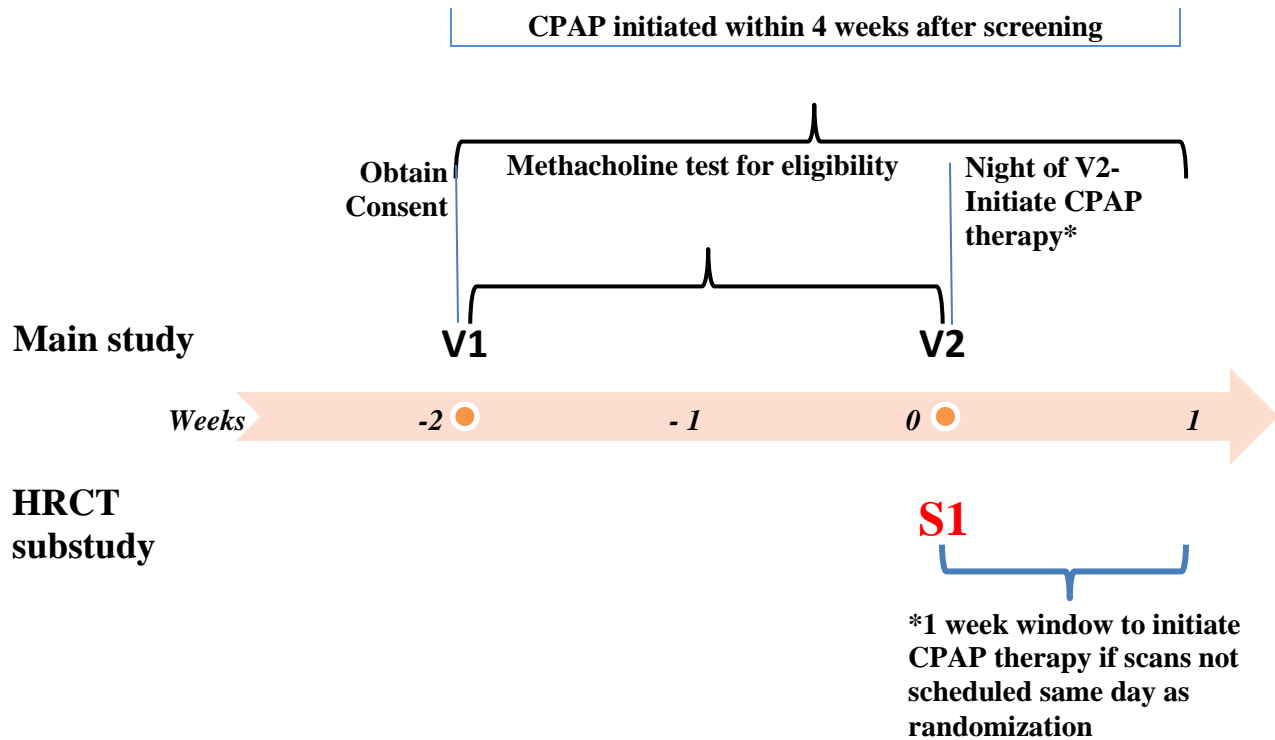
HRCT – S2

S2 HRCT scans should be performed before participant terminates CPAP treatment, as close as possible to when the treatment is terminated.

- Ideally scans should be scheduled on the same day or just prior to participant termination of treatment (10-12 weeks after randomization).

- If it is not possible to schedule scans within the last 2 weeks of the treatment, contact the DCC with details of event. Scheduling variances will be considered on a case by case basis.

Recommended scheduling for S1



7.5. Order of procedures

Randomization visit (V2)

- Participants who consent to participate in the substudy will be enrolled in the substudy as part of randomization into the main study. (CPAP RZ form includes a section for enrollment in the HRCT substudy).

Required order of procedures

- Required medication holds for scans are the same as those for the methacholine challenge test - See Section 7.9.5
- A pregnancy test must be conducted, if applicable, on the day of the scanning visit before scans are performed
- HRCT scans can be done on the same day as methacholine challenge testing but must be before methacholine challenge testing
- HRCT scans **SHOULD NOT** be done after methacholine challenge testing

Notes

- Participants **must not** use their CPAP device prior to their first scanning visit S1

- Participants **should** use their CPAP device prior to their second scanning visit S2

7.6. HRCT visits

Screening visit (V1) of the main CPAP study

- Review substudy requirements with participant
- If participant is interested, assess participant for the ability to hold breath for 15 seconds, lie flat and still for 30 minutes and to follow instructions. Participants who are unable to do these things or who are claustrophobic in a CT scanner should not be enrolled in the HRCT substudy.
- Consent participant
- Instruct participant to hold medications listed on their Instruction for HRCT scans information sheet (ISC) prior to S1 and S2.

Information Sheets (abbreviation)

- Instruction for HRCT scans (ISC)*

**Not entered into database*

HRCT visit 1 (S1)

Overview

S1 includes confirmation of eligibility, pregnancy testing (for women of child bearing potential), HRCT scanning at inspiration (TLC) and expiration (FRC), radiologist over-read for incidental findings, and shipments of HRCT scans and forms to the DCC

Time frame



- After participant is randomized in the CPAP main study and enrolled in HRCT substudy
- Target: The day of Randomization (V2), before starting on CPAP therapy
- Window: 0-1 week after randomization
- Duration: 1 hour

Equipment and materials

- S1 forms
- CPAP - HRCT scanning procedure
- 2 HRCT disks (Pre-printed labels on disks)
- Shipping materials

Tasks

- Conduct pregnancy testing, if applicable
- Medication holds
 - Confirm that participant held medications by completing HRCT Scan Acquisition form (RT)
 - If medications were not held, STOP; scans should not be conducted
- Participant prep
 - Practice breathing instructions with participant. See MOP Section (7.9.7)
 - Accompany participant to Radiology CT suite
- Technologist prep

- Give technologist appropriate CT Technologist Instruction (ICT) form according to the type of scanner used
 - Remind technologist to use CPAP HRCT scanning procedure; provide printout of HRCT scanning procedure if he/she does not have it available (Appendix B of this MOP)
 - Conduct scans – (technologist)
 - Scout AP/PA (CT topogram) at TLC
 - Inspiratory (TLC) scan
 - Expiratory (FRC) scan
-  **Note: Scans must not be repeated for any reason!**
-  **Note:** Prior to scans, coordinator should confirm scanner settings
 - Complete HRCT Scan Acquisition form (RT); technologist completes Section F
 - Review and archive scans (technologist)
 - Send both scans (TLC and FRC) to radiologist to over-read; over-reading should be completed within **24 hours** of scan acquisition
 - Confirm scans are saved in radiology archive
 - Disks burned and labeled (technologist)
 - De-identify scans per local guidelines and assign participant ID to scans per CPAP HRCT scanning procedure instructions in Appendix B
 - Burn scans on the 2 pre-labeled disks - do NOT burn the reader software
 - Fill in the Clinic ID, Participant ID, visit ID, and Date of Acquisition on the disk label
 - Complete Radiologist Review (RR) form upon receipt of radiologist report
 - Obtain radiologist report (radiologist should over-read scans within 24 hours)
 - Notify study physician of any incidental findings; study physician or coordinator should give information to participant and with his/her permission to participant's usual caregiver for appropriate medical care or follow-up.
 - Transmit disks and forms to DCC
 - Ship one disk and copies of completed forms (RT, RR, HCT) to the DCC according to instructions within 3 days of acquisition (see MOP Section 7.14)
 - Also fax completed forms to the DCC (775-871-4030)
 - Retain second disk at clinical center


Forms (abbreviation)

- HRCT Scan Acquisition (RT)
- Radiologist Review (RR)*

Information Sheets (abbreviation)

- Instruction for HRCT scans (ISC)*
- CT Technologist Instruction (ICT)*

**Not entered into database*

 **Note:** If a participant is randomized in the CPAP study and enrolled in the HRCT substudy, but for a reason does not perform the HRCT scan at S1, **do NOT** conduct an HRCT S2.

HRCT visit 2 (S2)

Overview

S2 includes pregnancy testing (for women of child bearing potential), HRCT scanning at TLC and FRC, radiologist over-read for incidental findings, and shipments of HRCT scans and forms to DCC

Time frame

- Several days before S2, participant should be reminded about medication holds and to use CPAP the night before S2
- Target: End of treatment (V6) – right before terminating CPAP therapy
- Window: 10-12 weeks after randomization
- Duration: 1 hour

Equipment and materials

- S2 forms
- CPAP - HRCT scanning procedure
- 2 HRCT disks (Pre-printed labels on disks)
- Shipping materials

Tasks

- Conduct pregnancy testing, if applicable
- Medication holds
 - Confirm participant held medications by completing HRCT Scan Acquisition form (RT)
 - If medications were not held, STOP; scans should not be conducted
 -
- Participant prep
 - Practice breathing instructions with participant. See MOP Section (7.9.7)
 - Accompany participant to Radiology CT suite
- Technologist prep
 - Give technologist appropriate CT Technologist Instruction (ICT) form according to the type of scanner used

Note: The same scanner and settings MUST be used for HRCT scans for the participant as their S1

 - Remind technologist to use CPAP HRCT scanning procedure ; provide printout of HRCT scanning procedure if he/she does not have it available (Appendix B of this MOP)
- Conduct scans (technologist)
 - Scout AP/ PA (CT topogram) at TLC
 - Inspiratory (TLC) scan
 - Expiratory (FRC) scan

Note: Prior to scans, coordinator should confirm scanner settings
- Complete HRCT Scan Acquisition form (RT); technologist completes Section F
- Review and archive scans (technologist)
 - Send both scans (TLC and FRC) to radiologist to over-read; over-reading should be completed within 24 hours of scan acquisition
 - Confirm scans are saved in radiology archive
- Disks burned and labeled (technologist)
 - De-identify scans per local guidelines and assign participant ID to scans per CPAP scanning procedure instructions in Appendix B
 - Burn scans on the 2 pre-labeled disks - do NOT burn the reader software
 - Fill in the Clinic ID, Participant ID, visit ID, and Date of Acquisition on the disk label
- Complete Radiologist Review (RR) form upon receipt of radiologist report
 - Obtain radiologist report (radiologist should over-read scans within 24 hours)

Note: Scans must not be repeated for any reason!

- Notify study physician of any incidental findings; study physician or coordinator should give information to participant and with his/her permission to participant's usual caregiver for appropriate medical care or follow-up
- Transmit disks and forms to DCC
 - Ship one disk and copies completed forms (RT, RR, HCT) to the DCC according to instructions within 3 days of acquisition (see MOP Section 7.14)
 - Also fax completed forms to the DCC (775-871-4030)
- Retain second disk at clinical center

Forms (abbreviation)

- HRCT Scan Acquisition (RT)
- Radiologist Review (RR)*

Information Sheets (abbreviation)

- Instruction for HRCT scans (ISC)*
- CT Technologist Instruction (ICT)*

**Not entered into database*

7.7. Missed procedures/missed visits

- If a participant does not complete their HRCT scans at S1, **do not perform HRCT scans at S2**. Complete a Missed Data (MD) form to indicate that for S1 and S2, no Scan acquisition form (RT) form is completed.
- If a participant completes their HRCT scans at S1, but does not perform HRCT scans at S2, complete a Missed Data (MD) form to indicate that for S2, no Scan acquisition form (RT) form is completed.

7.8. HRCT certification requirements

Each clinical center participating in the CPAP HRCT substudy must be certified for the substudy before enrolling any participant to have HRCT scans. For certification the DCC must receive the following:

1. The HRCT Substudy Certification (SS) form
2. A Phantom Acquisition (PT) form and corresponding disk for the scanner to be used for the substudy. The phantom must be scanned for one scanner used in the study PRIOR to enrolling participants in the HRCT substudy.
3. Image quality evaluation and dosimetry reports
 - a. Each clinical center should be accredited by the Joint Commission or the American College of Radiology (ACR).
 - i. If your site is accredited with ACR, send the ACR CT phantom and dosimetry reports along with the other certification forms to the DCC
 - ii. If your site is not accredited with ACR, send any other medical physicist report that includes image quality evaluation and radiation dosimetry along with the other certification forms to the DCC

Fax completed forms to the DCC (775-871-4030) to be certified.

Note: Receipt of a notification of HRCT substudy certification (SS) form from the Coordinating Center (via e-mail) is required. Clinics cannot enroll participants into the substudy or perform HRCT visits (SI) until written notification of certification is received.

Forms (abbreviation)

- HRCT Substudy Certification (SS) *
- Phantom Acquisition (PT)*

**Not entered into database*

7.8.1. Phantom scanning requirements

Overview

For the clinic to be certified for HRCT, a phantom should be scanned prior to start enrolling participants in the substudy. Phantoms will be scanned twice at each clinic center throughout the study; once before the start of the substudy, and again halfway through the study.

Equipment and materials

- CPAP Lung Phantom (received from the DCC)
- PT form
- Phantom scanning procedure
- 2 disks (pre-labeled)
- Shipping materials

Tasks

- Schedule a time with the radiology technologist to scan the phantom. Once confirmed, inform the DCC to ship a phantom to the clinic
- If a site will be using multiple scanners for the study, the phantom **MUST** be scanned for each scanner used. Complete a separate Phantom Acquisition (PT) form for each scanner
- Technologist prep
 - Give technologist the Phantom scanning procedure (Appendix A of this MOP)
- Conduct scans – (technologist)
 - inspiratory (TLC) scan
 - expiratory (FRC) scan
- Complete Phantom Acquisition (PT) form. Technologist completes Section B
- Review and archive scans (technologist)
- Disks burned and labeled (technologist)
 - Assign phantom ID to scans per CPAP phantom scanning procedure instructions in Appendix A
 - Burn scans on the 2 pre-labeled disks- do NOT burn the reader software
 - Fill in the Clinic ID, Scanner serial number, and Date of Acquisition on the disk label
- Transmit disks and forms to DCC
 - Ship phantom, one disk, and copies of completed forms (PT, HCT) to the DCC according to instructions within 3 days of acquisition (see MOP Section 7.14)
 - Also fax completed forms to the DCC (775-871-4030) with the rest of the certification materials
- Retain second disk at clinical center

Forms (abbreviation)

- Phantom Acquisition (PT)* form

**Not entered into database*

7.8.1.1. Phantom scanning procedure

- Phantom scanning procedure is attached in Appendix A (version date: 1 Jan 2013)

7.8.2. Scanner requirements

- Scanners must be certified by ARRT
- Scanners **MUST** have a minimum of 64 slices/detectors
- Each site should use only ONE scanner for the HRCT substudy. The phantom **MUST** be scanned for the scanner to be used. Complete a Phantom Acquisition (PT) form
- If a site will be using a new scanner after the site is certified, the phantom must be scanned for the new scanner before it is used for the CPAP substudy. Contact the DCC to get a phantom shipped to the site and complete a Phantom Acquisition (PT) form.

7.8.3. Personnel requirements

- Personnel administering the HRCT scans should be radiology technologists certified by the American Registry of Radiologic Technologists (ARRT), and/or licensed according to the local state.
- Radiology technologist must follow the instructions of the CPAP Phantom Scanning Procedure and the CPAP HRCT Scanning Procedures when performing scans for the CPAP substudy. Both procedures are attached (Appendix A and B)
- Each clinic center must also have a certified radiologist on site who will perform the over-read of the HRCT scans within 24 hours of acquisition to identify any incidental findings on the scans. The scans also should be inspected for adequate inspiration, absence of motion artifact and inclusion of all parts of the chest.

