Study of Asthma and Nasal Steroids (STAN)

Manual of Operations

Version 1.1

6 Jan 2011

Revision History

Version 1.0 (23 Nov 2010)
- Based on protocol 2.0 (9 Apr 2010)
- Posted on the STAN website

Version 1.1 (6 January 2011)
- Based on PPMs subsequent to Version 1.0
- Incorporates revisions, clarifications and corrections to Version 1.0

Section	Change/addition
1.2	Exclusion criteria • Medication use: Added additional bullet "No plan to start anti-leukotriene medication during trial"
1.3	Study visit time windows and data collection schedule *(clarification)* • Clarified administration of General Quality of Life measures to be collected at V4 not P3. General Quality of Life measures should be administered at V1, V2, V3, V4, and V5 • Clarified abbreviations and notes on study visit time windows and data collection schedule
2.1	Order of procedures (V1) *(clarification)* • Added information about physical exam required prior to MeCl test
2.2	Screening (V1) • Equipment/materials: added spirometer • Complete Screening form: added information about meeting eligibility criteria at time of randomization • Have participant complete questionnaires: added instructions for scoring the Sinus Symptom Score
2.8	Rescreening and recycling *(clarification)* • Tasks: clarified V1 forms for rescreening – Mark original set of forms as "screen failure" and keep on file
3.1.1	Clinical center staff certification *(clarification)* • Purpose: added ensure consistent conduct of study procedures over time within and across clinics so that findings from all clinics are comparable • Clarified task section – Separated tasks into "clinical center and satellite certification" and "staff certification"

STAN MOP

Revision History

Section	Change/addition
	– Added under "Tasks-staff certification" bullet: Entering names and contact information of all new main and satellite center staff requiring a PIN into the online ACRC directory (Lead Coordinator only) – Added additional bullet under "Tasks: clinical center and satellite certification": All ACRC staff members conducting procedures for STAN must be certified for that procedure
3.1.2	Data system certification • Fourth paragraph deleted, "the system will assign a dummy password. This password must be changed." edited as "use 'changeme'. The system will instruct the user to create a unique password the first time that user logs into the data system from that time forward, only the user's unique password will work."
3.6.1	Spirometry procedures • Removed references to inspiratory flow Standardization of equipment • Added KoKo spirometer using software version 4.11 Testing procedure • Updated section on quality assurance values so that they do not have to be recorded only noted to assess the quality of the maneuver and session Pre and post bronchodilator procedures • Removed FEV1 requirement for taking up to four puffs of albuterol
3.7.2	Methacholine challenge– Purpose and schedule *(clarification)* • Re-wrote "when" to clarify instructions, "Methacholine challenge test is a V1and V5 procedure. However the methacholine challenge test and pre/post spirometry (also required at V1 and V5) **cannot** be conducted together. As such, the methacholine challenge test must be schedule another day within the visit window.
3.7.6	Medications to hold prior to methacholine challenge testing Added: • Ultra long-acting β-agonists 72 hrs • Antihistamines 48 hrs
3.7.11	Preparation of methacholine solutions, Storage of solutions • Updated to reflect Vials I and J may be made and stored in the refrigerator less than 24 hours
3.7.12	Administration of methacholine challenge • Added list of required equipment • Administration of bronchodilator-update dose at baseline to > 80%

STAN MOP

Revision History

Section	Change/addition
3.8	Allergy skin testing (PPM # 10 and 13) • Changes made to section to condense/streamline and for clarity
3.8.9	Medications to hold prior to allergy skin testing (PPM #10 and 13) • Added additional comment before listing medications. If participant does not observe medication holds for listed medications, skin testing should still be conducted and the medications will be treated as confounders; in the previous version of MOP instructions were to re-schedule test if medications were not held • Deleted antidepressant holds • Added list of confounder medications not held
3.9	Exhaled NO measurement • Equipment for testing: added 2 test cards are labeled STAN A and STAN B; use one card until DCC collects card to archive tests, then use other card • Additional supplies section renamed 'Replacement supplies' • Added to 'Replacement supplies': note that Aeocrine staff track the expiration date of each QC filter and will send you a new filter at the appropriate time at no cost • Exhaled Nitric Oxide Comparison sub-study: added clarification that for eNO substudy added clarification that order of testing (i.e., whether to use MINO A or MINO B first) should be obtained from data system for each study visit
Various spelling and grammatical mistakes corrected throughout	

STAN MOP

Contents

Contents

Contents

STAN MOP

1. Study overview

1.1 Design and outcome measures

Title

Study of **A**sthma and **N**asal Steroids (STAN)

Objective

To test the hypothesis that children and adults with symptomatic asthma and chronic rhinitis and/or sinusitis have improved asthma control when treated with nasal corticosteroid spray, mometasone, as compared to children and adults treated with placebo.

Type of study

- Randomized, double-masked, placebo-controlled, parallel group clinical trial
- Multicenter, 19 centers
- Fixed sample size, 380 (190 adults; 190 children 6-17 years old)

Study drugs

- Intranasal mometasone (Nasonex®) spray
  - Participants less than 12 years at randomization:
    1 spray per nostril once daily in the morning (total: 2 sprays)
  - Participants 12 years and greater at randomization:
    2 sprays per nostril once daily in the morning (total: 4 sprays)
- Intranasal placebo spray
  - Participants less than 12 years at randomization:
    1 spray per nostril once daily in the morning (total: 2 sprays)
  - Participants 12 years and greater at randomization:
    2 sprays per nostril once daily in the morning (total: 4 sprays)

Primary outcome

- Change in Asthma Control Test (ACT) score

Secondary outcomes

- Rate of Episodes of Poor Asthma Control (EPAC types 1* and 2†)
- Bronchial Hyperreactivity (methacholine PC_{20})
- Sinusitis and rhinitis symptom scores (SS)
- Sinusitis and rhinitis quality of life (SN or SV)

** EPAC type 1 is defined by one or more of the following:*

- *Decrease of ≥ 30% morning peak expiratory flow (PEFR) from baseline personal best for 2 consecutive days (definite yellow zone event), or*
- *Addition of oral prednisone or prednisilone to treat asthma symptoms, or*

Unscheduled contact with a health care provider (emergency department visit, physician office, hospital) for asthma symptoms

† EPAC type 2 is any of the type 1 events and/or the following:
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

Tertiary outcomes

- Daily Asthma and nasal symptom scores (DC)
- Asthma Symptom Utility Index score (AS)
- Asthma-specific Quality of Life (MQ, PQ)
- Lung function variables (FEV_1, FVC)
- Generic health-related quality of life (MO, CH)
- Rhinitis/Sinusitis Exacerbations (DC and CV)
- Eotaxins and eosinophilic and cationic protein levels in serum and nasal lavage specimens
- Exhaled nitric oxide (NO)

Other data

- Data on potential confounders and study adherence will be collected, including:
  Baseline Questionnaires ascertaining demographics, general health, medication use, rhinitis or sinusitis severity and duration, asthma symptoms and menstruation, smoke exposure, asthma severity and asthma triggers
  Allergy skin testing
  Pollen counts
  Closeout questionnaires for global assessment of treatment, procedures, study personnel, and participation in future studies

1.2 Eligibility criteria

The goal of STAN patient selection is to enroll children and adults who have both inadequately controlled asthma and symptoms of chronic rhinitis and/or sinusitis as determined by their Sino-Nasal Questionnaire (SI) score, and whom asthma physicians might consider for treatment with a nasal steroid to improve asthma symptoms.

Inclusion criteria

Gender and Age

- Males and females, age 6 years or older

Asthma diagnosis

- Physician diagnosed asthma
- Lung function criteria (must have one or more of the following documented in the 24 months before Visit 1 or demonstrated before randomization, Visit 2):
  - At least 12% increase in FEV_1 following administration of bronchodilator OR
  - Positive methacholine challenge (20% fall in FEV1 at less than 16 mg/ml)

Poor asthma control - defined by one of the following (Visit 1 and Visit 2):

- 6-11 years old - Score of 19 or less on the Childhood Asthma Control Test
- 12 years or older - Score of 19 or less on the Asthma Control Test

Chronic rhinitis and sinusitis

- Chronic symptoms of rhinitis and/or sinusitis as measured by a mean score of 1 or greater on the Sino-Nasal Questionnaire (Visit 1 and 2)
  - The Sino-Nasal Questionnaire (SI) is scored by averaging the responses from the 5 questions. The range of scores possible are 0-3.
  - Scoring: Never (0), 1-4 times per month (1), 2-6 times per week (2), Daily (3).

Exclusion criteria

Pulmonary function

- FEV1 less than 50% predicted normal pre-bronchodilator (Visit1 and Visit 2)

Other illnesses/surgery

- History of upper airway symptoms for less than 8 weeks at the time of randomization
- Fever greater than 38.3°C, or history of fever in last 10 days at the time of randomization

Surgery

- Sinus surgery within last 6 months

Medication use
- Systemic/nasal steroids within last 4 weeks at the time of randomization
- Anti-leukotriene medication within last 2 weeks at the time of randomization
- No plan to start anti-leukotriene medication during the trial
- Any investigational drug in the last 6 weeks at the time of randomization

Drug allergies or sensitivities
- Allergy or intolerance to nasal mometasone

Non-adherence
- Inability or unwillingness of the adult participant to provide consent
- Inability or unwillingness of the legal guardian to provide consent or inability or unwillingness of the child to provide assent
- Inability to take study medication
- Inability to perform baseline measurements
- Completion of less than 10 of the 14 days of diary entry prior to randomization
- Inability to be contacted by telephone
- Intention to move out of the area within 6 months

Pregnancy
- Cannot participate if pregnant or lactating
- Females of childbearing potential that are unwilling to practice adequate birth control methods (abstinence, combination barrier and spermicide or hormonal)

Other major chronic illnesses
- Co-morbidity that predisposes to complicate rhinosinusitis (e.g. cystic fibrosis, insulin dependent diabetes mellitus, immunodeficiency disorder)
- Chronic diseases (other than asthma) that in the opinion of the investigator would prevent participation in the trial or put the participant at risk by participation, e.g. chronic diseases of the lung (other than asthma), heart, liver, kidney or nervous system
- Current cataract
- History of glaucoma or other conditions resulting in increased intraocular pressure