7.9. Procedures

7.9.1. Overview

Although there are some variations between CT scanners, a standardization of the parameters has been developed to allow multiple scanners to output reliable quantitative measures across a given patient population. Parameters such as dose have been adjusted to accommodate large, medium and small subjects using independent mAs settings for each body size.

Each subject will have one standard scout (AP/PA) topogram scan over the chest at Total Lung Capacity (TLC).

Two CT scans will be performed each at a different lung volume. The first volume will be at Total Lung Capacity (TLC) followed by another CT scan at Functional Residual Capacity (FRC).

7.9.2. HRCT scanning procedure

- HRCT scanning procedure is attached in Appendix B.
- **The HRCT scans taken at S1 and S2 MUST be performed using the same scanner and settings for each participant.**

7.9.3. Participant instructions prior to day of HRCT scan

Two to three days before the scan, remind participant

- To hold medications as detailed in Section 7.9.5
- To abstain from caffeine, cola drinks, and chocolate on the day of the scan
- To abstain from exercise and smoking for 6 hours before his/her HRCT scan appointment

7.9.4. HRCT Contraindications and participant assessment

If the following contraindications occur, do not perform HRCT scanning:

- Pregnancy
- Inability to lie flat for 30 minutes
- Inability to hold breathe for 15 seconds
- Inability to follow instructions
- Claustrophobic in CT scanner
 - Participants should be assessed prior to scanning as to their general physical condition and ability to perform the scan. They should also be assessed regarding appropriate withholding of medications and other potentially confounding issues as above
 - A pregnancy test should be done at each scanning visit if the female participant is of child bearing potential
 - If the participant is wheezing, showing other signs of asthma, or has other conditions that may affect the HRCT scan, the study physician must review and approve the performance of the HRCT scan.

It is important that the HRCT scans are performed under the same conditions as methacholine challenge testing. Hence, study physician should evaluate the event as they would do for the methacholine challenge testing.

7.9.5. Medication holds prior to HRCT scan

The following medication hold periods must be observed prior to performing HRCT scans

| | |
|--------------------------------------------------------------------------------------------------------------------------------------|----------------|
| Short-acting bronchodilators (<i>eg, Ventolin, albuterol, Proair, Proventil, Xopenex, isoproterenol, metaproterenol</i>) | 6 hrs |
| Cromolyn | 8 hrs |
| Medium-acting bronchodilators (<i>eg, ipratropium, Combivent, oral albuterol, Choledyl</i>) | 24 hrs |
| Long-acting bronchodilators (<i>eg, salmeterol, formoterol, Advair, Serevent, Symbicort, Dulera</i>) | 24 hrs |
| Nedocromil | 24 hrs |
| Leukotriene modifiers (<i>eg, Singulair, Accolate, Montelukast, Zafirlukast</i>) | 24 hrs |
| Oral theophylline (<i>eg, Theodur, Uniphyl</i>) | 48 hrs |
| Antihistamines (<i>eg, Zyrtec, cetirizine, fexofenadine, Xyzal, hydroxyzine</i>) | 48 hrs |
| Ultra long-acting bronchodilators (<i>eg, tiotropium</i>) | 48 hrs |
| Inhaled steroids (<i>eg, Flovent, Alvesco, Mometasone</i>) | No hold |
| Study treatment – CPAP <i>Participant should use the CPAP night before S2</i> | No hold |

Participant may use rescue medication because of asthma symptoms if needed. If they do they should call the clinic.

 *Note:* Participant should use their CPAP device the night before HRCT scanning for S2

7.9.6. Other confounders

The HRCT scan could be confounded by the following:

- Caffeine, cola drinks, and chocolate on the day of the scan
- Exercise or smoking within past 6 hours
- Upper respiratory infection within past 4 weeks
- Known allergen exposures within past week

If any of these confounders are present, they should be noted on the HRCT Acquisition form (RT), but the scanning can proceed as scheduled.

7.9.7. HRCT breathing instructions

Instructions prior to scan

- Practice the breathing techniques with participant according to the instructions below PRIOR to accompanying them to the Radiology Department
- It is important for the coordinator and Radiology Technologist to ensure that the subject is able to follow the commands appropriately and also that the subject is appropriately coached PRIOR to performing the actual imaging procedures. Below are the breathing instructions to give the participant.
- Ask if participant would like to use the bathroom before the scan (stress incontinence could be precipitated)

(a) Practice Breathing (TLC)

- For the first part of this scan, I am going to ask you to take a couple of deep breaths in an out before we have you hold your breath all the way in.
- First let's practice
- Take a deep breath in (*watch chest to ensure a deep breath as far in as possible*)
- Let it out (*watch chest to ensure air is out*)
- Take a deep breath in (*watch chest to ensure a deep breath in*)
- Let it out (*watch chest to ensure air is out*)
- Now breathe all the way IN...IN...IN...and hold it (*watch chest to ensure a deep breath in as far as possible*)
- Keep holding your breath- DO NOT BREATHE! (*watch chest to ensure spine remains on the table, patients is not shaking- watch for these throughout the study!*)
- Breathe and relax

(b) Scout views (TLC): AP/PA (CT topogram)

- OK let's get started
- Take a deep breath in (*watch chest to ensure a deep breath in*)
- Let it out (*watch chest to ensure air is out*)
- Take a deep breath in (*watch chest to ensure a deep breath in*)
- Let it out (*watch chest to ensure air is out*)
- Now breathe all the way IN... IN... IN... and hold it (*watch chest to ensure a deep breath as far in as possible*)
- Keep holding your breath- DO NOT BREATHE! (*watch chest to ensure the spine remains on the table, subject is not shaking and then start the scout scan*)
- *Perform scout*
- *At the end of the scout- Breathe and relax*

(c) Inspiratory CT (TLC)

- Now we're ready again so please:
- Take a deep breath in (*watch chest to ensure a deep breath in*)
- Let it out (*watch chest to ensure air is out*)
- Take a deep breath in (*watch chest to ensure a deep breath in*)
- Let it out (*watch chest to ensure air is out*)
- Now breathe all of the way IN...IN...IN as far as possible and hold it in (*watch chest to ensure a deep breath in as far as possible*)
- Keep holding your breath – DO NOT BREATHE!
- *Perform TLC scan*
- *As the scan ends: Hold your breath for 3...2....1*
- *At the end of scan- Breathe and relax*

(d) Practice Breathing (FRC)

- For the second part of this scan, I am going to ask you to breathe normally in and out before we have you hold your breath at the end of breathing out.
- First let's practice
- Take a breath in (*watch chest to ensure a breath in*)
- Let it out (*watch chest to ensure air is out*)
- Take a breath in (*watch chest to ensure a breath in*)
- Let it out (*watch chest to ensure air is out*)
- Take another breath in (*watch chest to ensure a breath in*)
- Let it out, hold your breath
- Keep holding your breath- DO NOT BREATHE! (*watch chest to ensure spine remains on the table, patients is not shaking- watch for these throughout the study!*)
- Breathe and relax

(e) Expiratory CT (FRC)

- Now we're ready again so please
- Take a breath in (*watch chest to ensure a breath in*)
- Let it out (*watch chest to ensure air is out*)
- Take a breath in (*watch chest to ensure a breath in*)
- Let it out (*watch chest to ensure air is out*)
- Take another breath in (*watch chest to ensure a breath in*)
- Let it out, hold your breath
- Keep holding your breath – DO NOT BREATHE!
- *Perform FRC scan*
- *As the scan ends: Hold your breath for 3...2....1*
- *At the end of scan- Breathe and relax*

7.10. Equipment and supplies

Data Coordinating Center will distribute the following:

- CPAP Lung Phantom (CTP674 Lung Phantom™-The Phantom Laboratory, Salem, New York) – to be shipped back to the DCC
- Disks for burning phantom and HRCT scans that are pre-labeled

Ordering additional supplies from Data Coordinating Center

- Order supplies as needed
- Complete CPAP Supply order (CO) form
- Requests should include number of items and date needed
- Fax or mail to the DCC (775-871-4030)

Clinical centers will provide

- FedEx mailing labels
- Study forms and questionnaires (downloaded from CPAP website)
<http://www.jhcct.org/Secure/CPAP/CPAPHome.htm>)
- Pregnancy test kits

Form (abbreviation)

- CPAP Supply order form (CO)

7.11. Forms

HRCT Substudy Certification (SS) form

- To be completed by each clinical center participating in the HRCT substudy prior to enrolling participants to the HRCT substudy
- Used to document that both the main ACRC clinical center and any satellite clinics have the necessary equipment, qualifications, and personnel to conduct the CPAP HRCT substudy
- The lead coordinator at the main ACRC clinical center must review and submit this form for any satellite clinics
- Participants may not undergo HRCT scans until notice of certification is received from the DCC
- Fax form to the DCC (775-871-4030)
- Form is not data entered

Phantom Acquisition (PT) form

- To be completed when phantoms are scanned (before start of study and halfway of study)
- Used to record the collection inspiratory and expiratory phantom scanning information
- The technologist should complete Section B on the form
- Copy of the form should be shipped with the disk to the DCC. Keep original to retain at clinic
- Fax form to the DCC (775-871-4030)
- Form is not data entered

HRCT Scan Acquisition (RT) form

- To be completed for each HRCT scan visit (S1 and S2)

- Used to record information of HRCT scans collected
- The technologist should complete Section F on the form
- Copy of the form should be shipped with the disk to the DCC. Keep original to retain at clinic
- Fax form to the DCC (775-871-4030)
- Enter the form in the data system within 10 days

Radiologist Review (RR) form

- The radiologist should review both TLC and FRC scans within 24 hours of scan acquisition. Attach radiologist report and comments to the RR form
- One Radiologist Review (RR) form should be completed for each visit per participant
- Each form should include reports from radiologist for both TLC and FRC for that visit
- Copy of the form should be shipped with the disk to the DCC. Keep original to retain at clinic
- Fax form to DCC (775-871-4030)
- Form is not data entered

 **Note:** If the RR form is missed or not completed for a visit that collected HRCT scans, complete a UE form indicating a protocol deviation.

CT Technologist Instruction (ICT) form

- This form assists the radiologist technologists to use the proper scanner settings and breathing instructions to complete the scans within the guidelines of the study.
 - Each form will contain proper breathing instructions and scan parameters for clinical center scanners.
 - The form should be handed out to the technologist prior to each time a scan is performed
 - There are 8 ICT forms. Each scanner will have a specific ICT form according to the scanner settings

HRCT Transmittal Sheet (HCT)

- Completed whenever phantom disks or HRCT scan disks are shipped to the DCC
- Copy of the form should be shipped with the disk to the DCC. Keep original to retain at clinic
- Fax a copy of the form to DCC (775-871-4030)
- Form is not data entered

7.12. Scan de-identification

- HRCT scans MUST be de-identified per local procedures prior to burning to disk
- Scan identification must include, scanner make and serial number, and have Participant ID on the scan label description. Example: a GE Scanner with SN 123456 and participant ID PD000 will be: PD000GE123456 (participant ID, scanner make, scanner SN)

7.13. HRCT labels

Labels

- Each DVD will be pre-labeled. After a scan is performed, fill in the following information
 - Clinic ID
 - Phantom or Participant ID
 - Visit ID
 - Date of acquisition
- Each clinic will be sent disks with labels similar to the examples below

Example of HRCT disk Label Sheet

| |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>HRCT scans/CPAP</p> <p>Effects of CPAP on Airway Size in Patients with Asthma</p> <p>Clinic ID: ____ _</p> <p>Participant ID: ____ _</p> <p>Visit ID: <u>S</u> ____</p> <p>Date: ____ - ____ - ____ (dd - mmm - yy)</p> |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Example of Phantom disk Label Sheet

| |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>HRCT/CPAP</p> <p>Effects of CPAP on Airway Size in Patients with Asthma</p> <p>Phantom ID: _____</p> <p>Clinic ID: ____ _</p> <p>Scanner Serial #: _____</p> <p>Date: ____ - ____ - ____ (dd - mmm - yy)</p> |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

7.14. Shipping instructions

Tasks

- Ship phantoms in the original box that they are received back to the DCC within 3 days of phantom scanning
- Ship phantom disks or HRCT scan disks within 3 days of acquisition
- Shipping supplies

- HRCT Transmittal Sheet (HCT)
 - FedEx envelope – provided by clinic
- Shipping tasks
 - Insert labeled disk in FedEx envelope
 - Complete HRCT Transmittal Sheet (HCT) and make copy to retain at clinic
 - Ship original HCT with the disk
- Place a copy of HRCT Scan Acquisition (RT) form with the disk, keep original to retain at clinic
- Place a copy of Radiologist Review (RR) form and reports with the disk, keep original to retain at clinic
- If phantom scanning is shipped, include a copy of the Phantom Acquisition (PT) form with the disk, keep original to retain at clinic

Ship to:

ACRC Data Coordinating Center
911 S. Ann St.
Baltimore, MD 21231

**! Address changed to: -
415 N Washington St. -
2nd floor -
Baltimore, MD 21231**

- Use FedEx account number: 3053-6089-9
- Ship Priority-Overnight
- Immediately upon shipment, notify the DCC by faxing the forms to 775-871-4030

Form (abbreviation)

- HRCT Acquisition (RT)
- Phantom Acquisition (PT)*
- HRCT Transmittal Sheet (HCT)*
- Radiologist Review (RR)*

**Not entered into database*

8. Data collection and forms completion

8.1. List of forms, questionnaires, logs

| Forms/Log name | Abbreviation | Purpose | Data entered |
|-------------------------------------|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| Forms | | <ul style="list-style-type: none"> Record study data on standardized data collection instruments Guide data collection and visit procedures | |
| Baseline Asthma and Medical History | BA | Establishes asthma history, asthma treatment, and smoking history | ✓ |
| Clinic Visit | CV | records information about Diary Cards, treatment compliance, asthma symptoms, and interim medications | ✓ |
| CPAP Diary Card | DC | Completed by the participant on a daily basis to record peak flow, asthma medication use, severity of asthma episodes, and nightly use of the CPAP device. Participants should bring completed CPAP Diary Cards to each clinic visit. More details in Section 8.2.1 | ✓ |
| Device Dispensing and Return | DD | Records the issuing and collecting of study device and masks to and from participant Form is expected at V2 for dispensing and V6 for returning study equipment | ✓ |
| Nitric Oxide | NO | Records eNO levels | ✓ |
| Methacholine Challenge Testing | MC | Records the results of Methacholine Challenge Testing and PC ₂₀ | ✓ |
| Missed Data | MD | Records information about visits/contacts or procedures that were missed by an enrolled participant | ✓ |
| Phone Contact | PC | Records information from a phone interview conducted at V3 to assess compliance, and assists coordinators in troubleshooting | ✓ |
| Physical Exam | PE | completed by study physician at V2 to assess participant's general health and note any abnormalities | ✓ |
| Participant Information | PI | Records participant location and contact information at V1. This form is kept in the participant's folder located at the clinic | No |
| Randomization | RZ | Records participant eligibility to be randomized for the study. Completed and entered into the database at V2 after all other forms and activities for that visit have been completed, except for initiating CPAP therapy. Once the form is data entered, treatment assignment should be recorded on the form. | ✓ |
| Screening | SC | Records preliminary eligibility at V1. Completed after initial forms and procedures are completed. | ✓ |
| Serious Adverse Event Report | SR | Completed if an event deemed reportable occurs according to Section 9 of the MOP. The form must be faxed to the DCC within 72 hours and keyed to the database within 10 working days | ✓ |

| Forms/Log name | Abbreviation | Purpose | Data entered |
|--------------------------------------------|--------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| Treatment Termination | TT | Records permanent termination of study device use, either before V6 or when the participant ends the treatment at V6 | ✓ |
| Unusual Event | UE | Reports protocol deviations, unusual medical problems, events that require expedited review, devices or masks not returned at end of study, or device, masks, or accessories returned to DCC due to malfunction or damage. Refer to Section 9 | ✓ |
| Unmasking | UM | Completed when the participant is unmasked either before the end of the study or at the end of the study | ✓ |
| Methacholine Challenge Worksheet – 11-Step | MW | Assists coordinators in completing the Methacholine Challenge Testing and guides them to perform the appropriate sequence of spirometry efforts for the test. | No |