Smoking
- Greater than or equal to 10 pack year smoking history or active smoking within the last 6 months

1.3 Study visit time windows and data collection schedule

(Please regard this schedule as the definitive version)

Visit	V1	V2	V3	P1	V4	P2	P3	V5
Time window (weeks)▪	-4 to -2	0	2-6	6-10	10-14	14-18	18-22	22-26
Target (week)	-2	0	4	8	12	16	20	24
Consent, eligibility evaluation	•							
Methacholine challenge*	•†							•†
Spirometry pre- and post-BD	•	•	•		•			•
Physical exam	•							•
Pregnancy test‡	•	•						•
Instruction in diary, PEFR, action plan	•	•	•	•	•	•	•	•
Return asthma diary		•	•		•			•
Randomization		•						
Treatment distribution		•	•		•			
Adherence monitoring			•		•			•
Baseline questionnaire	•							
Sino-nasal Questionnaire (SI)	•	•						
Interval Asthma and Sinus history		•	•	•	•	•	•	•
Asthma Control (TA or TP), ASUI (AS)	•	•	•		•			•
Sinus symptom questionnaire (SS)	•	•	•		•			•
Asthma QoL Measures (MQ or PQ)	•	•	•		•			•
Sinusitis QoL (SN or SV)	•	•	•		•			•
General QoL MO-SF36 (MO) or Child Health Questionnaire (CH)	•	•	•		•			•
Smoking Questionnaire (SQ)		•						
Asthma in Females Questionnaire (FQ)		•						
Adverse event screen			•	•	•	•	•	•
Exhaled nitric oxide (NO)		•						•
Allergy skin testing		•						
Nasal Lavage		•						•
Venipuncture		•						•

Abbreviations:
V# = Visit
P1-3= Phone contact
PEFR - peak expiratory flow
Qol - Quality of Life

▪ Minimum of 1 week required between study visits
* Only performed if participant has FEV_1 greater or equal to 70%
† Procedure conducted on different day from visit
‡ Females of childbearing potential

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 and asthma control questionnaires be completed at the beginning of the visit so that the responses are not influenced by study visit procedures.

MeCl test, spirometry, and physical exam

Physical exam must be completed prior to MeCl challenge test. A MeCl challenge test cannot be performed on the same day as pre and post spirometry. Thus, methacholine challenge tests associated with V1 and V5 must be conducted on separate days from the clinic visit.

Note: *MeCl test cannot be performed on someone with FEV_1 less than 70% on the day of the test. If participant has FEV_1 less than 70% at V1 or V5, do not perform MeCl test and consider results to be missed data.*

Eligibility testing for patients with $FEV_1 \geq 70\%$ predicted at Visit 1

- If historical lung function criteria demonstrated, no other lung function procedure is required for eligibility. However, participant must have a MeCl test and pre and post spirometry performed as part of required Visit 1 procedures.

- If historical lung function criteria not demonstrated:
  - Conduct pre and post spirometry at Visit 1

    If reversibility demonstrated, patient has met eligibility and must return on another day for required MeCl test

    If reversibility not demonstrated, patient has not met eligibility and must return for MeCl to establish eligibility

    OR

  - Conduct required MeCl test at Visit 1 and have participant return for pre and post spirometry

    If PC_{20} is positive, participant has demonstrated poor lung function for eligibility, but must return on another day for pre and post reversibility

    If PC_{20} is negative, participant has not demonstration poor lung function for eligibility and must return for pre and post spirometry to establish eligibility

Note: *Some clinics cannot perform MeCl test at Visit 1 because they must have a signed consent prior to requesting that a participant withhold medication*

2.1. Order of procedures

Randomization visit

The online randomization should be completed after all other Visit 2 procedures and lung function tests are performed

Required order of lung function procedures

Procedures for exhaled nitric oxide and spirometry can interfere with each other. Thus, it is critical that clinics preform these tests in a prescribed order. The tests below should be conducted in the order as listed:

- Exhaled nitric oxide (eNO)
  conducted before
- Spirometry, with or without bronchodilator

***Note**: All of these tests are not done at each visit. Occurrence will vary among the clinics and participants.*

2.2 Screening (VI)

Overview

- V1 consists of the initial screening visit, administration of the Asthma Control Test, a physical exam, methacholine challenge test, and FEV_1 to establish eligibility

Time frame

- Target – 2 weeks prior to Randomization (V2)
- Window – 2 to 4 weeks prior to Randomization (V2)
- Time period for completing V1 tasks – 2 weeks
- Duration of V1 – approximately 3-4 hours
- Methacholine challenge test will need to be scheduled on a different day than V1 spirometry (because it cannot be conducted the same day as a pre and post spirometry)

Equipment/materials

- Mini-Wright peak flow meters
- Participant binder, ACRC tote bag and magnet
- General Asthma Education material
- Spirometer

Tasks

- Explain study to participant
- Review consent and assent forms with participant and parent/legal representative, if applicable
- Sign and date consent and assent forms (assent required for participants less than 18 years of age; may be part of the consent form per local IRB requirements)
- Ask participant if initial spirometry results may be sent to their primary asthma doctor. If yes, have participant complete a release statement as applicable (sample release statement in Section 3.4.2 of MOP)
- Assign the participant an ID using the next sequentially numbered label on Clinic Label Sheet (see example, MOP Section 4.3)
  - Register participant number in STAN data system
  - Place label in box on item 2 of Screening form (SC)
- Complete Baseline Asthma and Medical History (BA)
- Complete Participant Information Sheet (PI)
- Conduct pregnancy test, if applicable
- Collect PFT data and record on Pulmonary Function Testing form (PF)
  - Peak flow
    - Distribute peak flow meter
    - Instruct participant in use of peak flow meter
    - Have participant perform 3 peak flows
    - Instruct participant to bring peak flow meter to all study visits

  - Spirometry (Pre and Post bronchodilator)
    - If $FEV_1 \geq 50\%$ predicted pre-bronchodilator, conduct pre and post BD spirometry
    - If $FEV_1 < 50\%$ predicted pre-bronchodilator, patient is ineligible; terminate screening; notify asthma care provider
    - Complete section on FEV_1 using pre-bronchodilator FEV_1 and FEV_1 % predicted pre-bronchodilator from Pulmonary Function Testing form (PF) if applicable
- Have participant complete questionnaires:
  - Asthma Control Test (TA) (ages 12 years and older)

    OR

    Childhood Asthma Control Test (TP) (ages 6 - 11 years)
  - Sino-Nasal Questionnaire (SI)
  - Asthma Symptom Utility Index (AS)
  - Marks Asthma Quality of Life Questionnaire (MQ) (ages 16 years and older)

    OR

    Children's Health Survey for Asthma (PQ) (ages 6 - 15 years)
  - Your Health and Well-Being (Medical Outcomes Study SF-36 v2) (ages 18 years and older) (MO)

    OR

    Child Health Questionnaire Parent Form 50 (CH) (ages 6 - 17 years)
  - Sino Nasal Outcome Test-22 (SN) (ages 18 years and older)

    OR

    Sinus and Nasal Quality of Life-SN-5 (SV) (ages 6 - 17 years)
  - Sinus Symptom Score (SS)
    - The sinus symptom questionnaire is score by totaling the score for the six individual components, which give a score out of 60. (Do not average the total score)

- Complete Screening form (SC). Physical exam and methacholine challenge may be conducted before or after SC is completed
  - Some eligibility requirements may not be met at V1 (e.g. Systematic/nasal steroids within last 4 weeks at the time of randomization) however, patient can still continue to V2 if they will be able to meet all eligibility criteria at time of randomization
  - If screen failure or incomplete screening, do not data enter SC form. Record on patient screening log
  - Records of all screen failures should be kept with study materials
- Conduct brief physical exam (conducted by study physician or designee)
  - Must be completed prior to the methacholine challenge test
  - Recorded on Physical Exam (PE) form
- Schedule methacholine challenge test on a separate day
  - Distribute and review Instructions for Preparation for Methacholine Challenge Test (IME)

– Conduct according to procedures detailed in MOP Section 3.7

Note: Methacholine challenge tests are required for all STAN participants with FEV_1 of 70% predicted or greater at the V1 screening. If on the day of the methacholine challenge the participant's FEV_1 is less than 70% predicted, the methacholine test may not be conducted. Instead, conduct post-bronchodilator spirometry. See STAN Pulmonary Function/Methacholine Challenge Flowchart (MOP section 3.7.13), for further clarification.