Questionnaires


- **To collect information directly from the participant or parent/guardian concerning aspects of participant's asthma and quality of sleep**

| | | | |
|----------------------------------------------|----|------------------------------------------------------------------------------------------------------------|---|
| Asthma Symptom Utility Index | AS | Asks about asthma symptoms within the past 2 weeks | ✓ |
| Berlin Sleep Questionnaire | BQ | Assesses the risk of sleep apnea and other sleep related symptoms | ✓ |
| Epworth Sleepiness Scale | ES | Determines the level of daytime sleepiness | ✓ |
| Study Evaluation | EV | Completed at V6 and V7 by the participant to obtain the participant's impression of the treatment received | ✓ |
| Multivariable Apnea Prediction Questionnaire | MP | Assesses the risk of sleep apnea and other sleep related symptoms. See Section 8.2.3 for details. | ✓ |
| Marks Asthma Quality of Life Questionnaire | MQ | Measures asthma specific quality of life | ✓ |
| Sino-Nasal Questionnaire (SNQ-6) 6 week | NQ | Assesses symptoms of rhinitis and sinusitis for the past 6 weeks | ✓ |
| Pittsburgh Sleep Quality Index | SQ | Measures the quality and patterns of sleep | ✓ |
| Asthma Control Test (ACT) | TA | Asks about asthma symptoms during the past four weeks | ✓ |
| Quality of Life Questionnaires (WQ) | WQ | Assess general and asthma-specific quality of life | ✓ |

**All questionnaires will be provided in Spanish versions as well. Please refer to individual questionnaires for specific guidelines on administration, completion, and scoring.*

| Forms/Log name | Abbreviation | Purpose | Data entered |
|----------------------------------------------|--------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| Logs/Administrative Forms | | <ul style="list-style-type: none"> • Provide records of the tracking study kits, tracking participants screened for the trial, transmission of SD cards and specimens, and supplies ordered. | |
| Study Kit Accountability Log | DA | Used to account for study kit stock at a specific clinical center or satellite and to track study kits throughout the study | No |
| Participant Screening Log | PS | Used to keep a record of demographic information and disposition of all participants evaluated for eligibility for the trial. During prescreening, participant information is entered into the PS though the participant may not sign consent. All participants that are registered in CPAP are to be listed on the PS. Refer to enrollment diagram in Section 1 | ✓ |
| Specimen Transmittal Sheet | TS | Accompanies specimens ready to be shipped: printed directly from the data system after specimens are scanned) | |
| CPAP Device Transmittal Sheet | CT | Used as a packing slip and documentation for CPAP study kit and accessories return to the CPAP Device Distribution Center | No |
| SD Card Transmittal Sheet | SD | Used as a packing slip and documentation for SD card shipments to the DCC | No |
| ACRC General Supply Order Form | GO | Used is for requesting general ACRC study supplies | No |
| CPAP Supply Order Form | CO | Used to order supplies specific to the CPAP trial | No |
| Peak Flow Meter Order Form | PO | Used to order Peak Flow Meters from Bayview Medical Inc. | No |
| Methapharm Provocholine Order form | LP | Used to order Provocholine from Methapharm | No |
| Participant Information Sheets | | <ul style="list-style-type: none"> • Provide instructions about study procedures for participants • Copies should be included in participant binders or given to participant after randomization | • |
| Asthma Action Plan Card | AAP | Outlines how to respond to asthma symptoms for participant. Refer to Section 8.2.2 | No |
| CPAP Device User Instructions | ICD | Includes information regarding CPAP device set up, mask fitting, equipment cleaning and maintenance, and troubleshooting | No |
| Instructions for CPAP Diary Cards | IDC | Includes details on how to complete the CPAP Diary Card every day. This is also to be used by staff to review CPAP Diary Card procedures with a participant. | No |
| Instructions for Methacholine Challenge Test | IMC | Indicates preparations before Methacholine testing for participants in terms of medication holds and other confounders that may affect the testing | No |
| Instructions for Measuring Peak Flow | IPF | Reviews procedures of measuring peak flow for participants every morning. This is also to be used by | No |

| Forms/Log name | Abbreviation | Purpose | Data entered |
|------------------------------------------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| CPAP Schedule of Visits | SOV | staff while instructing participants how to use the Peak Flow Meter. highlights visit procedures and future appointments. This sheet can be used as a reference for participants and should be included in the Participant Binder | No |
| CPAP Wallet Card | --- | wallet size card with study title and treatments, contact information for study, and primary asthma physician | No |
| CPAP Participant Instructional Video on flash drive |  | Includes a video "Guide to using your CPAP" illustrating CPAP device set up, mask fitting, equipment cleaning and maintenance | No |
| General Asthma Educational Materials | --- | General information on asthma distributed at screening (V1) | No |
| CPAP Brochure | CB | Summarizes the CPAP trial and used to recruit potential participants into the trial | No |
| Clinical Center Certification | | <ul style="list-style-type: none"> Provide documentation that the main ACRC clinical center and any additional satellite centers have obtained the required approvals, facilities, equipment, personnel, and training necessary to conduct CPAP Ensure consistent conduct of study procedures over time within and across clinics so that findings from all clinics are comparable | |
| Clinical Center Certification | CC | Documents that a clinical center has the necessary facilities, equipment, personnel, and approvals for enrollment, treatment, and follow up of participants | No |
| Personnel Certification | CE | Specifies roles of staff for CPAP and the certification requirements for each role | No |
| CPAP Methacholine Challenge Test Assurance Statement | MA | To be completed by PIs or satellite PIs involved with CPAP | No |
| CPAP Personnel Assurance Statement | PA | To be completed by all personnel involved with CPAP | No |
| HRCT Substudy Certification | SS | To be completed by sites participating in HRCT to document certified scanners | |
| Satellite Center Certification | ST | Documents that a satellite center has the necessary facilities, equipment, personnel, and approvals for enrollment, treatment, and follow up of participants | No |
| Diary Card Scenario | | Provides a one week scenario as an example to assist coordinators in completing Diary Cards | No |
| General Knowledge Assessment for CPAP | GEN | Online assessment on the CPAP protocol | N/A |
| Data System Operator Knowledge Assessment | DSO | Online assessment on data entry and the data system | N/A |
| Device Troubleshooting | DEV | Online assessment on device troubleshooting and maintenance. Based on the CPAP Coordinator Instructional Video: <i>Guide to using your CPAP</i> . | N/A |

| Forms/Log name | Abbreviation | Purpose | Data entered |
|----------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| Consent Checklists | | | |
| Main CPAP study consent checklist | --- | Lists all required items that need to be in each consent form for the CPAP trial | No |
| HRCT consent checklist | --- | Lists all required items that need to be in each HRCT consent form for the CPAP trial | No |
| Online tools | | | N/A |
| Multivariable Sleep Apnea Calculator (MAP) | --- | Calculates probability of sleep apnea for participant depending on their Age, gender, BMI, and MAP responses for items 1, 5, and 8 of the questionnaire | |
| BMI calculator | --- | Calculates BMI using participant's height and weight <i>BMI=[(weight (kg))/(height (m))²]</i> Height: <i>1cm = 0.3937 in</i> <i>1in = 2.54 cm</i> Weight: <i>1kg = 2.2 lbs.</i> <i>1lb = 0.454 kg</i> | |
| PFT Calculators | --- | Calculates % predicted FEV ₁ | |
| Methacholine Calculators | --- | Calculates PC ₂₀ for the 11-step Methacholine Challenge Test | |
| Asthma Action Plan Peak Flow Zones Calculator | --- | Calculates red, yellow, and green zones for the AAP card based on the personal best of 3 peak flow efforts at V1 | |
| CPAP Coordinator Instructional Video (DVD provided to clinics) |  | Instructional video for coordinators that includes information regarding CPAP device set up, mask fitting, equipment cleaning and maintenance, and troubleshooting. | |

HRCT

List of forms for the HRCT substudy are listed in Section 7

8.2. Description of specific study forms

8.2.1. CPAP Diary Cards

Purpose:

- To track adherence to using CPAP, record peak flow, asthma medication use, and severity of asthma episodes.

When:

- Participants should complete CPAP Diary Cards (DC) on a daily basis from enrollment date. They should bring completed CPAP Diary Cards (DC) to each clinic visit.

Tasks:

At Screening visit (V1)

- Distribute CPAP Diary Cards (in participant binder)
 - Fill out CPAP Diary Cards to cover study period (study period is approximately 16 weeks)
 - Complete item 1 (date) on each CPAP Diary Card manually, or print out CPAP Diary Cards with pre-printed dates by clicking on the appropriate link on the data system menu of CPAP homepage.

To get the preprinted CPAP Diary Cards, you will be asked to enter the following information:

 - Clinical Center ID
 - Participant ID
 - Name code
 - Starting date of first diary
 - Number of sequential CPAP Diary Cards (You have the option of choosing upto 6 sequential cards)

To print additional CPAP Diary Cards for the entire period, you can choose the following start date and print next set of sequential CPAP Diary Cards

 - For the first CPAP Diary Card, cross out days before the start date. (For example, if a participant started on Wednesday, then Mon and Tue would be crossed out. All subsequent DCs should start on Monday)
 - Give each card a sequential number in the box labeled "Diary Card #" in the bottom left of the form
 - CPAP Diary Card is a 2-page card. Try to print the CPAP Diary Cards front and back. If this is not possible, staple both pages of the diary card and make sure that both pages have the same dates. This assists in case the pages were separated from each other.
 - Spare CPAP Diary Cards - include 4-5 blank cards
- Review Instructions for CPAP Diary Cards (IDC) with the participant
 - Since participants do not have their CPAP devices yet, they should not complete the second page of the CPAP Diary Card.

At Randomization visit (V2)

- Collect CPAP Diary Cards (DC) distributed at V1
- Review CPAP Diary Cards (DC) with participant
- Edit CPAP Diary Cards (DC) as appropriate


- Reinforce daily CPAP Diary Card (DC) completion
- Instructions for CPAP Diary Cards (IDC)
 - Participants should start completing the second page of the CPAP Diary Card as well: CPAP Device Use Log
 - Instruct participant to shade in the boxes from the time they went to bed and turned the CPAP device on until the time they woke up and turned the CPAP device off.
 - Participants should complete the CPAP Diary Card as accurately as possible, however remind participants that they do not have to record short times they are awake on the log, e.g. using the restroom, drinking water, answering a phone call...etc.
 - On the second page of the CPAP Diary Card, participants should complete the device log only (item 17). Coordinators should complete item 18 (number of hours device used)
 - For item 18, count the number of boxes shaded and enter the number of hours used for each night. Always round to the nearest hour. i.e.. if a participant shades any part of a box, count the whole box as 1 hour.

At Phone visit (V3)

- Reinforce daily CPAP Diary Card (DC) completion
- Remind participant to bring CPAP Diary Cards (DC) for the next clinic visit


At all other follow up visits (V4-V6)

- Collect CPAP Diary Cards (DC) distributed at the previous clinic visit
- Review CPAP Diary Cards (DC) with participant.
- Edit CPAP Diary Cards (DC) as appropriate
- Fill in the number of hours device used by participant on the log
- Distribute CPAP Diary Cards (DC) as needed

 Note: Between V6 and V7, participant should only complete the first page of the CPAP Diary Card since the CPAP treatment ends at V6

At the Final visit (V7)

- Review returned CPAP Diary Cards (DC)

 Note: Document missing CPAP Diary Cards since last visit as associated with the upcoming visit

Forms (Abbreviations)

- CPAP Diary Card (DC)

Information sheets (abbreviation)

- Instructions for CPAP Diary Cards (IDC)*

**Not entered into database*

8.2.2. CPAP Asthma Action Plan

Purpose

- To outline for participant how to respond to asthma symptoms

When

- At all study visits, participants will be counseled to follow the guidelines on his/her CPAP Asthma Action Plan Card (AAP) and will be told to seek medical attention at an urgent care facility for emergencies.

Tasks

CPAP does NOT have a temporary Asthma Action Plan Sheet. The Asthma Action Plan Card (AAP) will be given to the participants at V1 based on the personal best peak flow at that visit.

At Screening visit (V1)

- Fill in “personal best” peak flow on Asthma Action Plan Card (AAP) “Personal best” for AAP is the highest of the three peak flow readings done at V1. Values should be recorded on the Screening (SC) form
- Fill in green, yellow, and red zone cut-off values on AAP. Cut-off values may be obtained using the CPAP calculator or hand calculated using the following:
 - green zone: greater than **0.80** of personal best
 - yellow zone: **0.50 to 0.79** of personal best
 - red zone: less than **0.50** of personal best
- Fill in contact information
- AAP values are also to be recorded on the SC form
- Review instructions for use of card
- Values for the Asthma Action Plan Card (AAP) should also be recorded on the Screening (SC) form

At all other study visits (V2, V4-V7)

- Review CPAP Asthma Action Plan Card (AAP)

Forms (abbreviation)

- Screening (SC)

Information sheets (abbreviation)

- CPAP Asthma Action Plan Card (AAP)*

**Not entered into database*

8.2.3. Multivariable Apnea Prediction (MAP) Questionnaire

Purpose

- Assesses the risk of sleep apnea and other sleep related symptoms.

When

- At Screening visit (V1)

Tasks

- The Multivariable Apnea Prediction (MAP) Questionnaire (MP) is to be completed by the participant, with the assistance of coordinator or parent/guardian if needed
- Review the completed questionnaire for missing responses and resolve any problems
- Calculate the probability of sleep apnea risk using the online calculator on the CPAP website.
 - To calculate the probability of sleep apnea, enter the following into the calculator:
 - **Height, weight, BMI, and age- these values should match measurements on the Screening (SC) form.**
 - Gender- this value should match the Baseline Asthma (BA) form
 - If calculator is not working online, contact the DCC
 - If the probability calculated is greater than or equal to 20%, participant is **NOT** eligible for the CPAP trial at this time.
 - If participant is eligible (probability less than 20%), record the probability on the Multivariable Apnea Prediction (MAP) Questionnaire (MP)
- Key into CPAP data system at www.cctrials.org/alaacrc within 10 working days.

Forms (abbreviation)

- Screening (SC)
- Multivariable Apnea Prediction (MAP) Questionnaire (MP)

8.3. ID codes

Codes

- Reference #
- Participant ID
- Name code
- Visit ID
- Personnel Identification Number (PIN)
- Clinical Center ID

Reference

- Assigned by data system after the second keying of a form is completed
- Unique to every form entered into the data system
- Recorded onto form by data entry personnel after form is entered into database

Participant ID

- 5 digit clinic-specific alphanumeric code taken sequentially from the sheet of Clinic Labels
- Distributed to the clinical center by the Data Coordinating Center (see example in Section 8.3.1)
- Unique ID assigned to each potential participant who starts the Screening visit (V1)
- All participant forms will be identified by that ID

Namecode

- 5 character code, unique for every participant enrolled at a site
- Assigned by coordinator at participant registration
- Site to determine an assignment scheme
 - e.g. can use a 5-letter word
- It is strongly suggested that the unique participant ID NOT be included in this name code

Visit ID

- May be pre-printed on the form or label by the DCC or hand recorded
- Screening visit (first clinic visit) = V1; Randomization visit (second clinic visit) = V2, etc.
- N = not associated with a study visit; e.g., Serious Adverse Event Report

Personal Identification Number (PIN)

- Unique 3 digit alpha-numeric identification code for each clinic staff member completing data forms
- Staff members must be “registered” in the online directory by the Lead Coordinator for a PIN to be generated
- PIN is activated to access the ACRC website automatically after registration
- Steps for generating PIN (can be performed by the lead coordinator only)
 - Click on the “ACRC staff directory” link on CPAP homepage
 - Click on “Access Directory Functions” link situated in a box below the directory
 - Login with your Clinic ID, PIN and Password in the login page
 - From the “Edit Directory Menu” choose “Add New Personnel”
 - Fill in all information (registration information, administrative information, and contact information as available) on the page displayed.
 - Once the information is submitted, the new personnel will be added to the directory and a PIN will be automatically generated and activated by the system.

Clinical Center ID

- 2-4 letter code identifying primary clinical center site
- All satellites should use code of primary site

| Clinic | Code |
|------------------------------------------------------------------------------------------------------------------------|-------------|
| Baylor College of Medicine | BCM |
| Columbia University - New York University Consortium | NYC |
| Duke University Medical Center | DUKE |
| Hofstra North Shore – LIJ School of Medicine | LIJ |
| Illinois Consortium | IC |
| Louisiana State University Health Sciences Center, The Ernest N. Morial Asthma, Allergy and Respiratory Disease Center | LSU |
| Maria Fareri Children's Hospital at Westchester Medical Center and New York Medical College | NYMC |
| National Jewish Health | NJC |
| Nemours Children's Clinic | NCC |
| Northern New England Consortium | NNEC |
| Ohio State University Medical Center/Columbus Children's Hospital | OSU |
| University of Arizona | UAZ |
| University of California, San Diego | UCSD |
| University of Miami/University of South Florida | UMSF |
| University of Missouri, Kansas City School of Medicine | UMKC |
| University of Virginia | UVA |
| Washington University/St. Louis University | STL |
| St. Vincent Hospital and Health Care Center, Inc. | STV |

8.3.1. Example of a Clinic Label sheet

Clinics will receive a sheet of participant ID labels at the start of the trial. A participant's ID will start with "P" (for CPAP), followed by your assigned clinic letter and 3 numbers starting at 100 and continuing sequentially.

To assign a participant ID, attach the next sequential label to item #2 on the participant's Screening (SC) form.

CPAP Clinic Label Sheet (example)

| | | |
|-------|-------|-------|
| PZ100 | PZ101 | PZ102 |
| PZ103 | PZ104 | PZ105 |
| PZ106 | PZ107 | PZ108 |
| PZ109 | PZ110 | PZ111 |
| PZ112 | PZ113 | PZ114 |
| PZ115 | PZ116 | PZ117 |
| PZ118 | PZ119 | PZ120 |
| PZ121 | PZ122 | PZ123 |

8.4. Completing forms

General guidelines

- Use dark blue or black ink
- Written responses should be legible to other people
- Limit use of abbreviations
- All completed forms should be reviewed by clinic coordinator to ensure that
 - All items are answered
 - Written responses are legible
 - Data are consistent
- Never change the wording of questions, decimal places, or the unit for a response that is pre-coded on a form
- A response should have only one letter or digit per space
- Numeric responses are to be right justified with all spaces completed. Use lead zeros as necessary, i.e. 0 0 3 2
- Alpha or alphanumeric responses are to be left justified. If blank spaces remain, leave them blank, i.e. P 1 2 _; D C C
- Data on forms should always match what is entered into the data system
- All forms must be signed by a study physician or a clinic coordinator who is certified for the study

Error correction

- Do not obliterate erroneous responses
- Never use correction fluid or tape or erase a response
- Draw a single line through the incorrect response and indicate correct response clearly, above or next to the erroneous response
- Use a different colored ink; e.g. green or red, to make edits
- Staff member making changes to a form should initial and date each change in the margin and provide a brief explanation for the change, e.g. “error”, “participant changed mind”
- Be sure to update the database with the revised information

Rounding rules

- Responses should have only one letter or digit per space
- The number of spaces or location of a decimal point on a form must never be added to or changed
- If a response has a greater number of digits to the right of a decimal point than spaces allow, the response should be rounded as follows:
 - If the first digit following the last data space is less than 5, round down; e.g., if the form has spaces for a 2 digit response with one decimal between the digits (.), then 4.71 would be rounded to 4.7 and 4.14 would be rounded to 4.1
 - If the first digit following the last data space is 5 or more, then round up; e.g., if the response field is for 2 digits with a decimal between the digits (.), then both 4.78 and 4.75 would be rounded to 4.8, and 4.15 would be rounded to 4.2
- More examples:
 - For a response field of three digits (), 79.485 would be recorded as 079 and 79.584 would be recorded as 080
 - For a response field of . , 4.2745 would be recorded as 4.27 and 4.2754 would be recorded as 4.28

Note: Round responses ONLY if the number of spaces in a response field requires it. Otherwise, record data as collected.

For CPAP Diary Cards (DC), round the number of hours device is used by participant to the nearest hour (i.e. if part of a box is shaded, count the box as 1 hour)

If there are more integer digits (digits to the left of the decimal point) than the response field allows, contact the Data Coordinating Center immediately. Do NOT attempt to squeeze the number into the spaces provided.

8.5. Distributed data entry

Online data system background

- Distributed data entry for the ALA-ACRC CPAP trial will be conducted via the internet
- Clinic staff will be able to enter and edit data from any computer connected to the internet running Internet Explorer 5+ on Microsoft Windows
- Data will be double entered to ensure accuracy
- Error and consistency checks will be built-in to the data entry application
- The data entry application and clinical data will be secured with passwords and user names stored in the CPAP database
- Data will be stored in redundant databases residing on a web server in a password-protected area. Data will be archived daily to a computer at the DCC
- The DCC will conduct audits of clinical center data during the course of the trial

Purpose

- To collect all trial data
- To issue treatment assignments
- To track participant activity
- To monitor clinical center performance

Tasks/Timeframe

- Clinical center staff will log into the data entry system on the CPAP web site at <http://www.jhcct.org/Secure/CPAP/CPAPHome.asp>
- Clinical center staff will be assigned an ACRC Personal Identification Number (PIN) and passwords that will be required for data entry and will limit access to only their clinic's data
- Once logged into the data entry section, users will be able to
 - Register a new participant
 - Enter/edit data for an existing participant
 - View reports for their clinic
 - Get treatment assignments

- Participants must be registered before any forms can be entered for that participant; registration consists of creating a record for a new participant including his/her CPAP ID and name code
- Randomization (RZ) forms must be keyed in real-time, while the participant remains in the clinic, in order to receive a treatment assignment (Kit ID)
- Missed Data (MD) forms should be keyed within 10 working days of the window closing for the missing data at issue
- All other forms should be keyed within 10 working days of collection
- Errors and warnings
 - While keying these forms, clinical center staff will be prompted regarding **errors** (which must be corrected) and **warnings** (which should be checked, but may not require correction)
 - **Errors** are responses which cannot be accepted, such as missing key form fields, illogical date combinations, mismatches between entry fields (i.e. date of birth does not confirm participant age), etc.
 - **Warnings** are things that could potentially be mistakes, and to which the data system would like to call your attention, such as an age outside the recruitment range. Most numeric ranges are warnings.
- Data should be edited as necessary for form corrections or edit requests from the DCC
- Forms should be retained by clinics in an accessible location
- Clinical center staff should check the reports for their clinic at least twice per week. These pages will include real-time recruitment reports, forms status, and other information

9. Event reporting: SAEs and unusual events

9.1. Definitions

Adverse Events (AE)*

Any untoward medical occurrence associated with the use of a drug/device in humans, whether or not considered drug/device related.

Serious Adverse Event (SAE)*

An SAE is any adverse event or serious suspected adverse reaction. An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Examples of such medical events include:

- Allergic bronchospasm requiring intensive treatment in an emergency room or at home
- Blood dyscrasias (e.g., leukemia) or convulsions that do not result in inpatient hospitalization, or
- Development of drug dependency or drug abuse

Unexpected adverse event or unexpected suspected adverse reaction*

An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

Suspected adverse reaction*

Any adverse event for which there is a reasonable possibility that the drug/device caused the adverse event.

Relatedness^{†‡}

Relatedness refers to the extent to which an adverse event is considered to be related to the intervention or study procedures. An adverse event is considered related if there is a reasonable possibility that the event may have been caused by the procedure. The following definitions apply:

The following definitions apply to relatedness:

- Unrelated
 - Adverse event is clearly due to extraneous causes (e.g., underlying disease, environment)
- Unlikely (Adverse event must have 2 of the following):
 - Does not have temporal relationship to intervention,
 - Could readily have been produced by the subject's clinical state,
 - Could have been due to environmental or other interventions,
 - Does not follow known pattern of response to intervention,
 - Does not reappear or worsen with reintroduction of intervention
- Possible (Adverse event must have 2 of the following):
 - Has a reasonable temporal relationship to intervention,
 - Could not readily have been produced by the subject's clinical state,
 - Could not readily have been due to environmental or other interventions,
 - Follows a known pattern of response to intervention
- Probable (Adverse event must have 3 of the following):
 - Has a reasonable temporal relationship to intervention,
 - Could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions,
 - Follows a known pattern of response to intervention
 - Disappears or decreases with reduction in dose or cessation of intervention
- Definite (Adverse event must have 4 of the following):
 - Has a reasonable temporal relationship to intervention,
 - Could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions,
 - Follows a known pattern of response to intervention,
 - Disappears or decreases with reduction in dose or cessation of intervention and recurs with re-exposure

Unanticipated Problems[‡]

An unanticipated problem is an adverse event that meets all 3 of the following:

- **Unexpected**, and
- **Related** or **possibly related** to study participation, and
- Suggest that the research places subjects or others at a **greater risk of harm** than was previously know or recognized

*Code of Federal Regulation Title 21, Revised as of April 1, 2011

† National Institutes of Health, Office of Human Subjects Research, Adverse Event Reports, May 26, 2000, Appendix 2

‡ US Department of Health and Human Services, Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, January 15, 2007

9.2. Serious adverse event reporting

Purpose

- To report an occurrence of a serious adverse event (SAE)

Events to be reported

- Any serious adverse event that meets the definition of serious adverse event Section 9.1 above.
- Pregnancy (if occurs, or becomes known of, after enrollment it must be reported as an SAE)

By whom

- Identification of a serious adverse event is the responsibility of the study physician

When

- As needed whenever a serious unexpected adverse event associated with study treatment or study procedures is first reported or whenever a follow-up information is received
- If the SAE is pregnancy, event is followed until completion/end of pregnancy. Outcome of the pregnancy is to be reported
- Must report to the DCC within 72 hours of becoming aware of the SAE

To Whom

- DCC
- IRB per institution's IRB guidelines

Tasks

- Report a serious adverse event to the DCC by telephone (443-287-3170) **within 72 hours**
- Fax a completed Serious Adverse Event Report (SR) form to the DCC at 775-871-4030
- Confirm receipt of fax.
- Key Serious Adverse Event Report (SR) forms within 5 working days of learning of the event
- To update report, complete a new SR form. A follow-up report is to be filed when:
 - the serious adverse experience is resolved, or
 - if there has been a significant change in the patient's condition or
 - if the physician's judgment regarding the event has changed
- The study physician should use his/her judgment in deciding what is significant
- As a consequence of the SAE, treatment (e.g., continuation of study drug/device, other asthma treatment) should be determined per best medical judgment of the study physician
- Record event on appropriate Clinic Visit (CV) form, in Interim Medical History section

Forms (abbreviation)

- Clinic Visit (CV)
- Serious Adverse Event Report (SR)

9.3. Unusual event reporting

Purpose

- To report an occurrence of an unusual event

Definition

Five categories of unusual events are to be reported:

- Protocol deviations: these include minor or administrative departures from the protocol procedures approved by the IRB
 - Example: Methacholine Challenge test not performed according to protocol
 - **Out of window visits do not need to be reported on Unusual Event (UE) form** to the DCC (DCC will determine out of window visit status from data keyed into the data system)
- Unanticipated medical events: medical events that are not Serious Adverse Events but the principal investigator or coordinator feel should be brought to the attention of the medical officer at the DCC. These can include:
 - Medical events that are not considered “serious” but may be important for the study
 - Examples
 - Sudden rash that may be related to study drug/device
 - Adverse reaction to a study procedure, such as unusual or severe reaction to Methacholine Challenge
 - A suspected safety issue concerning any aspect of the trial
 - Unaccounted for study drug/device
- Return of device, mask, and/or other accessories due to malfunctioning or damage
- Study device and/or mask not returned at end of study
- Other
 - Atypical problems
 - Examples
 - Breach of confidentiality
 - Destruction of study records
 - Communications that need to be recorded but are not captured on other data forms

When

- Unusual events are to be reported within 7 working days of an ACRC clinical center learning of an unusual event. If the event requires follow-up an additional Unusual Event (UE) form should be submitted.

Tasks

- Fax form to DCC (775-871-4030)
- Key into CPAP data system at www.cctrials.org/alaacrc within 10 working days
- To update report, complete a new form.

Forms

Unusual Event (UE)

10. Quality assurance

10.1. ACRC clinical center responsibilities

- A clinical center is comprised of one main ACRC clinical center which may have additional satellite clinics associated with it
- The ACRC clinical center staff must include a Principal Investigator, Study Physician, Lead Coordinator, Data System Operator, Methacholine Tester, and eNO Operator. Staff may carry out the duties for more than one role, but additional staff members are recommended for sufficient coverage
- Study treatment is distributed by the CPAP Device Distribution Center to the main ACRC clinical center only. The ACRC clinical center is to designate one staff member at one address for receipt of CPAP study kits. The ACRC clinical center must record distribution of CPAP study kits to satellite centers on the Study Kit Accountability Log (DA) residing at the main clinical center
- The main ACRC clinical center is responsible for distributing supplies to satellites
- The Lead Coordinator (main ACRC clinical center) is responsible for keeping the ALA-ACRC web-based directory current for the main clinical center and all satellites
- Changes to the ALA-ACRC web-based directory can be made by the Lead Coordinator only
- The Lead Coordinator is responsible for the distribution of correspondence and study materials to all other ACRC staff members at the main clinical center and satellite clinic(s) as appropriate
- The Principal Investigator is responsible for the distribution of correspondence and study materials to other study investigators at the main clinical center and satellite clinic(s) as appropriate
- The main ACRC clinical center is responsible for ordering all Peak Flow Meters from Bayview Medical, Inc (the Peak Flow Meter distributor)
- The main ACRC clinical center is responsible for ordering methacholine or methacholine kits from Methapharm, Inc.