- Distribute and Review
  - Instructions for Measuring Peak Flow (IPF)
  - Instructions for Diary Cards (IDC)
  - Mini-Wright peak flow meter
  - Participant binder
  - Diary Cards (DC)
    - Complete items 1 and 2 on Diary Cards
      OR
    - Print out Diary Cards with pre-printed dates by clicking on appropriate link on the data system menu of STAN homepage
  - Temporary Asthma Action Plan Sheet (TAP)
    - Fill in "personal best" peak flow on TAP. "Personal best" for TAP is the highest of the three peak flow readings done at Visit 1
    - Fill in green, yellow, and red zone cut-off values on TAP. Cut-off values may be obtained using the STAN calculator or hand calculated using the following:
      - green zone: greater than or equal to .80 of personal best
      - yellow zone: .50 - .79 of personal best
      - red zone: less than .50 of personal best
    - Fill in contact information
  - Canvas bag with ACRC logo and ACRC magnet
  - General Asthma Education materials
  - STAN Schedule of Visits (SOV) with dates and times for all subsequent visits recorded
  - Instructions for Preparation for Methacholine Challenge Test (IME)
- After the visit, send Physician Introduction Letter to primary asthma physician. (Sample letter in section 3.4.1 of MOP). Include initial spirometry results only if participant has signed release or permission was given in consent form
- Data enter the Screening form (SC) into the data system immediately after visit. This form must be data entered before a participant can be randomized at visit 2.
- Data enter remaining forms within 10 working days

Forms (abbreviation)

- Baseline Asthma and Medical History (BA)
- Consent Statement*
- Diary Card (DC)
- Methacholine Challenge Testing (MC)
- Participant Information (PI)*
- Physical Exam (PE)
- Pulmonary Function Testing (PF)
- Screening Form (SC)

Questionnaires (abbreviation)

- Asthma Control Test (TA)
  OR
  Childhood Asthma Control Test (TP)
- Asthma Symptom Utility Index (AS)
- Marks Asthma Quality of Life Questionnaire (MQ)
  OR
  Children's Health Survey for Asthma (PQ)
- Your Health and Well-Being (Medical Outcomes Study SF-36)(MO)
  OR
  Child Health Questionnaire Parent Form (CH)
- Sino Nasal Outcome Test-22 (SN)
  OR
  Sinus and Nasal Quality of Life-SN-5 (SV)
- Sinus Symptom Score (SS)
- Sino nasal Questionnaire (SI)

Information sheets (abbreviation)

- Instructions for Diary Cards (IDC)*
- Instructions for Preparation for Methacholine Challenge Test (IME)*
- Instructions for Measuring Peak Flow (IPF)*
- STAN Schedule of Visits (SOV)*
- Temporary Asthma Action Plan Sheet - Visit 1 (TAP)*

*not entered into database

2.3 Randomization visit (V2)

Time frame

- Target – 2 weeks after Screening Visit (V1)
- Window – 2 to 4 weeks after V1
- Duration of V2 – approximately 3 hours

Tasks

- Have participant complete self-administered questionnaires:
  - Asthma Control Test (TA) (ages 12 years and older)
    OR
    Childhood Asthma Control Test (TP) (ages 6 - 11 years)
  - Asthma Symptom Utility Index (AS)
  - Sino-Nasal Questionnaire (SI)
  - Marks Asthma Quality of Life Questionnaire (MQ) (ages 16 years and older)
    OR
    Children's Health Survey for Asthma (PQ) (ages 6 - 15 years)
  - Your Health and Well-Being (Medical Outcomes Study SF-36) (MO) (ages 18 years and older)
    OR
    Child Health Questionnaire (CH) (ages 6 - 17 years)
  - Sino Nasal Outcome Test -22 (SN) (ages 18 years and older)
    OR
    Sinus and Nasal Quality of Life-SN-5 (SV) (ages 6 - 17 years)
  - Sinus Symptom Score (SS)
  - Asthma in Females Questionnaire (FQ)
  - Home Smoking Activity and Exposure to Tobacco Smoke Questionnaire (SQ) (ages 12 - 17 years)
- Collect Diary Cards distributed at V1
  - Review Diary Cards with participant
  - Edit Diary Cards as appropriate
  - Must have completed at least 10 of the last 14 days of diary entries to be eligible
- Collect interval medical history data, record on Clinic Visit form (CV)
- Collect exhaled nitric oxide (eNO) and complete Nitric Oxide form (NO) - eNO procedure must be conducted prior to spirometry
- Collect Specimen samples
  - Nasal lavage for eotaxins and eosinophilic cationic protein (ecp)
  - Blood serum for eotaxins
  - Blood serum for eosinophilic cationic protein (ecp)
  - Packed blood cells for genotyping (optional)
- Collect pulmonary function data, record on Pulmonary Function Testing form (PF):
  - Conduct peak flow procedure
  - Conduct pre- and post- bronchodilator spirometry procedures
- Conduct allergy skin test
- Conduct pregnancy test (if applicable)
- Review participant eligibility for study treatment using Randomization (RZ) form

2.3. Randomization (V2)

Note: The Screening (SC) form must be data entered before randomization.

- If participant meets eligibility criteria, enter Randomization (RZ) form
  - Obtain study drug Kit ID
  - Obtain values for green, yellow, and red zone cut offs from data system
  - Obtain participant's personal best peak flow calculated by data system
- Complete Asthma Action Plan card (AAP)
  - Fill in zone cut-offs and personal best peak flow calculated by data system and give card to participant
  - Remove Temporary Asthma Action Plan Sheet (TAP) from participant binder and put in participant's file
  - Review instructions for use of card
- Distribute STAN Wallet Card
- Distribute spray bottle(s) from assigned study drug Kit
- Complete Drug Accountability Log (DA)
- Complete Drug Dispensing and Counting (DD) form
- Distribute Diary Cards (DC)
- Review instructions for Diary Card and peak flow meter use with participant
- Review study visit schedule with participant
- Key remaining forms into STAN data system within 10 working days

Forms (abbreviation)

- Clinic Visit (CV)
- STAN Diary Card (DC)
- Drug Dispensing and Counting (DD)
- Nitric Oxide (NO)
- Pulmonary Function Testing (PF)
- Randomization (RZ)

Participant Information

- STAN Wallet Card
- Asthma Action Plan (AAP)

Questionnaires (abbreviation)

- Asthma Control Test (TA) (ages 12 years and older)
- Childhood Asthma Control Test (TP) (ages 6 - 11 years)
- Sino-Nasal Questionnaire (SI) (ages 18 years and older)
- Asthma Symptom Utility Index (AS)
- Marks Asthma Quality of Life Questionnaire (MQ) (ages 18 and older)
- Children's Health Survey for Asthma (PQ) (ages 6 - 15 years)
- Your Health and Well-Being (Medical Outcomes Study SF-36) (MO)
- Child Health Questionnaire (CH) (ages 6 - 17 years)
- Sino Nasal Outcome Test-22 (SN) (ages 18 years and older)
- Sinus and Nasal Quality of Life-SN-5 (SV) (ages 6 - 17 years)

- Sinus Symptom Score (SS)
- Asthma in Females Questionnaire (FQ)
- Home Smoking Activity and Exposure to Tobacco Smoke Questionnaire (ages 12 - 17 years) (SQ)

Log/Administrative forms (abbreviation)

- Drug Accountability Log (DA)*

* not entered into database

2.4 Telephone contact (P1-3)

Time frame

- Target – 8, 16, and 20 weeks after Randomization (V2)
- Window – P1 is conducted between V3 and V4, P2 and P3 is conducted between V4 and V5
- Duration of phone contacts – approximately 15 minutes

Tasks

- Conduct telephone interview using Phone Contact (PC) form

  Note: Do not complete a second PC form for any additional unscheduled calls

- Reinforce daily Diary Card completion
- Remind participant to fax or mail completed Dairy Cards to clinic
- Reinforce peak flow monitoring
- Review Asthma Action Plan
- Screen for adverse events
- Discuss any problems participant may have with study procedures/compliance
- Confirm date of second followup visit (V4) or final visit (V5) and remind participant to bring:
  - All study nasal spray bottles
  - Peak flow meter
  - Diary Cards

- At phone contact 3, (P3) schedule the participant for methacholine challenge testing (can be done 1 to 2 weeks before final visit, V5)

Form (abbreviation)

- Phone Contact (PC)

2.5 Followup visits (V3 and V4)

Time frame

- Targets – weeks 4 and 12 from randomization (V2)
- Windows – 2 weeks before and after target
- Duration of each followup visit – approximately 2 hours

Tasks

- Have participant complete self-administered questionnaires
  - Asthma Control Test (TA) (ages 12 years and older)
    OR
    Childhood Asthma Control Test (TP) (ages 6 - 11 years)
  - Asthma Symptom Utility Index (AS)
  - Marks Asthma Quality of Life Questionnaire (MQ) (ages 18 years and older)
    OR
    Children's Health Survey for Asthma (PQ) (ages 6 - 17 years)
  - Medical Outcomes Study 36-Item Short-Form Health Survey (MO) (ages 18 years and older)
    OR
    Child Health Questionnaire (CH) (ages 6 - 17 years)
  - Sino Nasal Outcome Test-22 (SN) (ages 18 years and older)
    OR
    Sinus and Nasal Quality of Life-SN-5 (SV) (ages 6 - 17 years)
  - Sinus Symptom Score (SS)

- Review returned Diary Cards (DC)
- Conduct interval asthma/health history and adverse event screening by completing CV form
- Collect study nasal spray distributed previously.
- Review returned Diary Cards and distribute additional Diary Cards as needed
- Conduct adverse event screening and interval asthma health history by completing Clinic Visit Form (CV)
- Collect PFT data
  - Conduct peak flow procedure
  - Conduct pre- and post-bronchodilator spirometry procedures
- Check study nasal sprays dispensed previously. Provide adherence counseling if necessary
- Collect spray bottles distributed at previous clinic visit(s). Record on Drug Dispensing and Counting Form (DD)
- Distribute additional study nasal spray bottle(s). Record any additional nasal spray bottles distributed on Drug Dispensing and Counting Form (DD)
- Key data as recorded on forms into STAN data system within 10 working days of visit

2.5. Followup visits (V3 to V4)

Forms (abbreviation)

- Clinic Visit (CV)
- Diary Cards (DC)
- Drug Dispensing and Counting Form (DD)
- Pulmonary Function Testing (PF)

Questionnaires (abbreviation)

- Asthma Control Questionnaire (TA)
- Asthma Symptom Utility Index (TP)
- Marks Asthma Quality of Life (MQ)

  OR

  Children's Health Survey for Asthma (PQ)
- Medical Outcomes Study 36-Item Short-Form Health Survey (MO)

  OR

  Child Health Questionnaire (CH)
- Sino Nasal Outcome Test (SN)
- Sinus Symptom Score (SS)

Log/Administrative form (abbreviation)

- Drug Accountability Log (DA)*

*not entered into database

2.6 Final visit (V5)

Time frame

- Target – week 24
- Window – weeks 22-26
- Duration of Clinic Visit 5 – approximately 3 hours

Methacholine challenge test should be scheduled 1-2 weeks before the rest of the V5 visit. (Methacholine challenge cannot be conducted the same day as pre and post bronchodilator).