10.2. Satellite clinics

- Satellite clinics are an adjunct to their main clinical center (see Section 8.3 for list of main clinical centers and respective ID codes) but need to be certified separately after the review and approval of the lead coordinator at the main clinical center
- Each satellite clinic is to have a coordinator who is responsible to the Lead Coordinator at the main clinical center
- Other study personnel (e.g., Data System Operator, Methacholine tester, and eNO Operator) are recommended at the satellite clinic
- Study treatments are received from the main clinic and returned to the CPAP Device Distribution Center
- Forms for study visits conducted at a satellite clinic are to be completed and maintained at the satellite
- All study procedures performed by the satellite clinic must conform to the CPAP protocol and Manual of Procedures (MOP)

- A Study Kit Accountability Log (DA) are to be maintained by each satellite clinic

10.3. Data checks

Data for the study will be entered from data forms into an online data system. The data system works with Microsoft Internet Explorer, versions 5.0+, on computers running Microsoft Windows. The user interface employs standard web controls and does not require any additional software to be installed. The user's browser must have JavaScript enabled.

Data validation consists of four distinct levels

1. Field-level validation upon entry of each data element
2. Double-data-entry requiring duplicate entry of form and resolution of any inconsistencies
3. Intra-form validation permitting logic-checking between fields on a single form
4. Inter-form validation with logic-checking across fields on different forms

All validation is completed before data is committed to the study database. The data system employs redundant data storage, in both a flat text format and Microsoft .MDB format, with complete date-stamped storage of all changes for full audit reports.

The data system also features a Data Quality Query (DQQ) Management function to allow for feedback to clinics regarding data entries that are incorrect or questionable. Samples of data forms will be audited to ensure consistency between the source documents and the data system; inconsistencies are added to the DQQ Management system for subsequent resolution by the clinics. DQQs are added on a regular basis and are expected to be resolved by the clinics in a timely manner.

10.4. Data audits and data quality queries

On-going data audits

- Periodically during and after the clinical phase of the trial, the DCC will audit clinic data
 - DCC will send an email to a clinic requesting copies of forms for particular participant(s)
 - Within 2 weeks clinics should send copies of the requested forms via FedEx (FedEx number to be distributed to clinics)
 - The DCC will review the data on the paper form and compare it to entries in the data system

Data Quality Queries (DQQs)

- The DCC will generate a Data Quality Query (DQQ) for a discrepancy found during an audit. A separate DQQ is created for each discrepancy found on a form
- All DQQs will be posted on the DQQ Management System. To access the DQQ page go to the CPAP website, <http://www.jhcct.org/Secure/CPAP/CPAPHome.asp> and follow the link to the Data System page
- Clinics will receive a pop-up message alerting them that new DQQs are posted
- Clinics should respond to the posted DQQs
 - After reviewing the DQQs, investigate the problem (usually by inspecting the source document) and make any necessary changes to the data system, the paper form, or both

- Changes to the paper form must be made according to the error correction procedures outlined in Section 8.4.
- Changes to the data system
 - After necessary changes to paper forms have been made, go to the DQQ page, click on “View/Edit DQQ” choose one of the available options to indicate how the DQQ has been resolved (i.e., data system edited, data form altered, etc) and click “Submit” button. The DQQ will be removed from the clinic’s DQQ list
 - Contact Debbie Amend-Libercci (damend@jhsph.edu) at the DCC if there are questions concerning the proper resolution of a DQQ
- Many coordinators find it easiest to go to the DQQ page, print out their list of pending DQQs, investigate and resolve each one, and mark on the paper list how each DQQ has been resolved. Then, they go back to the DQQ system and mark each as resolved by choosing and submitting the appropriate response

Device Accountability Audits

- Periodically, the DCC will request materials from centers to audit CPAP device distribution
- The DCC will email Lead Coordinators who are responsible for collecting the requested materials for their site as well as for any satellite centers and submitting to the DCC
- The DCC will request:
 - A copy of current Study Kit Accountability Log (DA) (one per clinic)
 - List of Kit IDs of all kits currently at the clinic

First randomization audits

- The full set of forms for V1 and V2 will be audited for the first participant randomization completed by a coordinator
- If problems are identified, forms from the second and possibly third randomization completed by that coordinator may be audited

Methacholine audits

- All methacholine KoKo printouts will be audited by the DCC for correctness and completeness. Clinics are to submit methacholine reports to the DCC for overreading on a weekly basis. Reports will be graded on three criteria as follows:
 1. Were the baseline maneuvers acceptable as per the study MOP?
 2. Was the appropriate number of efforts performed at each stage?
 3. Was the challenge halted at the appropriate stage?
- Each criterion is graded on a pass/fail basis; scores are then totaled and converted to a letter grade for the purpose of clinical feedback. Meeting all three criteria is marked as an “A” (3/3), two criteria is a “B” (2/3), one is a “C” (1/3), and failing to meet any of the criteria on a single challenge will result in a “D” grade (0/3).
- The DCC will issue a monthly report to clinics informing them of their grades to date and of any late or outstanding reports. The DCC may also follow up individually with clinics or staff to address performance or operational issues in more detail. Coordinators should send all Methacholine KoKo reports to Razan Yasin (ryasin@jhsph.edu).

11. References

11.1. Asthma medications

Quick relief (rescue bronchodilator)

- Albuterol (Nebulizer 0.083%, 0.5%, Metered Dose Inhaler, Ventolin)
- Levalbuterol (Xopenex)
- Pirbuterol (Maxair)
- Ipratropium bromide (Atrovent Nebulizer, Atrovent HFA)
- Ipratropium bromide and albuterol (Combivent DuoNeb, Combivent HFA)

Long-acting beta-agonists

- Salmeterol (Serevent inhalation aerosol, Serevent Diskus inhalation powder)
- Albuterol, sustained-release (Volmax, Proventil Repetabs, VoSpire ER)
- Formoterol (Foradil, Perforomist)

Long-acting muscarinic antagonist

- Tiotropium bromide (Spiriva)

Single agent inhaled corticosteroid

- Beclomethasone (Beclivent, Vanceril, QVar, Vanceril Double Strength)
- Budesonide (Pulmicort)
- Flunisolide (AeroBid, Aerospan)
- Fluticasone (Flovent)
- Triamcinolone (Azmacort)
- Mometasone furoate (Asmanex)
- Ciclesonide (Alvesco)

Combination of inhaled corticosteroid and long-acting beta-agonist

- Budesonide and Formoterol (Symbicort)
- Fluticasone and Salmeterol (Advair, Advair HFA)
- Mometasone and Formoterol (Dulera)

Oral corticosteroid

- Prednisone (Cortan, Deltasone, Orasone, Prednicen-M, Sterpred)
- Prednisolone (Pepiapred, Prelone, Delta-Cortef)
- Methylprednisolone (Medrol)

Methylxanthines

- Theophylline, sustained-release (Slo-Phyllin, Uniphyl, Theo-Dur, Slo-Bid)

Oral antileukotrienes

- Montelukast (Singulair)
- Zafirlukast (Accolate)
- Zileuton (Zyflo)

Other asthma medications

- Cromolyn sodium/nedocromil (Intal Nebulizer, Intal Metered Dose Inhaler, Nasalcrom/Alocril, Tilade)
- Nedocromil sodium (Tilade)
- Omalizumab (Xolair)

Sinus medications

- Nasal spray decongestants (Afrin, phenylephrine)
- Nasal steroids (Rhinocort, Nasonex, Flonase, Nasocort)
- Oral decongestants (Sudafed, Contac)
- Antihistamines (Benadryl, Claritin, Allegra, Astelin, Zyrtec)
- Nasal saline
- Allergy immunotherapy (allergy shots, sublingual immunotherapy)

11.2.ACRC Centers

| Clinic ID | Name of Clinical Center | Center Director | Designated letter for participant IDs |
|------------------|------------------------------------------------------------------------------------------------------------------------|------------------------|----------------------------------------------|
| BCM | Baylor College of Medicine | Nicola Hanania, MD | A |
| DUKE | Duke University Medical Center | John Sundy, MD, PhD | B |
| IC | The Illinois Consortium | Lewis Smith, MD | D |
| LIJ | Hofstra University School of Medicine | Rubin Cohen, MD | G |
| LSU | Louisiana State University Health Sciences Center, The Ernest N. Morial Asthma, Allergy and Respiratory Disease Center | Kyle Happel, MD | H |
| NCC | Nemours Children's Clinic | John Lima, PharmD | K |
| NJC | National Jewish Health | Rohit Katial, MD | L |
| NNEC | Northern New England Consortium | Charles Irvin, PhD | M |
| NYC | Columbia University - New York University Consortium | Joan Reibman, MD | N |
| NYMC | Maria Fareri Children's Hospital at Westchester Medical Center and New York Medical College | Allen Dozor, MD | O |
| OSU | The Ohio State University Medical Center/Columbus Children's Hospital | John Mastronarde, MD | P |
| STL | Washington University/St. Louis University | Mario Castro, MD | Q |
| STV | St. Vincent Hospital and Health Care Center, Inc | Michael Busk, MD | R |
| UAZ | University of Arizona | Lynn Gerald, PhD | V |
| UCSD | University of California, San Diego | Stephen Wasserman, MD | U |
| UMSF | University of Miami/ University of South Florida | Adam Wanner, MD | T |
| UMKC | University of Missouri, Kansas City School of Medicine | Gary Salzman, MD | S |
| UVA | University of Virginia | W. Gerald Teague, MD | W |
| DCC | Johns Hopkins University | Robert Wise, MD | X |

11.3. Frequently used acronyms

| | |
|------------------|-----------------------------------------------------------------------------------------------|
| ACQ | Asthma Control Questionnaire |
| ACRC | Asthma Clinical Research Centers |
| ACT | Asthma Control Test |
| ALA | American Lung Association |
| AQLQ | Asthma Quality of Life Measures |
| ASUI | Asthma Symptom Utility Index Score |
| BD | Bronchodilator |
| CPAP | Continuous Positive Airway Pressure |
| CT | Computed tomography |
| DC | CPAP Diary Card |
| DCC | Data Coordinating Center |
| DQQ | Data Quality Queries |
| DSMB | Data and Safety Monitoring Board |
| EC | Executive Committee |
| EPAC | Episodes of Poor Asthma Control |
| FAQ | Frequently Asked Questions |
| FEV ₁ | Forced Expiratory Volume in one second |
| FRC | Functional Residual Capacity |
| FVC | Forced Vital Capacity |
| GEE | Generalized estimating equations |
| HIPAA | Health Insurance Portability and Accountability Act |
| HRCT | High resolution computed tomography |
| ICS | Inhaled corticosteroids |
| IDE | Investigational Device Exemption |
| MAP | Multivariable Apnea Prediction |
| MDI | Metered dose inhaler |
| MeCIS | Methacholine bronchoprovocation – influence of high potency inhaled corticosteroids in asthma |
| MOP | Manual of Procedures |
| mSv | millisievert |
| NHLBI | National Heart, Lung, and Blood Institute |
| NSR | Non significant risk |
| OSA | Obstructive Sleep Apnea |
| PC ₂₀ | Provocative concentration that results in a decrease in FEV ₁ by 20% |
| PEFR | Peak expiratory flow rate |
| PIN | Personal identification number |
| PPM | Policy and Procedure Memoranda |
| rem | roentgen equivalent in man |
| RZ | Randomization |
| SAE | Serious adverse event |
| SC | Steering Committee |
| SOV | Schedule of visits |
| SR | Significant risk |
| TLC | Total Lung Capacity |
| UE | Unusual event |

Appendix A
Scanning Procedure for the CPAP Lung
Phantom*

CPAP HRCT Substudy
1 Jan 2013

***CTP674 Lung Phantom™**
(The Phantom Laboratory, Salem, New York)

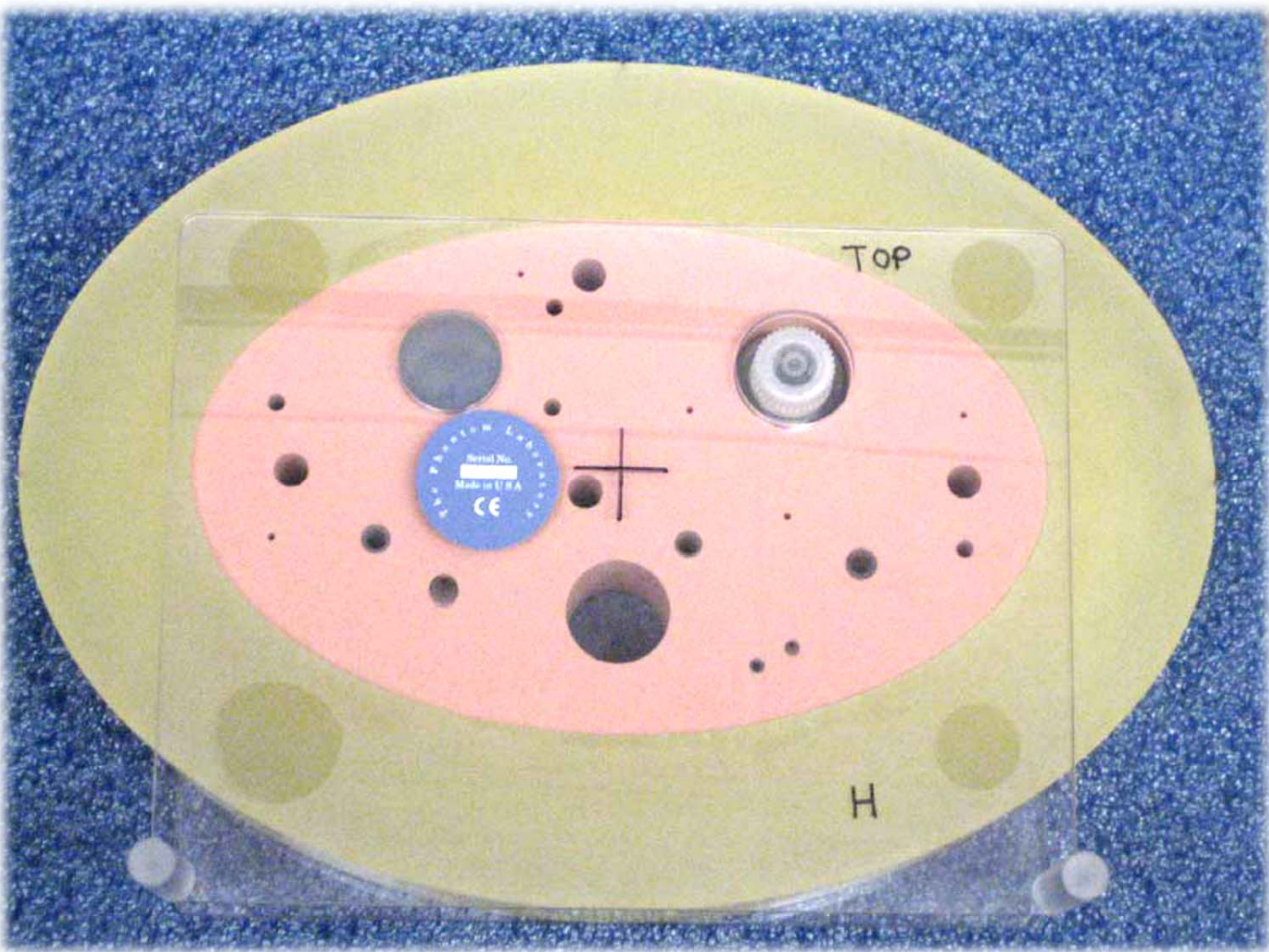


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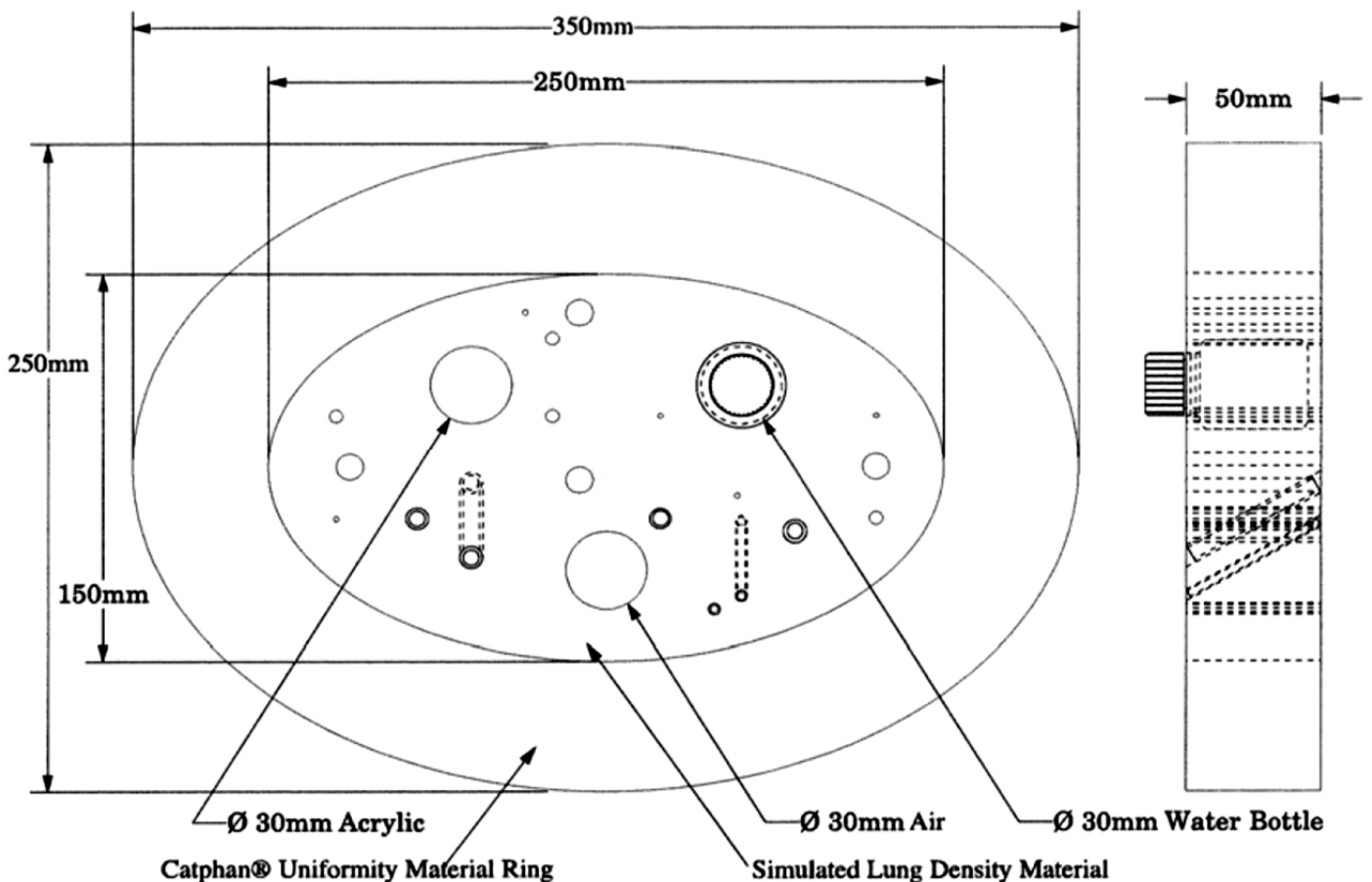
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1. Phantom Description

1.1. CPAP Lung Phantom

- The CPAP Lung Phantom is designed for performing comparative measurements between CT scanners. This phantom is not intended to replace current methods of comprehensive quality assurance testing. It is intended to offer additional density and geometrical information in monitoring CT scanners used in clinical “quantitative based” lung studies.
- Each site must maintain its normal Standard Operating Procedures for regular calibration and maintenance on your CT scanner.
- The CPAP Lung Phantom consists of an outer ring (Catphan® Uniformity Material Ring) which simulates tissue attenuation and a central oval insert which simulates lung attenuation.

Figure 1 - Schematic Drawing



Scanning Procedure CPAP Phantom

- The blue line on the outer ring is to assist alignment of the phantom with the CT scanner's alignment lights

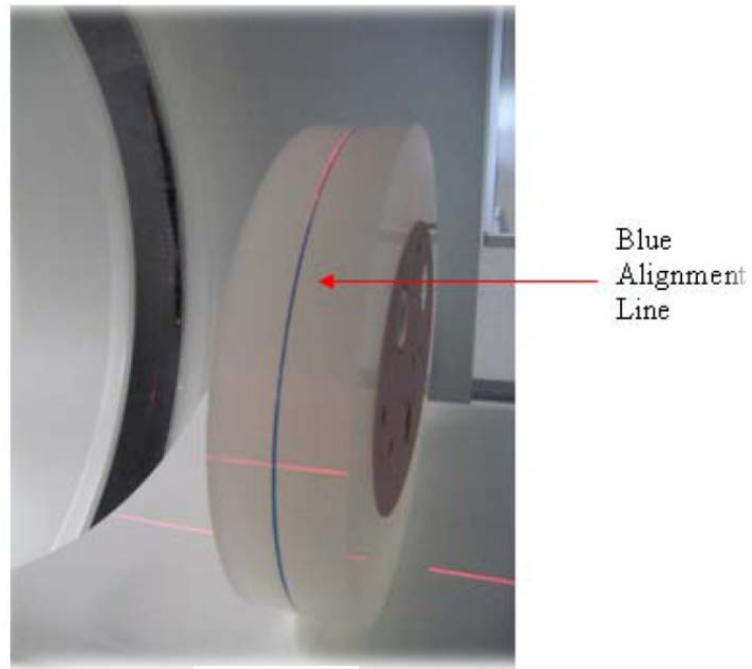


Figure 2

- The reference materials used are air, water and acrylic

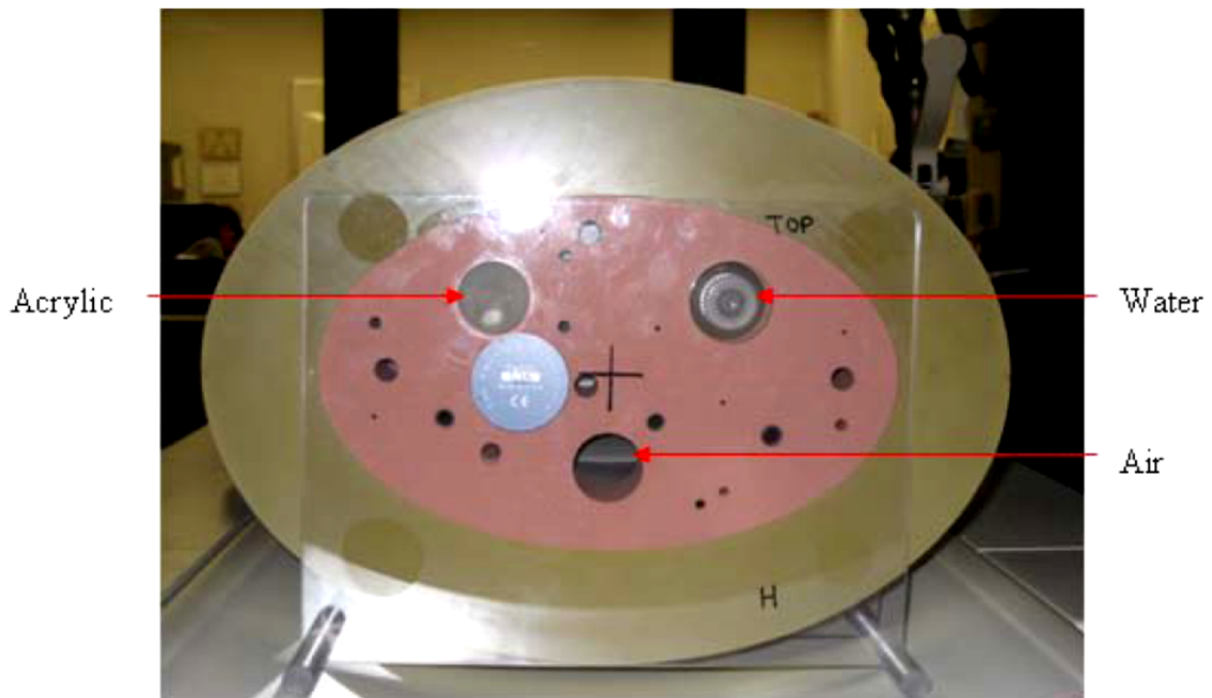


Figure 3

2. Phantom Setup

IMPORTANT: Prior to scanning ensure that the water bottle is completely filled with DISTILLED WATER. The phantom should arrive at your site filled.

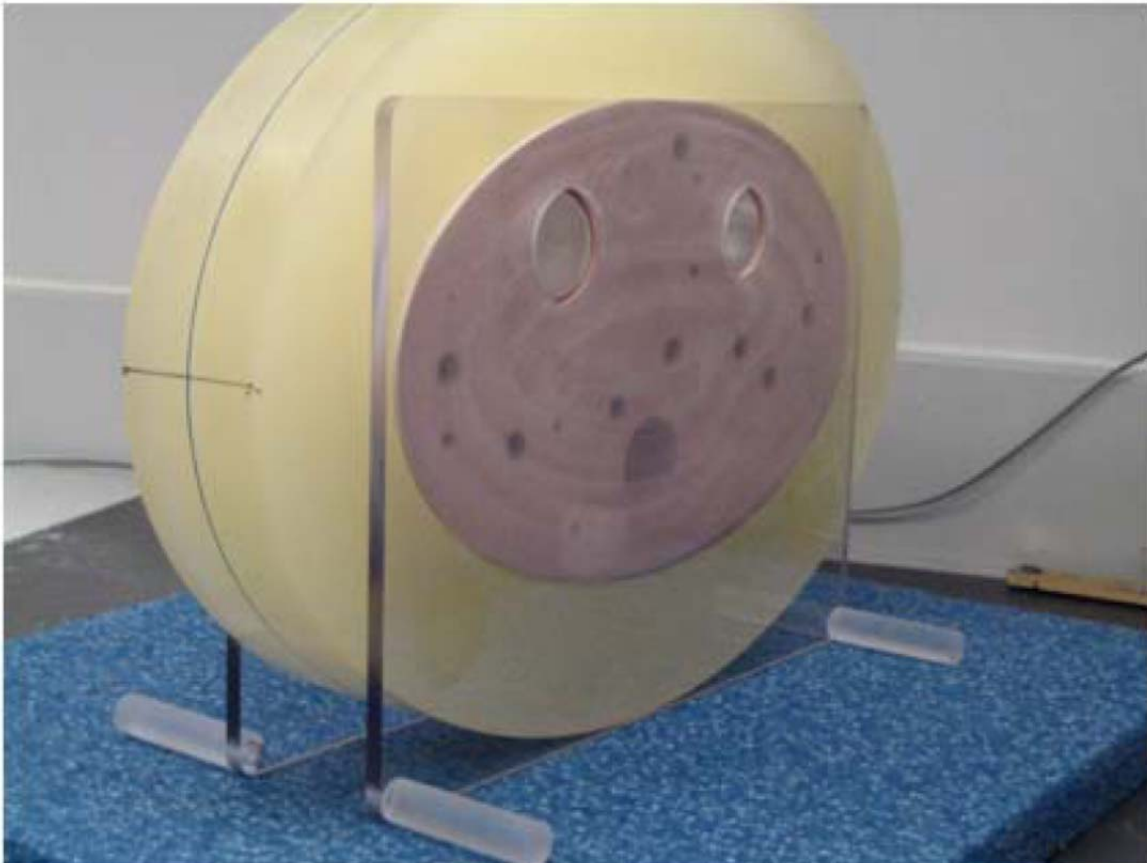


Figure 4

- STEP 1** The phantom will arrive to you without the legs of the base attached. Screw the legs into the acrylic plates.
- STEP 2** Prior to placing the phantom on the scanner table you must first ensure the water bottle top is sufficiently level with the back edge of the phantom. **The bottle must be level with the phantom foam material not the protective plate.**
- STEP 3** Place the phantom directly on the scanner table. There must be no other tables or boards below the phantom. The pad is removed for better leveling.