Tasks

- Methacholine challenge test conducted 1-2 weeks before rest of V5
- Have participant complete self-administered questionnaires
  - Asthma Control Test (TA) (ages 12 years and older)
    OR
    Childhood Asthma Control Test (TP) (ages 6 - 11 years)
  - Asthma Symptom Utility Index (AS)
  - Marks Asthma Quality of Life Questionnaire (MQ) (ages 18 years and older)
    OR
    Children's Health Survey for Asthma (PQ) , if applicable
  - Your Health and Well-Being (Medical Outcomes Study SF-36) (ages 18 years and older) (MO)
    OR
    Child Health Questionnaire (CH) (ages 6 - 17 years)
  - Sino Nasal Outcome Test-22 (SN) (ages 18 years and older)
    OR
    Sinus and Nasal Quality of Life-SN-5 (ages 6 - 17 years) (SV)
  - Sinus Symptom Score (SS)

- Review returned Diary Cards (DC)
- Conduct interval asthma/health history and adverse event screening by completing CV form
- Collect study nasal spray bottles(s) distributed previously
- Measure exhaled Nitric Oxide (eNO) and complete Nitric Oxide form (NO) - must be conducted prior to spirometry
- Collect PFT data
  - Peak flow
  - Spirometry
- Collect blood for eotaxins and eosinophilic cationic protein
- Collect nasal lavage for eotaxins and eosinophilic cationic protein
- Conduct exit interview using Exit Interview (EI) form
- Complete Treatment Termination (TT) form, if appropriate

- Give participant exit envelope which includes
  - Patient exit letter
  - Sealed treatment unmasking envelope
  - Copy of final spirometry results
- Send physician exit letter to participant's primary asthma care physician
- Key data as recorded on forms into STAN data system within 10 working days, as applicable

Forms (abbreviation)

- Clinic Visit (CV)
- Diary Cards (DC)
- Drug Dispensing and Counting Form (DD)
- Exit Interview (EI)
- Methacholine Challenge Testing (MC)
- Treatment Termination (TT)
- Pulmonary Function Testing (PF)
- Unmasking (UM)

Questionnaires (abbreviation)

- Asthma Control Questionnaire (TA) (ages 12 years and older)
  OR
  Childhood Asthma Control Test (TP) (ages 6 - 11 years), if applicable
- Asthma Symptom Utility Index (AS)
- Marks Asthma Quality of Life Questionnaire (MQ) (ages 18 years and older)
  OR
  Children's Health Survey for Asthma (PQ) (ages 6 - 17 years)
- Medical Outcomes Study 36-Item Short-Form Health Survey (MO) (ages 18 years and older)
  OR
  Child Health Questionnaire (CH) (ages 6 - 17 years)
- Sino Nasal Outcome Test (SN)
  OR
  Sinus and Nasal Quality of Life-SN-5 (SV) (ages 6 - 17 years)
- Sinus Symptom Score (SS)

Log/Administrative form (abbreviation)

- Drug Accountability Log (DA)*

*not entered into database

2.7 Missed procedures/missed visits

Time frame

- After time window has closed for a specified study visit and the following were missed:
  - all requirements for a visit (missed visit)
  - one or more of the procedures or forms required for a visit (missing data at a visit)
  - one or more phone contacts (P1-3)
  - Diary Cards since last visit

Tasks

- Attempt to schedule next visit at 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 missed on Missed Data (MD) form

Participants who have missed one or more visits

- Once randomized, a participant is never considered "off study" until after the scheduled followup periods ends; i.e., after Clinic Visit 5 window closes
- A Missed Data form (MD) is required at the close of each time window of visits missed
- Continue attempts to contact participants unless told in no uncertain terms not to contact
- Return for study visits after an absence of any length is acceptable and encouraged
- Be sure Missed Data forms (MD) are up-to-date
- The participant should resume in whatever time window he/she would be in currently (e.g., if participant missed Visits 3 and 4, and returned to the study during the time window for Visit 5, then a Visit 5 should be conducted)

Forms (abbreviation)

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

2.8 Rescreening and recycling

Rescreening

Purpose

- To re-evaluate patients who did not meet eligibility criteria during screening at V1

Tasks

- Maintain folder on patients who were not able to meet entry criteria at V1, but who may be eligible in the future
- After a 4 week waiting period you may try to re-screen a participant
- Use the participant ID number and name code as originally assigned
- Redo V1 procedures
- Contact DCC to determine if MeCl test needs to be repeated
- Complete a new set of forms for V1. Mark original set of forms as "screen failure" and keep in file
- If participant is eligible, enter new forms into the database. NOTE: If any form from failed screen was data entered. (DO NOT delete this form from the database)
- There is not a limit on the number of times a patient 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 (V2) visit

Tasks

- Maintain folder on patients who were not able to meet eligibility criteria at Randomization (V2), but may be eligible in the future
- After a 4 week waiting period you may try to randomize a participant who previously did not meet randomization requirements (other than an asthma exacerbation)
- If RZ failure due to an asthma exacerbation between V1 and V2, contact DCC with details of event. Possibility of recycling to be determined on a case by case basis
- Redo V2 procedures as applicable (use original namecode and Pt ID # assigned to the participant)
- Complete a new set of forms for V2
- If participant is eligible, enter new forms into the database (DO NOT delete original forms from the database)
- A potential participant may be recycled **two** times

Forms

- Forms associated with Screening (V1) or Randomization (V2), as applicable

3. Procedures

3.1 Clinic certification

3.1.1 Clinical center and staff 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 STAN
- Ensure consistent conduct of study procedures over time within and across clinics so that findings from all clinics are comparable

When

- Before an ALA-ACRC clinical center may recruit participants and conduct study procedures for the Study of Asthma and Nasal Steroids (STAN)
- Prior to receiving study drug

Tasks

clinical center and satellite certification

- To be completed by main ACRC clinical center and satellites and all STAN staff
- Acquisition of approval of protocol and consents from the IRB of all clinics (main ACRC center and satellites, as applicable)
- Submission of a copy of IRB's notice of protocol approval and a copy of each approved consent statement (with the stamp of approval from the clinical center's IRB, if applicable) to the Data Coordinating Center
- Review of STAN protocol and procedures
- Arrangements for facilities, equipment, and supplies that are needed to conduct STAN procedures
- Completion of the Clinical Center Certification form (CC) by the main ACRC clinical center
- Completion of Satellite Certification form (CT) by each satellite center
- All staff members conducting procedures for STAN must be certified for that procedure

staff certification

- Completion of General Knowledge Assessment (GEN)
- Personnel Assurance Statement (PA)

Requirements for all staff members

- Certification and a Personal Identification Number (PIN) is required to complete study forms and/or enter data
- Knowledge Assessments are to be completed online. To access General Knowledge Assessment (GEN) log onto STAN website home page
  - Click on Certification; Knowledge Assessments
  - 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
- Attendance by key study personnel at 10-11 February 2010 training meeting or other training authorized by the Data Coordinating Center
- Training of all personnel who did not attend formal STAN training meeting in study procedures and form completion, as well as Good Clinical Practice and research integrity

– **Additional requirements for ACRC Center Director and each satellite Co-PI**
  - Completion of Methacholine Challenge Test Assurance Statement (MA)
  - Completion of Spirometry Assurance Statement (SA)
  - Sign off on Clinical Center Certification (CC) form completed by Lead Coordinator
    OR
    Sign off on Satellite Certification (CT) form completed by satellite coordinator
  - Completion of FDA Conflict of Interest form (Form 3455)

– **Additional Lead coordinator certification requirements**
  - Entering names and contact information of all new main and satellite center staff members requiring a PIN into the online ACRC Directory (Lead Coordinator only)
  - Completion of sample Diary Cards (DC): complete 2 weeks of diary, starting on a Wednesday, using made up responses
  - Completion of Data System Operator requirements (see data system operator requirements below)
  - Certification for methacholine challenge, allergy skin tester, spirometry tester strongly recommended for lead coordinator

– **Additional Data System Operator requirements**
  - Certification as a Data System operator from a previous ACRC trial
    OR
    Completion of the certification data system (online, under Data System) by completing STAN data entry tutorial for staff members who will be entering data into the STAN database (see MOP section 3.1.2).
  - Completion of Data System Operator Knowledge Assessment (DSO) (online, under Certification Materials)

– **Additional Allergy Skin tester requirements**
  - Certification as a Allergy Skin Testing from a previous ACRC trial
    OR
    Conduct allergy skin test certification practical exams (sessions 1 and 2; section 3.8.6 of MOP) and complete Certification Skin Testing (CS) form. Only successful tests should be submitted to the DCC

– **Additional Methacholine Challenge tester requirements**
  - Certification as a Methacholine Challenge tester from a previous ACRC trial
    OR
    Completion of 1 approved methacholine challenge test using protocol per section 3.7 of MOP

– **Additional Spirometry tester requirements (any staff conducting spirometry or ACRC studies must be certified)**
  - Individuals previously ACRC certified for spirometry are not required to re-certify for STAN
  - Certification as a Spirometry tester from a previous ACRC trial
    OR
    New spirometry testers
    – Conduct 1 pre and post spirometry procedure per section 3.6 of MOP
    – Record results on Pulmonary Function Test (PF) form. Submit PF along with the lab report (ACRC spirometry report from which the PF form was completed) and print out from on-line calculator.

– **Additional eNO operator requirements**
  - eNO operators are not required to be certified but do need to be trained by an Aerocrine representative or someone previously trained by Aerocrine

Clinic Responsibilities
- Submission of Clinical Center Certification form (CC) or (CCT) as applicable, a copy of IRB's notice of protocol approval and a copy of each approved consent statement (with letter or stamp of approval from the clinical center's IRB), consent checklist, highlighted consent and all other required approvals, materials and printouts to the certification coordinator at Data Coordinating Center **(mailed or faxed)**. (See Certification Checklist in MOP section 3.1.4 for complete list of required materials).
- Main clinical center should review and submit all materials for their satellite clinics
- **NOTE: Receipt of a notification of clinical center and staff certification from the Data Coordinating Center (via e-mail) is required. Clinics cannot perform screening visits (v1) until written notification of certification is received**

Facilities
- Secure area for drug storage
- Private area to conduct health interviews, assess eligibility, and provide patient education
- Secure area for storage of study supplies, documents, and forms
- Facilities for disposal of unused drug supplies

3.1.1. Clinical center and staff certification

Equipment and materials required of Clinical Center

- KoKo spirometer to measure FEV_1 and FVC
- Equipment to measure height and weight
- Pregnancy test kits
- NIOX MINO eNO equipment
- Computer requirements for data entry
  - Microsoft Windows (95, 98, ME, NT, 2000, XP, or Vista)
  - Microsoft Internet Explorer (5.0, 5.5, 6.0 or 7.0)
  - Adobe Acrobat Reader 5.0 or above (available free from www.adobe.com)
  - printer (recommended)

General study supplies

- See MOP section 3.2 for list of supplies needed to conduct trial, and how supplies are obtained

Forms (abbreviation)

- Clinical Center Certification (CC)
- Satellite Certification (CT)
- STAN Personnel Assurance Statement (PA)
- Methacholine Challenge Test Assurance Statement (MA)
- Diary Card (DC)
- Pulmonary Function Testing (PF)
- Spirometry Assurance Statement (SA)
- Methacholine Challenge Testing (MC)
- Participant Instructions for Methacholine Challenge Test (IME)
- Participant Instructions for Allergy Skin Test (IAT)
- Certification Skin Testing (CS)

3.1.2 Data system certification

Access to the STAN data system will be restricted to clinical center staff that have been certified for data entry. Each 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 STAN.

The tasks for data system certification are as follows:

- Review the protocol and data forms
- Have Lead Coordinator obtain PIN# from DCC if never previously assigned
- Complete STAN Personnel Assurance Statement (PA)
- Complete General (GEN) and Data System Operator (DSO) Knowledge Assessments online (see section 3.1.1 for instructions) and print out results
- Log onto STAN home page using PIN and password (see written directions below). If staff member has not previously created a unique password, use the default password "changeme"
  - Under Data System, click on Certification Data System
  - Follow instructions including entry of the practice CV, DC, and RZ forms
- Submit (fax) printouts from data entry "test" along with the STAN GEN, DSO and PA, if not previously submitted, to the certification coordinator at the Data Coordinating Center
- Receive email verification from Data Coordinating Center of certification and activation for STAN data entry

The data system will be accessed via the internet using Microsoft Internet Explorer (version 5.0 or higher) on a PC running Microsoft Windows (95/98/ME/NT/2000/XP). The data system is available from the STAN web page at http://www.jhcct.org/Secure/STAN/STANHome.htm. Access to any part of the STAN data system requires a PIN, password, and activation by the DCC.

Each 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 "TEST" clinic is available to all users for practice with the data system. For submitting forms for data entry certification, the "Certification" link on the data system page should be used, (not the "TEST" login.) After a staff member becomes certified, his or her PIN will be activated 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 "changeme." The system will instruct the user to create a unique password the first time that user logs in to the data system. From that time forward, only the user's unique passcode will work.

*STAN certification data system tutorial links to SARA data system tutorial for purpose of certification. If a coordinator has been certified to enter data for SARA, SARCA or MeCIS, they do not need to redo this exercise for STAN. In this case, please note this when submitting other certification materials.

3.1.3 Consent statement checklist

Clinic: _____ Reviewer: _____ Date of review: _____

STAN CONSENT CHECKLIST - based on Protocol version 2.0, 9 Apr 2010

The NIH requires the DCC to review each center's consent form for completeness. To be certified, the following items must be included in each center's STAN consent form in addition to statements required by your local IRB. **Review your consent form for items listed below before submitting to your local IRB.** If you are unclear as to the inclusion of certain items in your consent, you may submit this completed checklist and your consent to the DCC for review prior to submission to your IRB. For STAN certification, this completed checklist must be submitted to the DCC along with your IRB-approved consent (with items from the checklist highlighted) as part of your certification package.

Record the page where item is found in your consent (in left-hand space below) and highlight the statement in your consent.

_____ 1. Letter or stamp of approval from IRB with date approved and expiration of approval

_____2. Full name of trial – Study of Asthma and Nasal Steroids (STAN)

_____ 3. Sources of funding/sponsorship – American Lung Association (ALA) and National Institutes of Health (NIH)

_____ 4. Participant encouraged to read the consent form carefully and to ask questions

_____ 5. No access to certain medical information and test results during study, but can be obtained in medical emergency

_____ 6. Participation in this research study not meant to replace usual care for asthma. (Participant must have a primary asthma care physician or clinic that cares for his/her asthma)

_____ 7. You should inform your physician of participation in the study

_____ 8. Clinic will notify primary asthma physician that patient is participating in the study

_____ 9. Physician may be contacted during the study if patient has poor asthma control and needs additional care

_____ 10. Purpose of trial: To determine if adding treatment with nasal inhaled corticosteroid (mometasone) for chronic rhinitis and /or sinusitis improves asthma control

11. Procedures

_____ General description of chronic rhinitis and sinusitis

_____ List of inclusion criteria
- Asthma diagnosed by a physician
- Chronic rhinitis and sinusitis
- Poorly controlled asthma
- Males and females, 6 years and above

_____ List of exclusion criteria
- Diabetes, glaucoma, cystic fibrosis, immune disorder
- Recent sinus surgery
- Recent respiratory tract infection
- Currently on anti-leukotriene medication
- Have used systemic or nasal steroids in the past 4 weeks
- Ever had an adverse reaction to nasal steroids
- Current or habitual smoker
- Females who are pregnant or breastfeeding

_____ Approximately 380 people will participate

_____ To be conducted at network of clinical centers across the United States

_____ Length of participation about 6½ months

_____ General description of mometasone and placebo

_____ General description of randomization

_____ Study treatment masked to participant and clinic staff. Study doctor can find out treatment in an emergency

_____ Description of 5 clinic visits and 3 phone calls – questionnaires and procedures (physical exam, spirometry, nasal lavage, peak flow, allergy skin test, asthma diary, pregnancy screening, and exhaled nitric oxide and methacholine challenge, as applicable).

_____ Methacholine Challenge test done on a day separate from the clinic visit.

_____ Blood samples collected for this research to be kept for future study

_____ Blood collection for DNA genetic testing is optional and not required for participation in the study. Check box for participant to agree to or decline genetic testing

_____ Timeline of the 5 clinic visits and 3 phone calls

12. Risks/Discomforts

_____ Possible side effects of study drug (mometasone)
- nosebleeds, headache, upper respiratory tract infection, viral infections, sinusitis, sore throat, painful menstruation, muscle pain, coughing and other rare effects

_____ Possible side effects of study procedures
- Spirometry – chest soreness or lightheadedness from forceful blowing into spirometer
- Albuterol – nervousness, rapid heartbeat, headaches; rarely arrhythmias, low potassium
- Methacholine challenge – chest tightness, cough, shortness of breath or wheezing
- Nasal lavage – slight discomfort with sneezing and coughing
- Exhaled nitric oxide – light-headedness if blown too hard
- Peak flow – chest soreness or lightheadedness if used standing up
- Allergy skin testing - itching and local hive at the site of positive skin test, rarely may result in systemic allergic reaction
- Blood draw – bruising, fainting, inflammation or infection at site of venipuncture.

_____ Genetic testing - possibility that someone you did not approve sees and uses the DNA information. Procedures in place to guard against this.

_____ Safety of study treatment and methacholine during pregnancy/nursing unknown. Cannot participate if pregnant or breastfeeding. If participant becomes pregnant during the study, they must inform study doctor immediately

_____ Females who have reached menarche to have pregnancy tests at screening and before each methacholine challenge test

13. Benefits

_____ No guaranteed health benefit for participating

_____ Might experience a decrease in sinus and asthma symptoms; but no guaranteed health benefit

_____ Results of the research may benefit others

_____ Peak flow meter provided

14. Payment/cost for participation

_____ No cost to participant

_____ Some financial compensation

15. Voluntary nature of participation

_____ If decide not to participate, access to medical care at (site) will not be affected

_____ Can agree to be in the study now and change mind later. Information collected up to that point cannot be retracted

_____ Participation may be discontinued early by study physician for various reasons as listed

16. HIPAA/Confidentiality – how personal data is handled

_____ Information collected includes contact information and personal health information

_____ Any information with participant's name to be kept in a locked cabinet. Unique ID used in place of name

_____ Unique number and special code will be used in place of your name

_____ Organizations such as governmental agencies, participating doctors and staff, processing labs, and sponsors may see your health information

_____ Can cancel permission to use and disclose information. If withdraw permission to use information, your part in study will end. Cancellation will not affect data already collected

_____ 17. Compensation for injury – ALA, NIH, and the Federal government noted as not responsible. Participant and his/her insurance company are responsible for costs due to injury

_____ 18. Contact person – at least one name and number for questions, problems, or reactions to study drug (i.e., PI or coordinator)

3.1.3. Consent statement checklist

_____ 19. If you join this study you will not own the data or specimens given by you to the investigator for this research

_____ 20. Researchers may ask to see your health care records

_____ 21. Assent statement and/or line for child's signature or separate assent form

_____ 22. Signing of consent – spaces for signature and date for participant, parent or legally authorized representative (if applicable), and/or the study investigator or person obtaining consent

3.1.4 Clinic and staff certification checklist

Clinic _____

Satellite (if applicable) _____

STAN Certification Checklist

The following documents and procedures need to be completed by each main and satellite clinic. **Please check off items as applicable, and submit to the DCC with your certification package as the cover page.** All certification packets for satellite should be submitted by their main clinic.