STEP 4 Orient the phantom on the scanner table head-first, supine. The cap of the bottle is the head. The phantom is also marked with “H” for “head”. (Figure 5) **Thus, H should be facing the gantry and F should be facing the foot of the table.**

STEP 5 Align the phantom along the z axis with the laser light on your scanner using the blue line on the phantom’s outer ring. (Figure 2)

STEP 6 Align the phantom in the scanner cross hairs. Line up with the front of the phantom. (Figure 5)

STEP 7 Move the scanner table. Do not allow the phantom to go past the detector center line. (Figure 5)

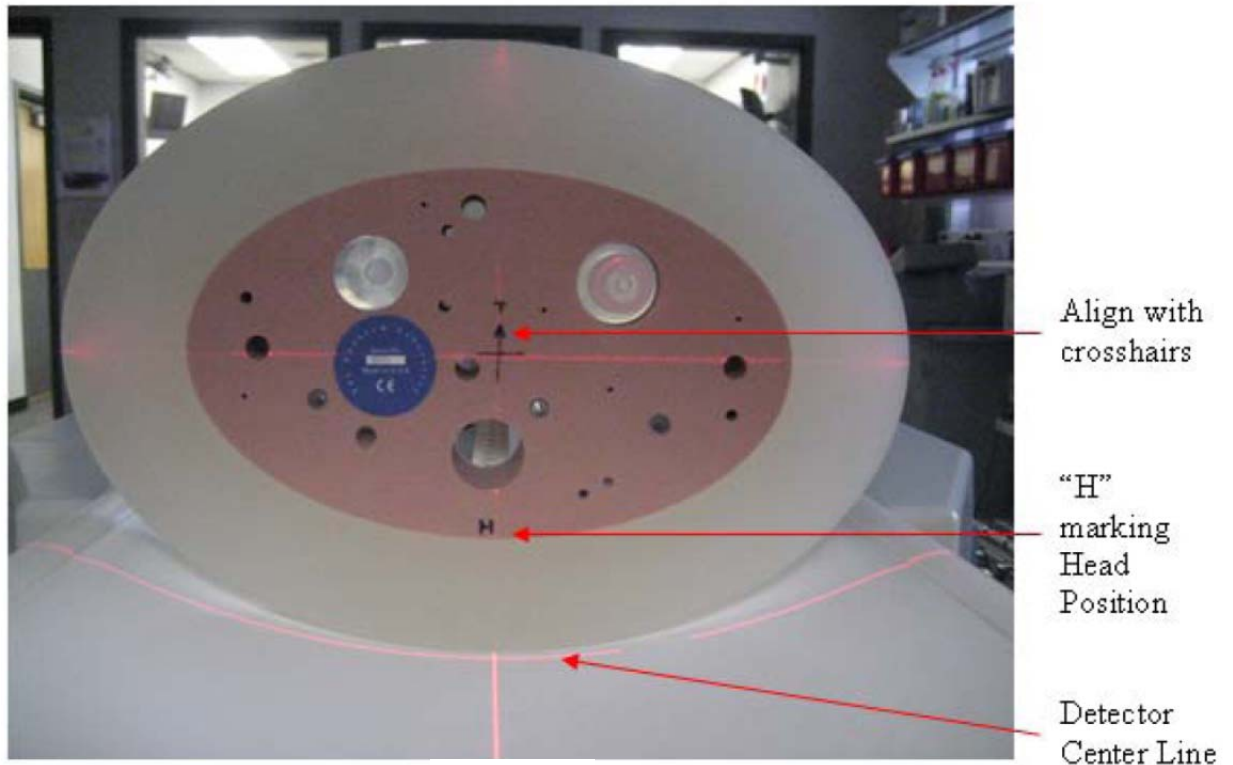
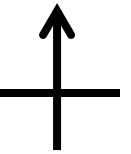


Figure 5

3. Phantom Scanning

- Each phantom should be scanned with the Inspiratory procedure and then repeated (without repositioning) following the Expiratory procedure. It is important to implement the scan parameters for a particular scanner. These parameters are provided below.
- The technologist should fill out a Phantom Acquisition (PT) form for each phantom scan performed and submit this form back to the study coordinator for scan verification.

4. Scan Parameters

Table 1.1 CT Inspiratory Scan Procedure

| Scanner make | SIEMENS | SIEMENS | SIEMENS | GE | GE | PHILIPS | PHILIPS | TOSHIBA |
|--------------------|--------------------------------|--------------------------|--------------------|-----------------------------|------------------------------|---------------------|--------------|-------------|
| Scanner model | Definition (AS Plus) 128 slice | Definition (DS) 64 slice | Sensation 64 slice | VCT 64 slice/ Discovery STE | Discovery CT 750 HD 64 slice | Brilliance 64 slice | iCT-256 | Aquilion 64 |
| Scan Type | Spiral | Spiral Single Source | Spiral | Helical | Helical-Standard | Spiral Helix | Spiral Helix | Helical |
| Scan FOV | No selection | No Selection | No selection | Large | Large | No selection | No selection | S/M/L |
| Rotation Time (s) | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Det. Configuration | (128) 64 x 0.6 | (64) 32 x 0.6 | (64)32 x 0.6 | 64 x 0.625 | 64 x 0.625 | 64 x 0.625 | 128 x 0.625 | 64 x 0.5 |
| Pitch | 1.0 | 1.0 | 1.0 | 0.984 | 0.984 | 0.923 | 0.993 | 0.828 |

Scanning Procedure CPAP Phantom

| Scanner make | SIEMENS | SIEMENS | SIEMENS | GE | GE | PHILIPS | PHILIPS | TOSHIBA |
|--------------------------------------------------------|--------------------------------|--------------------------|----------------------|-----------------------------|------------------------------|----------------------|----------------------|------------------------------------|
| Scanner model | Definition (AS Plus) 128 slice | Definition (DS) 64 slice | Sensation 64 slice | VCT 64 slice/ Discovery STE | Discovery CT 750 HD 64 slice | Brilliance 64 slice | iCT-256 | Aquilion 64 |
| Speed (mm/rot) | 36.9 | 19.2 | 19.2 | 39.37 | 39.37 | 38.4 | 74.4 | 26.5 |
| kVp | 120 | 120 | 120 | 120 | 120 | 120 | 120 | 120 |
| Siemens = Eff. mAs GE = mA setting Philips = mAs | Effective mAs: M-110 | Effective mAs: M-105 | Effective mAs: M-100 | mA: M:180 | mA: M:180 | mAs: M-130 | mAs: m: 130 | mA: M: 180 Effective mAs: M:109 |
| Dose modulation | Care Dose OFF | Care Dose OFF | Care Dose OFF | Auto mA OFF | Auto mA OFF | Dose Right (ACS) OFF | Dose Right (ACS) OFF | SURE Exp (Real EC) OFF |
| Recon 1 Algorithm | B35 | B35 | B35 | Standard | Standard | B | B | Standard |
| Recon 2 Algorithm | B30 | B31 | None | Detail | Detail | YB | YB | Detail |

Scanning Procedure CPAP Phantom

| Scanner make | SIEMENS | SIEMENS | SIEMENS | GE | GE | PHILIPS | PHILIPS | TOSHIBA |
|---------------------------------------------|--------------------------------|--------------------------|--------------------|-----------------------------|------------------------------|------------------------|------------------|--------------|
| Scanner model | Definition (AS Plus) 128 slice | Definition (DS) 64 slice | Sensation 64 slice | VCT 64 slice/ Discovery STE | Discovery CT 750 HD 64 slice | Brilliance 64 slice | iCT-256 | Aquilion 64 |
| Additional Image filters | No Selection | No Selection | No Selection | No Selection | IQ Enhance Off | Adaptive Filtering off | B | Standard |
| Thickness (mm) | 0.75 | 0.75 | 0.75 | 0.625 | 0.625 | 0.67 | 0.67 | 0.5 |
| Interval (mm) | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Iterative recon (noise reduction algorithm) | Do Not use IRIS | Do Not use IRIS | No Selection | Do not use ASIR | Do not use ASIR | Do not use iDOSE | Do not use iDOSE | No Selection |
| Scan Time (Sec) 30cm length | <10 | <10 | <10 | <10 | <10 | <10 | <10 | <10 |

Table 1.2 CT Expiratory Scan Procedure

| Scanner make | SIEMENS | SIEMENS | SIEMENS | GE | GE | PHILIPS | PHILIPS | TOSHIBA |
|--------------------|--------------------------------|--------------------------|--------------------|-----------------------------|------------------------------|---------------------|--------------|-------------|
| Scanner model | Definition (AS Plus) 128 slice | Definition (DS) 64 slice | Sensation 64 slice | VCT 64 slice/ Discovery STE | Discovery CT 750 HD 64 slice | Brilliance 64 slice | iCT-256 | Aquilion 64 |
| Scan Type | Spiral | Spiral Single Source | Spiral | Helical | Helical-Standard | Spiral Helix | Spiral Helix | Helical |
| Scan FOV | No selection | No Selection | No selection | Large | Large | No selection | No selection | S/M/L |
| Rotation Time (s) | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Det. Configuration | (128) 64 x 0.6 | (64) 32 x 0.6 | (64) 32 x 0.6 | 64 x 0.625 | 64 x 0.625 | 64 x 0.625 | 128 x 0.625 | 64 x 0.5 |
| Pitch | 1.0 | 1.0 | 1.0 | 0.984 | 0.984 | 0.923 | 0.993 | 0.828 |
| Speed (mm/rot) | 36.9 | 19.2 | 19.2 | 37.32 | 37.32 | 38.4 | 74.4 | 26.5 |

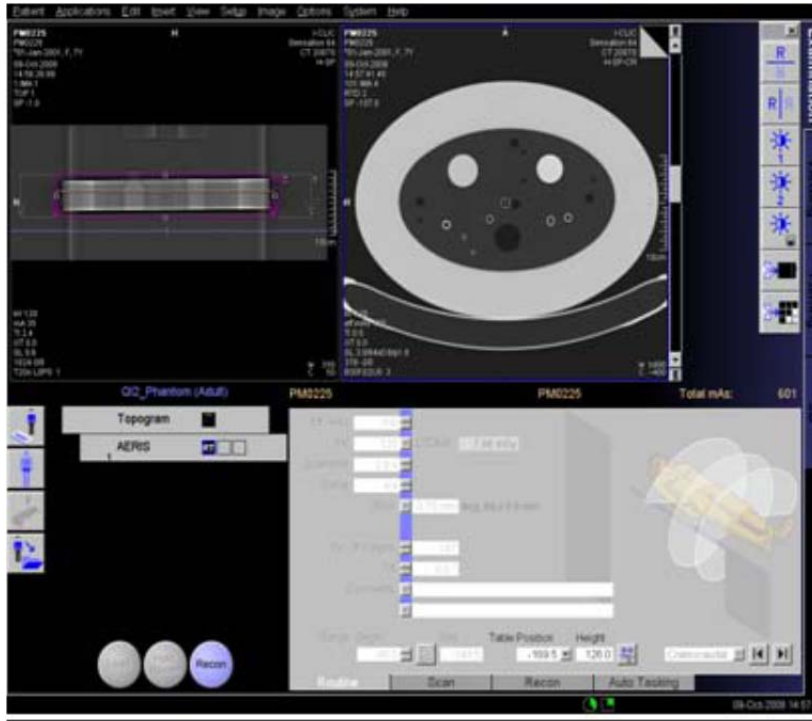
Scanning Procedure CPAP Phantom

| Scanner make | SIEMENS | SIEMENS | SIEMENS | GE | GE | PHILIPS | PHILIPS | TOSHIBA |
|--------------------------------------------------------|--------------------------------|--------------------------|-----------------------|-----------------------------|------------------------------|------------------------|----------------------|---------------------------------------|
| Scanner model | Definition (AS Plus) 128 slice | Definition (DS) 64 slice | Sensation 64 slice | VCT 64 slice/ Discovery STE | Discovery CT 750 HD 64 slice | Brilliance 64 slice | iCT-256 | Aquilion 64 |
| kVp | 120 | 120 | 120 | 120 | 120 | 120 | 120 | 120 |
| Siemens = Eff. mAs GE = mA setting Philips = mAs | Effective mAs: S/M-65 | Effective mAs: S/M-60 | Effective mAs: S/M-55 | mA: S/M:100 | mA: S/M:100 | mAs: S/M-70 | mAs: S/M: 70 | mA: S/M: 100 Effective mAs: S/M:61 |
| Dose modulation | Care Dose OFF | Care Dose OFF | Care Dose OFF | Auto mA OFF | Auto mA OFF | Dose Right (ACS) OFF | Dose Right (ACS) OFF | SURE Exp (Real EC) OFF |
| Recon 1 Algorithm | B35 | B35 | B35 | Standard | Standard | B | B | Standard |
| Recon 2 Algorithm | B30 | B31 | None | Detail | Detail | YB | YB | Detail |
| Additional Image filters | No Selection | No Selection | No Selection | No Selection | IQ Enhance Off | Adaptive Filtering off | B | Standard |

Scanning Procedure CPAP Phantom

| Scanner make | SIEMENS | SIEMENS | SIEMENS | GE | GE | PHILIPS | PHILIPS | TOSHIBA |
|---------------------------------------------|--------------------------------|--------------------------|--------------------|-----------------------------|------------------------------|---------------------|------------------|--------------|
| Scanner model | Definition (AS Plus) 128 slice | Definition (DS) 64 slice | Sensation 64 slice | VCT 64 slice/ Discovery STE | Discovery CT 750 HD 64 slice | Brilliance 64 slice | iCT-256 | Aquilion 64 |
| Thickness (mm) | 0.75 | 0.75 | 0.75 | 0.625 | 0.625 | 0.67 | 0.67 | 0.5 |
| Interval (mm) | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Iterative recon (noise reduction algorithm) | Do Not use IRIS | Do Not use IRIS | No Selection | Do not use ASIR | Do not use ASIR | Do not use iDOSE | Do not use iDOSE | No Selection |
| Scan Time (Sec) 30cm length | <10 | <10 | <10 | <10 | <10 | <10 | <10 | <10 |

5. Scan Acquisition



Phantom scan should include entire length of the phantom

Use 365mm field of view and 0.5mm slice spacing for isotropic resolution

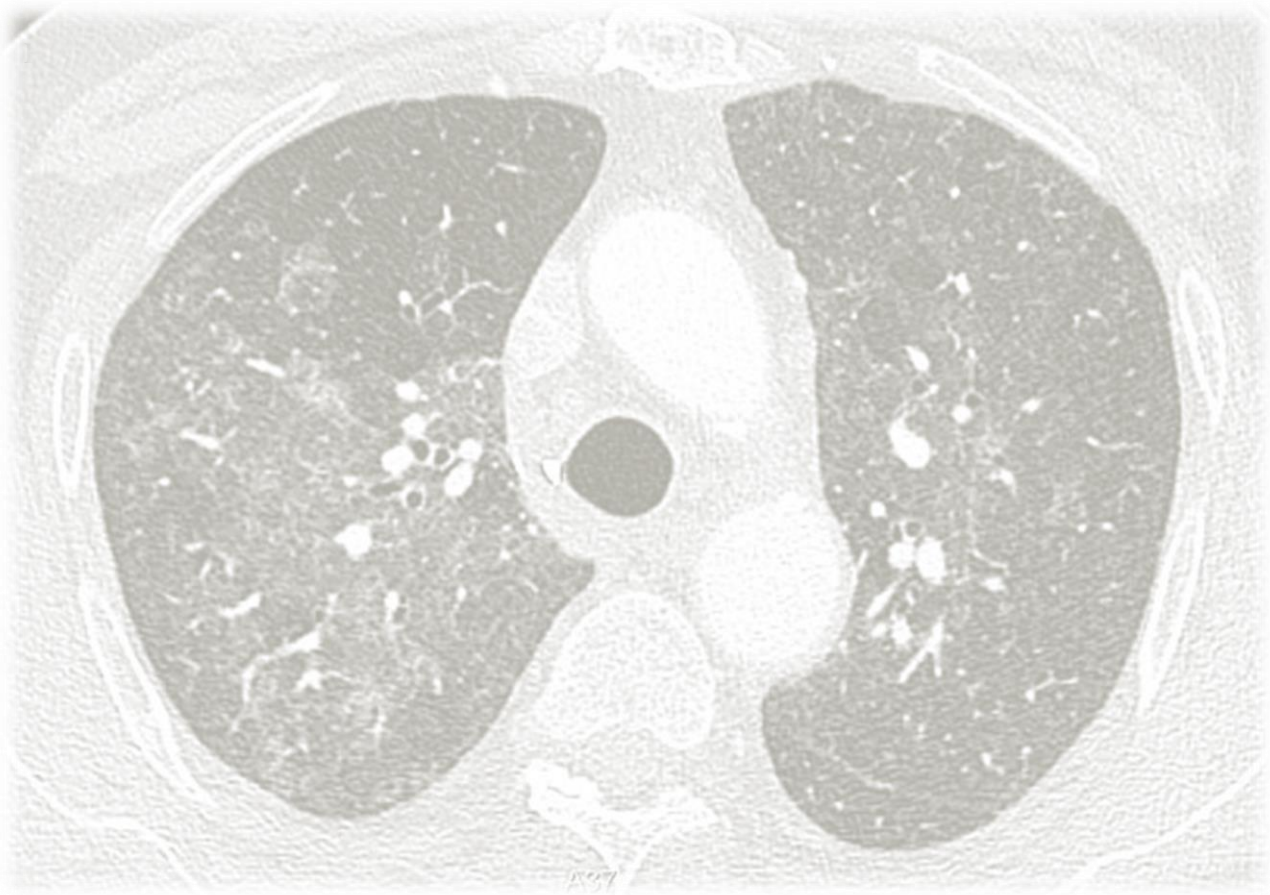
Figure 6

1. One scan for each approved scanner should be completed using the CT study procedure (Tables 1.1 and 1.2)
2. Scan identification must include study site abbreviations, scanner make and serial number, and have Phantom ID on the scan label description. (e.g. a GE Scanner with SN 123456 at DCC using phantom abcde will be: **DCCabcdeGE123456** (site abbreviation, phantom ID, scanner make, scanner SN))
3. Scan using both inspiration and expiration procedures listed in tables 1.1 and 1.2. Scanning must be accomplished with the phantom remaining in the same position for both scans.
4. Reconstruct the image using the proper GE, Siemens, & Philips kernels provided above (Figure 6). The Display Field of View (DFOV) must be **365mm.** and the (x,y) reconstruction coordinates must be (0,0) respectively.