Center Certification form

- ☐ Clinical Center Certification (CC) form (completed by Lead Coordinator only and signed by Principal Investigator)
- ☐ Satellite Certification (CT) form (completed by satellite staff and counter signed by lead coordinator at main clinic)

Study documents

- ☐ IRB notice of approval of STAN protocol (version 2.0)
- ☐ IRB approved consent statement with IRB stamp or notice of approval with consent "checklist" items highlighted
- ☐ Consent checklist denoting pages where items exist in the center's approved adult consent (if applicable)
- ☐ IRB approved assent statement with IRB stamp or notice of approval certification (as applicable)
- ☐ IRB approval to conduct allergy skin test certification procedure(if required by center IRB)
- ☐ HIPAA statement or other documents, if not included in main consent

All investigators/staff members requirements

- ☐ General STAN Knowledge Assessment (GEN) – printout from online test
- ☐ STAN Personnel Assurance Statement (PA)

Additional Center Director/Co- PI at satellite requirements

- ☐ Sign Clinical Center Certification (CC) form or Satellite Certification form (CT), as applicable
- ☐ Methacholine Challenge Test Assurance Statement (MA) form
- ☐ Spirometry Assurance Statement (SA) form
- ☐ FDA Conflict of Interest form (Form 3455)

3.1.4. Clinic and staff certification checklist

Additional Lead Coordinator requirements

- ☐ Complete Clinical Center Certification (CC) form
- ☐ Enter all new staff members seeking certification into the ACRC online directory
- ☐ Complete all certification procedures required for coordinator and data system operator; (if previously certified as data system operator for an ACRC trial, certification extends to STAN) Certification for methacholine challenge, allergy skin tester, spirometry tester and eNo tester strongly recommended for lead coordinators

Additional Coordinator requirements

- ☐ Complete sample STAN Diary Cards (DC) (2 weeks of diaries, starting on a Wednesday, using made up responses)
- ☐ Indicate on CC or CT form previous allergy skin testing certification or conduct certification practical exams (session 1 and 2) and complete CS form and IAT
- ☐ Indicate on CC or CT form previous methacholine challenge testing certification or conduct 1 Methacholine Challenge test and complete IME and MC forms - including:
  - printout of online calculator results
  - anonymized patient methacholine challenge test result report from which MC form was completed
- ☐ Indicate on CC or CT form previous spirometry certification for SOYA or conduct 1 pre and post spirometry procedure. Submission should include:
  - sample Pulmonary Function Testing (PF) form, with printout of online calculator results and patient pulmonary function test results report (patient name obliterated) from which the PF form was completed
- ☐ Submit a QA report to spiro@jhcct.org for grading
- ☐ Indicate on CC or CT form previous data entry certification or complete
  - online Data system knowledge assessment (DSO). Submit printout from online test
  - STAN Certification Data System exercise (link for Certification Data System on the STAN web page under Data System) and submit the 3 confirmation pages.

3.2 Study supplies

Bay View Medical Inc.

- Peak flow meters
  - Complete Peak Flow Meter Order Form (PO) and fax it to Bay View Medical Inc.
  - All orders received by 3 pm ET weekdays will arrive within five working days

Methapharm, Inc.

- Methacholine (Provocholine®) vials may be ordered at a discounted price using the Methacholine Order Form (MP) that is posted on the STAN website (http://www.jhcct.org/Secure/STAN/STANHome.htm)

Aerocrine

- Niox MINO sensor/filter kits
  - contact Maryan.fahim@aerocrine.com
    917-446-5429
  - Identify yourself as ACRC to get discounted price of $600 for 50 test kit or $1200 for 100 test kits
  - Sensors alone are the same price as the kit
- For sensor/filter kits for substudy, contact the DCC

Data Coordinating Center will distribute the following at the beginning of the study and as needed:

- Clinic Supplies
  - Sealed treatment unmasking envelopes
- Participant supplies
  - Asthma Action Plan cards
  - Canvas bags with ACRC logo
  - Labels for clinic contact information for participant binder
  - Magnets with ACRC logo
  - General Asthma Education materials
  - STAN Wallet Cards
  - 1" participant binders with STAN cover
- Specimen collection supplies
  - Serum for ECP and eotaxins
    - 3.5 mL serum separator clot activator tube
    - Two 1.2 mL cryovials
  - Whole blood for DNA analysis
    - 4 mL lavender EDTA coated vacutainer tube
  - Exhaled nitric oxide (eNO)
    - Aerocrine MINO eNO device
    - Patient Smart Card

  - Nasal lavage
    - Chux pad
    - Sterile specimen cups (3-4 oz)
    - 10 cc slip tip syringe
    - 1.2 mL cryovials
    - Transfer pipettes
    - Falcon polypropylene conical centrifuge tube (50cc or 50mL)
  - Allergy skin testing (some supplies previously distributed to clinics that participated in MeCIS)
    - Multi-Test II training DVD
    - Multi-Test II applicators (caterpillars)
    - Dipwell trays with cover
    - Pre-printed labels for Dipwell trays (for certification trays and for skin test allergens)
    - Allergen testing supply kit
      - Millimeter ruler
      - Timer
      - Transparent tape
      - Black felt tip pens
- General specimen supplies
  - Pre-printed Vacutainer Label Sheet
  - Pre-printed labels for cryovials
- Shipping supplies
  - Large Thermosafe styrofoam shippers (blood, serum, lavage sample)
  - Cryovial boxes
  - Plastic biohazard specimen bags (blood, serum, lavage sample)
  - Absorbent sheets (blood, serum, lavage sample)
  - Dry ice label (blood, serum, lavage sample)
- Methacholine testing supplies
  - Mouthpieces for nebulizer cups
  - Expiratory filters for T-piece
  - Step down adapters
  - T-pieces
  - Syringe filter for transferring MeCl solution to nebulizer cup

Data Coordinating Center will distribute the following upon request by Clinical Centers:

- Marking pens for labels
- 60" or 80" ACRC measuring tape (for waist, neck, and hip circumference)
- Characterized nebulizer cups for MeCl testing

Ordering additional supplies from Data Coordinating Center

- Complete STAN Order (ZO) form or ACRC General Order (GO) form, as applicable
- Fax request to: 775-871-4030; attention Debbie Amend-Libercci
- Requests should include number of items and date needed
- Shipment Receipt (SH) is included with shipment. Fax receipt to DCC when supplies are received

Clinical Centers will provide

- Blood collection supplies (needles, tourniquet, etc)
- Dry ice
- FedEx mailing labels
- Study forms and questionnaires (downloaded from STAN website (http://www.jhcct.org/Secure/STAN/STANHome.htm)
- Pregnancy test kits
- Nose clips for spirometry
- Mailing labels
- Disposable mouthpieces
- NIOX Mino replacement filters and sensors

Forms (abbreviation)

- Methapharm Order Form (MP)
- Peak Flow Meter Order Form (PO)
- STAN Supply Order Form (ZO)
- ACRC General Supply Order Forms (GO)

3.3 Participant binder

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

When
- Visit 1 (Screening)

Supplies
- 1" binder with STAN cover
- Labels, ML-1000

Instructions and materials included
- Information label - on front of inside pocket. Use ML-1000 labels provided by DCC or similar labels. For each clinical center or satellite print the mailing address for returning diary cards, study coordinator name, study physician name and clinic daytime and after hours phone numbers
- 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 Asthma Diary Cards (IDC) - place one copy of the instructions in the binder
- Asthma Diary Cards (DC) - fill out Diary Cards to cover run in and entire treatment period (treatment period is approximately 24 weeks). Clinics can create pre-filled Diary Cards by using the "pre-printed Diary Card" option on the STAN data system page (http://www.jhcct.org/Secure/STAN/STANHome.htm).
  - Fill out item 1 on each Diary Card if not pre-filled by data system. Note: For the first 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)
  - Fill out item one on each Diary Card if not pre-filled by data system
  - Give each card a sequential number in the box labeled "Diary Card #" in the bottom right of the form (optional)
- Spare Diary Cards - include 4-5 blank cards
- Temporary Asthma Action Plan Sheet (TAP)
- General Asthma Education material

Forms and instruction sheets (abbreviation)
- Diary Card (DC)
- Instructions for Asthma Diary Cards (IDC)
- Instructions for Measuring Peak Flow (IPF)
- Schedule of Visits (SOV)
- Temporary Asthma Action Plan Sheet (TAP)

3.4 Primary physician notification

3.4.1 Prototype: Physician introduction letter

Dear Dr. _____:

Your patient, _____, was recently enrolled in the clinical trial, the "Study of Asthma and Nasal Steroids" or STAN. This study is designed to test the hypothesis that patients with symptomatic rhinitis and/or sinusitis will have improved asthma control when receiving daily treatment with nasal inhaled corticosteroids. This randomized, double-masked, placebo-controlled trial involves 19 clinical centers in the United States and will enroll approximately 380 patients, 190 children and 190 adults, with poorly controlled asthma and chronic rhinitis/sinusitis. Participants will complete a series of questionnaires, diary cards, and pulmonary function tests as screening tools to confirm existing symptoms of chronic rhinitis/sinusitis and poorly controlled asthma. After screening procedures and a 2 to 4 week run-in period are completed, patients who meet eligibility criteria will be randomized to one of two treatment groups:

- Intranasal mometasone (Nasonex®)
  - Participants age ≥ 12 years: 2 sprays (100 µg) each nostril once a day
  - Participants age < 12 years: 1 spray (50 µg) each nostril once a day
- Matching placebo

Patients will receive the study nasal spray in addition to their regularly prescribed asthma medication. Treatment will last approximately 24 weeks with 2 follow-up clinic visits and 3 follow-up phone calls during the trial period. The trial will collect information concerning demographics, medical history, lung function results, as well as asthma and rhinitis/sinusitis symptoms (via diary cards and interviews).

An Asthma Action Plan card outlining how to respond to asthma symptoms will be distributed to all participants. Our clinic will provide study medication and monitoring of asthma symptoms during the study. However, your patient should continue to use you as their primary asthma care physician.

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 pulmonary function test. We will advise your patient to schedule an appointment with you to review his/her asthma treatment and to show you his/her treatment assignment and final spirometry results. Your patient will be counseled to follow the guidelines on his/her Asthma Action Plan card and told that he/she may contact our clinic for emergencies, if necessary, during the interim period.

Please feel free to contact our clinic (xxx-xxx-xxxx) or me personally if you have any questions.

Sincerely,

Principal Investigator
Institution Name

3.4.2 Prototype: Participant release to send spirometry results to asthma care providers

---

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

Title:	The Study of Asthma and Nasal Steroids (STAN)
Protocol No.:	IRB Name Protocol # XXXXX
Sponsor:	National Heart, Lung, and Blood Institute (NHLBI)/The American Lung Association (ALA) Bethesda, Maryland/New York, New York United States
Supporter:	Merck (formerly Schering Plough Corporation) Kenilworth, NJ 07033
Investigator:	Anne Dixon, MD 149 Beaumont Avenue Burlington, VT 05405
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 Anne Dixon, MD 802-847-6981 Research-related injury Robert Wise, M.D. 410-550-0545 443-287-5791 (24-hours)

3.4.2. Prototype participant release to send spirometry results to asthma care providers

SUB-INVESTIGATOR(S): Robert Wise, M.D.

Permission to Notify Physician (for subjects age ≥ 18):

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

_____
Printed Name of Subject

_____ _____
Signature of Subject Date

Permission to Notify Physician (for subjects age < 18):

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

_____
Printed Name of Subject

CONSENT SIGNATURE

_____
Printed Name of Subject's Parent or Legally Authorized Representative

_____ _____
Signature of Subject's Parent or Legally Authorized Representative Date

3.4.2. Prototype participant release to send spirometry results to asthma care providers

Authority of Subject's Legally Authorized Representative
or Relationship to Subject

CLINIC SIGNATURE(S)

Signature of Person Conducting Informed Consent Discussion — Date

Signature of Investigator (if different from above) — Date

3.4.3 Prototype: Physician exit letter

Dear Dr. _____:

Your patient, _____, recently completed participation in the clinical trial, the "Study of Asthma and Nasal Steroids" or STAN. This study is designed to test the hypothesis that patients with symptomatic rhinitis and/or sinusitis will have improved asthma control when receiving daily treatment with nasal inhaled corticosteroids. This randomized, double-masked, placebo-controlled trial involves 19 clinical centers in the United States and will enroll approximately 380 patients, 190 children and 190 adults, with poorly controlled asthma and chronic rhinitis/sinusitis. After screening procedures and a 2 to 4 week run-in period were completed, patients who met eligibility criteria were randomized to one of two treatment groups:

- Intranasal mometasone (Nasonex®)
  - Participants age ≥ 12 years: 2 sprays (100 µg) each nostril once a day
  - Participants age < 12 years: 1 spray (50 µg) each nostril once a day
- Matching placebo

Patients received the study nasal spray in addition to their regularly prescribed asthma medication. Treatment lasted approximately 24 weeks with 2 follow-up clinic visits and 3 follow-up phone calls during the trial period.

Your patient has now stopped taking the study medication and has received an envelope indicating the assigned study treatment and the results from his/her last pulmonary function test. We have recommended that your patient visit you within 3 weeks to review current asthma treatment and to show you the treatment assignment and the results of his/her final spirometry tests. Your patient was counseled to follow the guidelines on his/her Asthma Action Plan card and told that he/she may contact our clinic for emergencies, if necessary, during the interim period.

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

3.5 Peak flow procedures

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 all scheduled study clinic visits

Equipment

- Mini-Wright Peak Flow Meter (ordered from Bay View 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
    - At all clinic visits record on Pulmonary Function Testing (PF) form
    - Participant records daily on Diary Card (DC)
    - At Visit 1, record participant's personal best on Screening (SC) form and Temporary Asthma Action Plan sheet (TAP)

      Note: Personal best for Temporary Asthma Action Plan sheet (TAP) is the highest peak flow from Visit 1

    - At Visit 2, record participant's personal best on the Asthma Action Plan card (AAP)

Note: Personal best for AAP will be calculated by the STAN data system upon data entry of the Randomization (RZ) form. Personal best for AAP is defined as the highest value, reproducible within 10% from peak flows recorded on diary cards in the last 14 days

Forms (abbreviation)

- Diary Card (DC)
- Screening form (SC)
- Pulmonary Function Testing (PF)

Information sheets (abbreviation)

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

*not data entered

3.6 Spirometry

3.6.1 Spirometry procedures

Purpose

- Measure FEV_1 (the amount of air expired in the first second during a forced expiratory maneuver), FVC (forced vital capacity)

When

- Visits 1-5

By whom

- ACRC certified spirometry tester

Certification requirements

- All Spirometry testers for the ACRC must complete certification requirements approved by the DCC before they may conduct spirometry tests
- For certification, the spirometry tester should conduct 1 pre and post spirometry procedure. Record results on Pulmonary Function testing (PF) form. Submit the PF form along with the lab report (ACRC Spirometry Report from which the PF form was completed) and the print- out of online calculations
- Individuals that were previously certified and conducted spirometry tests in SOYA are not required to recertify.

Standardization of equipment and training

- KoKo spirometer using software version 4.11
- Equipment and procedures are based on the ATS recommendations for accuracy and precision
- All personnel performing spirometry should either be certified pulmonary function technologists (National Board of Respiratory Care) or receive sufficient instruction from qualified instructors to perform the procedure according to acceptable standards

Predicted values

- Calculated according to the published predicted values (Hankinson et al). Use values listed in Table 3.6.2 or calculate online using the STAN pulmonary function calculator. To access the online calculator go to the STAN website: http://www.jhcct.org/Secure/STAN/STANHome.htm and follow the link to the STAN data system page and then to the STAN calculator

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

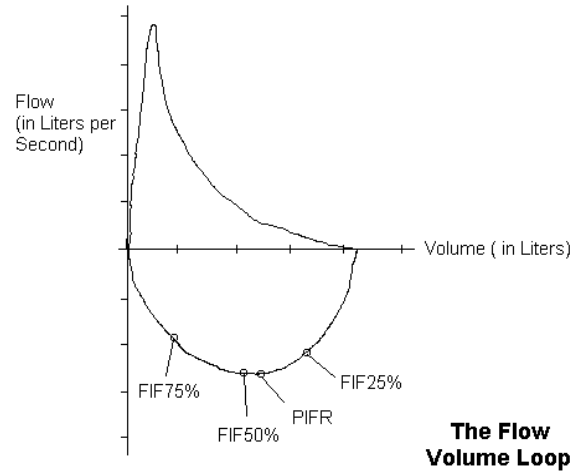
Participant preparation

- Test performed at least 4 hours after last dose of short-acting bronchodilator and at least 12 hours after the last dose of long-acting bronchodilator
- Participant is seated with feet flat on floor
- Participant is wearing noseclips
- Restrictive clothing is loosened

Testing procedure

- Instruct participant and demonstrate procedure
  - Lips should be sealed around the mouthpiece
  - Emphasize the necessity for deep, full inspiration, a hard and forceful expiratory "blast", a complete expiration for at least 6 seconds, and finally a forceful inspiration following the expiration (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 Flow Volume curve. Patients 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 patient to exhale SLIGHTLY less forcefully
  - **End of expiration:** When the expiratory effort lasts at least 6 seconds. Patients with severe obstructive lung disease may continue to exhale for 10 or more seconds. Occasionally, premature glottic closure causes abrupt test end. Patients 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 .2 L of the largest acceptable FVC
  - **FEV_1**: The second largest FEV_1 should be within .2 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
- The largest acceptable FEV_1 and FVC are recorded on the data collection form. These do not have to be taken from the same maneuver

- Inspiration may or may not be required but is shown in figure below.



The Flow Volume Loop

- 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 FEV_1 percent predicted value:
  - Use STAN online calculator from STAN website:
    http://www.jhcct.org/Secure/STAN/STANHome.htm
    Follow link to data system page and then to the STAN calculator
    OR
    Manually calculate using predicted FEV_1 value per Hankinson (formula in Table 3.6.2) and the following formula:
    Percent predicted = FEV_1/predicted FEV_1 x 100

Note: If your spirometry system uses Hankinson you must make sure the values obtained from your system are the same as those calculated by the STAN data system. Rounding conventions may be different causing discrepancies

Pre- and post-bronchodilator procedures

- Perform pre-bronchodilator spirometry on patient
  - Spirometry is performed before any bronchodilators are used
    - Short-term bronchodilator should be held for 4 hours prior to testing
    - Long-term bronchodilators should be held for 12 hours prior to testing
  - Record results on the Pulmonary Function Testing (PF) form
    - Pre-bronchodilator FVC (item 12 on PF form)
    - Pre-bronchodilator FEV_1 (item 13 on PF form)
- Administer bronchodilator
  - Administer 2 puffs of metered dose inhaler (MDI) albuterol
  - Wait 15 - 45 minutes after administering bronchodilator before retesting

  Note: For eligibility up to four puffs of albuterol may be used at V1 to obtain 12% reversibility

- Perform post-bronchodilator spirometry
  - Record results on Pulmonary Function Testing (PF) form
    - Post-bronchodilator FVC
    - Post-bronchodilator FEV_1
- Calculate pre- and post-bronchodilator percent predicted FEV_1
  - Use the following formula:
    Percent Predicted = FEV_1/predicted FEV_1 x 100
  - Percent predicted pre-bronchodilator FEV_1
    - Calculated using pre-bronchodilator FEV_1
  - Percent predicted post-bronchodilator FEV_1
    - Record on Pulmonary Function Testing (PF) Form

Forms (abbreviation)

- Pulmonary Function Testing (PF)
- Randomization (RZ)

References

- Hankinson, JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. Am J Resp Crit Care Med 1999; 159: 179 - 187
- Standardization of Spirometry - 1994 update. American Thoracic Society. Am J Resp Crit Care Med 1995; 152: 1107 - 1136
- Enright PL, et al. Spirometry in the Lung Health Study. Am Rev Resp Dis 1991; 143: 1215 - 1223
- Lung Function Testing: Selection of Reference Values and Interpretive Strategies. American Thoracic Society. Am Rev Resp Dis 1991; 144: 1202 - 1218

3.6.2 Table of Pulmonary Function Predicted Values

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

PFT	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 ethnic groups will be as for Caucasians
Participant's ethnic identity is self-defined
Adult $\geq$ 20 years old for males and $\geq$ 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.