6. Data Transfer

Complete the Phantom Acquisition Form (PT) and give the disk with the copied reconstructed images of the phantom to the study coordinator for scan verification. Data should be transferred using the DICOM Parser. Please save the DICOM images without any reader on the disks

A second disk with the scans should be retained at the clinic



Appendix B

HRCT Scanning Procedure

CPAP HRCT Substudy

1 Dec 2013

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1. Introduction

Although there are some variations between CT scanners a standardization of the parameters has been developed to allow multiple scanners to output reliable quantitative measures across a given patient population. Parameters such as dose have been adjusted to accommodate large, medium and small subjects using independent mAs settings for each body size.

Each subject will have one standard scout (AP/PA) scan over the chest at Total Lung Capacity (TLC).

Two CT scans will be performed each at different lung volume. The first volume will be at Total Lung Capacity (TLC) followed by another CT scan at Functional Residual Capacity (FRC).

The technologist should fill out a HRCT Scan Acquisition Form (RT) for each scan visit performed and submit this form back to the study coordinator for scan verification.

2. CT Parameters

2.1. CT Inspiration (TLC) and Expiration (FRC) procedures

| Scanner make | SIEMENS | SIEMENS | SIEMENS | GE | GE | PHILIPS | PHILIPS | TOSHIBA |
|---------------------------------|--------------------------------|--------------------------|--------------------|-----------------------------|-----------------------------|------------------------|------------------------|------------------------|
| Scanner model | Definition (AS Plus) 128 slice | Definition (DS) 64 slice | Sensation 64 slice | VCT 64 slice/ Discovery STE | Discovery CT 750HD 64 slice | Brilliance 64 slice | iCT-256 | Aquilion 64 |
| Scan type | Spiral | Spiral Single Source | Spiral | Helical | Helical-Standard | Spiral Helix | Spiral Helix | Helical |
| Scan FOV | No selection | No Selection | No selection | Large | Large | No selection | No selection | S/M/L |
| Rotation Time(s) | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Det. Configuration | (128) 64 x 0.6 | (64) 32 x 0.6 | (64) 32 x 0.6 | 64 x 0.625 | 64 x 0.625 | 64 x 0.625 | 128 x 0.625 | 64 x 0.5 |
| Pitch | 1.0 | 1.0 | 1.0 | 0.984 | 0.984 | 0.923 | 0.993 | 0.828 |
| kVp | 120 | 120 | 120 | 120 | 120 | 120 | 120 | 120 |
| Dose modulation | Care Dose OFF | Care Dose OFF | Care Dose OFF | Auto mA OFF | Auto mA OFF | Dose Right (ACS) OFF | Dose Right (ACS) OFF | SURE Exp (Real EC) OFF |
| Recon 1 Algorithm | B35 | B35 | B35 | Standard | Standard | B | B | Standard |
| Recon 2 Algorithm | B30 | B31 | None | Detail | Detail | YB | YB | Detail |
| Additional Image filters | No Selection | No Selection | No Selection | No Selection | IQ Enhance Off | Adaptive Filtering off | Adaptive Filtering off | No selection |
| Thickness (mm) | 0.75 | 0.75 | 0.75 | 0.625 | 0.625 | 0.67 | 0.67 | 0.5 |
| Interval (mm) | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |

HRCT Scanning Procedure for CPAP substudy

| Scanner make | SIEMENS | SIEMENS | SIEMENS | GE | GE | PHILIPS | PHILIPS | TOSHIBA | |
|------------------------------------------------------------------------------------|----------------------------------------------------|----------------------------------------------------|----------------------------------------------------|------------------------------------------|------------------------------------------|-------------------------------------------|-------------------------------------------|---------------------------------------|---------------------------------------------------|
| Scanner model | Definition (AS Plus) 128 slice | Definition (DS) 64 slice | Sensation 64 slice | VCT 64 slice/ Discovery STE | Discovery CT 750HD 64 slice | Brilliance 64 slice | iCT-256 | Aquilion 64 | |
| Iterative recon (noise reduction algorithm) | Do Not use IRIS | Do Not use IRIS | No Selection | Do not use ASIR | Do not use ASIR | Do not use iDOSE | Do not use iDOSE | No Selection | |
| Scan Time (Sec) 30cm length | <10 | <10 | <10 | <10 | <10 | <10 | <10 | <10 | |
| Recon Mode | N/A | N/A | N/A | N/A | Full | N/A | N/A | N/A | |
| Smart mA | N/A | N/A | N/A | N/A | OFF | N/A | N/A | OFF | |
| IQ Enhance | N/A | N/A | N/A | N/A | OFF | N/A | N/A | N/A | |
| Inspiratory (TLC) Siemens = Eff. mAs GE = mA setting Philips = mAs | <i>Effective mAs:</i> S: 90 M: 110 L: 165 | <i>Effective mAs:</i> S: 85 M: 105 L: 150 | <i>Effective mAs:</i> S: 80 M: 100 L: 145 | <i>mA:</i> S: 145 M:180 L: 270 | <i>mA:</i> S: 145 M: 180 L: 270 | <i>mAs:</i> S: 105 M: 130 L: 190 | <i>mAs:</i> S: 105 M: 130 L: 190 | <i>mA:</i> S:145 M:180 L:270 | <i>Effective mAs:</i> S: 91 M:109 L: 164 |
| Expiratory (FRC) Siemens = Eff. mAs GE = mA setting Philips = mAs | <i>Effective mAs:</i> S: 65 M: 65 L: 90 | <i>Effective mAs:</i> S: 60 M: 60 L: 85 | <i>Effective mAs:</i> S: 55 M: 55 L: 80 | <i>mA:</i> S: 100 M: 100 L: 145 | <i>mA:</i> S: 100 M: 100 L: 145 | <i>mAs:</i> S: 70 M: 70 L: 105 | <i>mAs:</i> S: 70 M: 70 L: 105 | <i>mA:</i> S:100 M:100 L:145 | <i>Effective mAs:</i> S:61 M:61 L:91 |

2.2. CT Radiation Dose Standardization

- CT Dose is standardized so each manufacturer and model is matched within $\pm 3\%$ of the Target CTDIvol.

2.3. CTDIvol Selection

Effective dose estimations for average-size adults (BMI 20-30)

Females

- 4 mSv (0.4 rem) for inspiration scans
- 3 mSv (0.3 rem) for expiration scans
- Cumulative dose total (both scans pre- and post-CPAP): 14 mSv (1.4 rem)

Males

- 3.5 mSv (0.35 rem) for inspiration scans
- 2.5 mSv (0.25 rem) for expiration scans.
- Cumulative dose total (both scans pre- and post-CPAP): 12 mSv (1.2 rem)

3. Size Definition (mAs Selection)

- Body Mass Index will be used to determine large, medium or small mAs setting. The BMI values will be provided by the study coordinator
- The technologist will use the chart below to select the mAs setting for a given BMI.

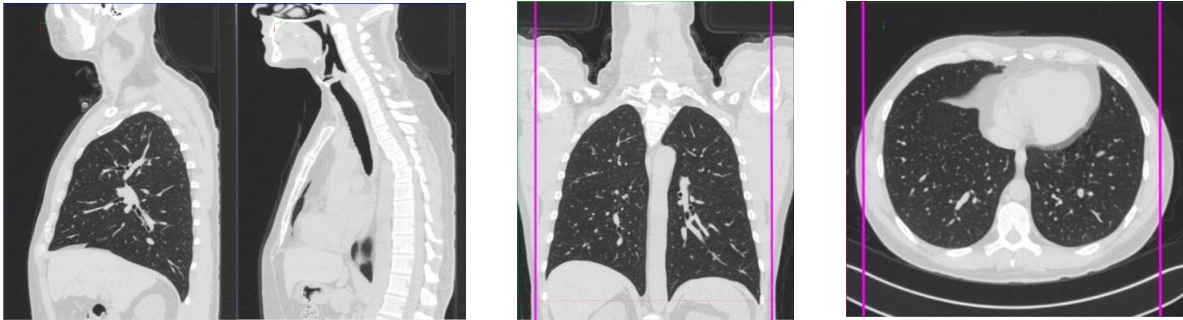
3.1. (mAs) selection

| BMI Range | mAs Selection |
|-----------|---------------|
| >30 | Large |
| 20 to 30 | Medium |
| < 20 | Small |

*Expiratory scan will only have medium or large mAs selection, so small and medium are combined for the lower setting.

4. CT Lung Volumes (per session)

- Each subject will have one standard chest scout scan (AP/PA) at Total Lung Capacity (TLC). The scout scan will be used by the Technologist to obtain the size of the subject and for positioning the CT scan over the lung field.
- Two different CT scans will be performed each at a fixed lung volume. The first volume will be at Total Lung Capacity (TLC) followed another CT scan at Functional Residual Capacity (FRC)
- Scans should include complete lung fields and upper airway to the nasopharynx. Scan should start below the bottom edge of the posterior left and right lower lungs and end at the nasal turbinates.



5. CT Breathing Instructions

- These will be the instructions given by the Coordinator and Radiology Technologist at the time of scanning.
- It is important for the Coordinator and Radiology Technologist to ensure that the subject is able to follow the commands appropriately and also that the subject is appropriately coached **PRIOR** to performing the actual scanning procedures.

(a) Practice Breathing (TLC)

- For the first part of this scan, I am going to ask you to take a couple of deep breaths in and out before we have you hold your breath all the way in.
- First let's practice
- Take a deep breath in (*watch chest to ensure a deep breath as far in as possible*)
- Let it out (*watch chest to ensure air is out*)
- Take a deep breath in (*watch chest to ensure a deep breath in*)
- Let it out (*watch chest to ensure air is out*)
- Now breathe all the way IN...IN...IN... and hold it (*watch chest to ensure a deep breath in as far as possible*)
- Keep holding your breath- **DO NOT BREATHE!** (*watch chest to ensure spine remains on the table, patients is not shaking- watch for these throughout the study!*)
- Breathe and relax

(b) Scout views: AP/PA (CT topogram at TLC)

- OK let's get started
- Take a deep breath in (*watch chest to ensure a deep breath in*)
- Let it out (*watch chest to ensure air is out*)
- Take a deep breath in (*watch chest to ensure a deep breath in*)
- Let it out (*watch chest to ensure air is out*)
- Now breathe all the way IN... IN... IN... and hold it (*watch chest to ensure a deep breath as far in as possible*)
- Keep holding your breath- DO NOT BREATHE! (*watch chest to ensure the spine remains on the table, subject is not shaking and then start the scout scan*)
- Perform scout
- At the end of the scout- Breathe and relax

(c) Inspiratory CT (TLC)

- Now we're ready again so please
- Take a deep breath in (*watch chest to ensure a deep breath in*)
- Let it out (*watch chest to ensure air is out*)
- Take a deep breath in (*watch chest to ensure a deep breath in*)
- Let it out (*watch chest to ensure air is out*)
- Now breathe all of the way IN...IN...IN as far as possible and hold it in (*watch chest to ensure a deep breath in as far as possible*)
- Keep holding your breath – DO NOT BREATHE!
- Perform TLC scan
- As the scan ends: Hold your breath for 3...2....1
- At the end of scan- Breathe and relax

(d) Practice Breathing (FRC)

- For the second part of this scan, I am going to ask you to breathe normally in and out before we have you hold your breath at the end of breathing out.
- First let's practice
- Take a breath in (*watch chest to ensure a breath in*)
- Let it out (*watch chest to ensure air is out*)
- Take a breath in (*watch chest to ensure a breath in*)
- Let it out (*watch chest to ensure air is out*)
- Take another breath in (*watch chest to ensure a breath in*)
- Let it out, hold your breath
- Keep holding your breath- DO NOT BREATHE! (*watch chest to ensure spine remains on the table, patients is not shaking- watch for these throughout the study!*)
- Breathe and relax

(e) Expiratory CT (FRC)

- Now we're ready again so please
- Take a breath in (*watch chest to ensure a breath in*)
- Let it out (*watch chest to ensure air is out*)
- Take a breath in (*watch chest to ensure a breath in*)
- Let it out (*watch chest to ensure air is out*)
- Take another breath in (*watch chest to ensure a breath in*)
- Let it out, hold your breath
- Keep holding your breath – DO NOT BREATHE!
- *Perform FRC scan*
- *As the scan ends: Hold your breath for 3...2....1*
- *At the end of scan- Breathe and relax*

6. Radiation Dose Calculation

The cumulative dose total is estimated to be 14 mSv (1.4 rem) for females and 12 mSv (1.2 rem) for males. In comparison, the maximum amount of radiation from the research related radiation procedures for a female in this study is equivalent to approximately 28% of the annual radiation limit for a radiation worker in the United States and for a male approximately 24% of the annual radiation limit for a radiation worker. One regular chest x-ray would give you .1 mSv (.01 rem). The natural radiation we are exposed to all the time – like from the sun – gives you about 3 mSv (.3 rem) each year.

The risk of getting cancer from the radiation given in this study is thought to be about 0.14% for females and 0.12% for males, and the risk of dying from cancer from that radiation is 0.07% for females and 0.06% for males. In comparison, 4 out of every 10 people will get cancer in our lifetime. And, 2 out of every 10 of us will die from cancer.

DOSE CALCULATIONS PRESENTED IN THIS PROTOCOL ARE BASED ON IMPACT CT PATIENT DOSIMETRY CALCULATOR. ALL SITES ARE RESPONSIBLE FOR PERFORMING THEIR OWN INDIVIDUAL CALCULATIONS USING THE CPAP HRCT PROTOCOL.

7. Data Transfer

Scans must be de-identified (no personal identifiers such as name, gender, age) before burning them to the disk. Scan identification must include scanner make and serial number, and have Participant ID on the scan label description. E.g. a GE Scanner with SN *123456* and participant ID *PD000* will be: PD000GE123456 (participant ID, scanner make, scanner SN)

Complete the HRCT Scan Acquisition Form (RT) and give the disk with the copied, **de-identified** reconstructed scans of the lungs to the study coordinator for scan verification. Data should be transferred using the DICOM Parser. Please save the DICOM images without any reader on the disks.

A second disk with scans should be retained at the clinical center.