3.7 Methacholine challenge

3.7.1 Overview

Methacholine bronchial challenge assesses the presence and degree of airway hyperresponsiveness to methacholine, a non-specific acetylcholine agonist. Airway responsiveness is described by the provocative concentration of methacholine causing a decrease in FEV_1 by 20% from post-diluent baseline (PC_{20}. All participants with $FEV_1 \geq 70\%$ predicted at V1, and who did not demonstrate either FEV_1 bronchodilator responsiveness $\geq 12\%$ or positive methacholine challenge in the past 2 years, will have a MeCl test.

3.7.2 Purpose and schedule

Purpose

- To measure airway reactivity to establish eligibility
- To assess whether treatment with a nasal inhaled corticosteroid affects methacholine challenge response

When

Methacholine challenge test is a V1 and V5 procedure. However, the methacholine challenge test and pre and post spirometry (also required at V1 and V5) cannot be conducted together. As such, the methacholine challenge test must be scheduled another day within the visit time window.

For V1: Schedule methacholine challenge test 1-2 weeks after Visit 1

For V5: Schedule methacholine challenge test 1-2 weeks prior to V5 but, after phone visit 3

3.7.3 Requirements for personnel administering the methacholine challenge

The methacholine challenge will be performed according to the methacholine protocol as outlined in this section of the MOP and which is posted on the STAN website (http://www.jhcct.org/Secure/STAN/STANHome.asp). The STAN methacholine protocol is based on ATS recommendations. The test is to be conducted by certified ACRC staff

For quality control and safety assurance, the following requirements must be met before any methacholine challenge tests are conducted

- All centers must use the KoKo spirometer, the external KoKo dosimeter, and characterized nebulizer cups. The nebulizer cups are supplied by DCC.
- The Principal Investigator (and Co-PIs at satellite clinics) must complete the Methacholine Challenge Test Assurance Statement (MA)
  - Submit the original completed statement to the certification coordinator at the DCC. A copy of the completed form should be kept on file at the clinical center
  - The assurance statement refers to all STAN methacholine challenge tests conducted at a clinical center. The statement asserts the following:
    - All methacholine challenge tests conducted at the clinical center and satellite clinics will be conducted in accordance with the STAN 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
- All methacholine challenge testers for the ACRC must complete certification requirements approved by the DCC before they may conduct methacholine challenge tests.

3.7.4 Certification requirements

- For certification, the methacholine challenge tester should instruct participant in preparation requirements for methacholine challenge and complete Instruction for Methacholine Challenge Test form (IME). Conduct 1 methacholine challenge test using the ACRC 10 step method and complete a Methacholine Challenge Testing (MC) form. Submit the MC form, the corresponding lab report (ACRC Methacholine Challenge report) from which MC form was completed, and print-out of the online calculator results (MeCl PC_{20} calculator) to the DCC
- Individuals that were previously certified for and conducted Methacholine Challenge tests in other ACRC are not required to recertify

3.7.5 Contraindications

Absolute contraindications

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

- FEV_1 less than 70% predicted or less than 1 L (using Hankinson predicted equations, or using the STAN online calculator). To access the online calculator access the STAN data system page through: http://www.jhcct.org/Secure/STAN/STANHome.asp and follow the link to the STAN calculator
- Myocardial infarction or stroke within last 3 months
- Known arterial aneurysm
- Uncontrolled hypertension (ie, SBP > 200, DBP > 100)
- Pregnancy or breast feeding (If participant is a women of child-bearing potential, a negative pregnancy test is required before every methacholine challenge test)
- Taking 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 patient has any of the following conditions:

- Epilepsy
- Bradycardia
- Vagotonia
- Peptic ulcer disease
- Thyroid disease
- Urinary tract obstruction
- Other conditions sensitive to cholinergics
- Current use of a cholinesterase-inhibitor medication

General contraindications

An acceptable methacholine test depends on the ability of a patient to perform acceptable spirometric maneuvers. If a patient is unable to perform reproducible and acceptable spirometry tests at baseline session, the methacholine challenge test should not be conducted.

3.7.6 Medications to hold prior to methacholine challenge testing

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 β-agonists	72 hrs
Inhaled/oral long-acting β-agonists	24 hrs
Anticholinergics	48 hrs
Liquid theophylline	12 hrs
Intermediate-acting theophylline	24 hrs
Sustained release theophylline	48 hrs
Antihistamines	48 hrs
Cromolyn	8 hrs
Nedocromil	24 hrs
Leukotriene modifiers	24 hrs
Inhaled steroids	no hold period

In addition, patient should be instructed to abstain from caffeine, cola drinks, and chocolate on the day of the test.

3.7.7 Other confounders

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

- Caffeine, cola 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.

3.7.8 Patient instructions

- Two to three days before the test, remind patient to
  - Hold medications as detailed in Section 3.7.6
  - Abstain from caffeine, cola drinks, and chocolate on the day of the test
  - Abstain from exercise and smoking for 6 hours before his/her methacholine challenge appointment

- Instructions prior to test
  - Keep explanation of the test as neutral as possible. Tell patients that they will inhale a mist of medication that could make them feel better, worse, or cause no change.
  - Ask if patient would like to use the bathroom before the test (stress incontinence could be precipitated)

3.7.9 Patient assessment

- Patients should be assessed prior to testing as to general physical condition and ability to perform the test. They should also be assessed regarding appropriate withholding of medications and other potentially confounding issues as above

- A pregnancy test should be done before each methacholine challenge test if the female participant is of child bearing potential

- Blood pressure should be taken before the test

3.7.10 Equipment and supplies

- Concentrations of methacholine solution (described in MOP section 3.12.10)
- KoKo External Dosimeter
- Step down adapter*
- T-pieces*
- Expiratory filters for T-piece*
- Characterized nebulizer(s)* (other nebulizers not acceptable)
- Mouth pieces for nebulizer cups
- Syringe for methacholine solutions
- Syringe filters for transferring methacholine solution to nebulizer*
- KoKo Spirometer (with nose clip, mouthpiece)
- Timer
- Oxygen
- Stethoscope, sphygmomanometer, pulse oximeter
- Resuscitation equipment
- Emergency medications including albuterol (MDI and for nebulization) and atropine
- Compressed air tank

Methacholine testing supplies and equipment not noted as supplied by DCC are the responsibility of the clinical center staff or pulmonary testing lab.

Methacholine (Provocholine®) may be ordered using the Methapharm Provocholine Order Form (MP)

*Supplied by DCC

3.7.11 Preparation of methacholine solutions for 10 step procedure

Methacholine must be compounded by a qualified individual (e.g., pharmacist) who has read and understands the protocol. The long dosing scheme recommended by the ATS 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.

Solutions are prepared using Provocholine® as follows:

Diluent will be 0.9% Normal Saline containing 0.4% phenol for preservative

- **Vial A** **16 mg/mL** 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 B** **8 mg/mL** remove 3 mL from vial A, transfer to another vial and add 3 mL of diluent. This makes a solution of 8 mg/mL (total vol = 6 mL)
- **Vial C** **4 mg/mL** remove 3 mL from vial B, transfer to another vial and add 3 mL of diluent. This makes a solution of 4 mg/mL (total vol = 6 mL)
- **Vial D** **2 mg/mL** remove 3 mL from vial C, transfer to another vial and add 3 mL of diluent. This makes a solution of 2 mg/mL (total vol = 6 mL)
- **Vial E** **1 mg/mL** remove 3 mL from vial D, transfer to another vial and add 3 mL of diluent. This makes a solution of 1 mg/mL (total vol = 6 mL)
- **Vial F** **0.5 mg/mL** remove 3 mL from vial E, transfer to another vial and add 3 mL of diluent. This makes a solution of 0.5 mg/mL (total vol = 6 mL)
- **Vial G** **0.25 mg/mL** remove 3 mL from vial F, transfer to another vial and add 3 mL of diluent. This makes a solution of 0.25 mg/mL (total vol = 6 mL)
- **Vial H** **0.125 mg/mL** remove 3 mL from vial G, transfer to another vial and add 3 mL of diluent. This makes a solution of 0.125 mg/mL (total vol = 6 mL)

3.7.11. Preparation of methacholine solutions for 10 step procedure

- **Vial I** **0.063 mg/mL** remove 3 mL from vial H, transfer to another vial and add 3 mL of diluent. This makes a solution of 0.063 mg/mL (total vol = 6 mL)
- **Vial J** **0.031 mg/mL** remove 3 mL from vial I, transfer to another vial and add 3 mL of diluent. This makes a solution of 0.031 mg/mL (total vol = 6 mL)

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

Storage of solutions

Solutions A-H may be stored up to 2 weeks in the refrigerator; however, Vial I and J, the lowest concentrations, may not be stored in the refrigerator longer than 24 hours.

OR

Solutions A-J 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.

3.7.12 Administration of methacholine challenge

1. All SOYA methacholine challenge tests will be performed using the following equipment:
   - KoKo spirometer running software version 4.11
   - 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 patient so that they will not know which dose they receive
4. Explain procedure to patient
5. Record baseline spirometry (best of 3 efforts)
   - Proceed if FEV1 ≥ 70% predicted and > 1.0 L
6. Begin challenge, starting with 2 mL of diluent:
   - Add 2 mL of diluent to nebulizer using a syringe with sterile filter; 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 patient place one end of the nebulizer in mouth and put on noseclips
   - Have patient exhale to 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 patient continue inhaling while the dose is being delivered. Have patient hold breath for about five seconds after reaching TLC
   - Repeat actual administration of solution four more times at each level keeping careful count of number of doses given
   - Record spirometry at 30 and 90 sec following the 5th breath, taking the highest FEV1 as the result for that time period. Obtain no more than 5 efforts to achieve acceptability and reproducibility criteria as set by ATS guidelines
7. Assess response:
   - If post-diluent FEV1 remains ≥90% of the baseline FEV1, proceed to the first methacholine dose
   - If post diluent FEV1 is < 90% but >80% of baseline FEV1, repeat diluent. (If after diluent repeated, FEV1 remains < 90% but >80% of baseline FEV1 proceed to first methacholine dose)
   - If post diluent FEV1 is ≤ 80% of baseline FEV1, terminate challenge

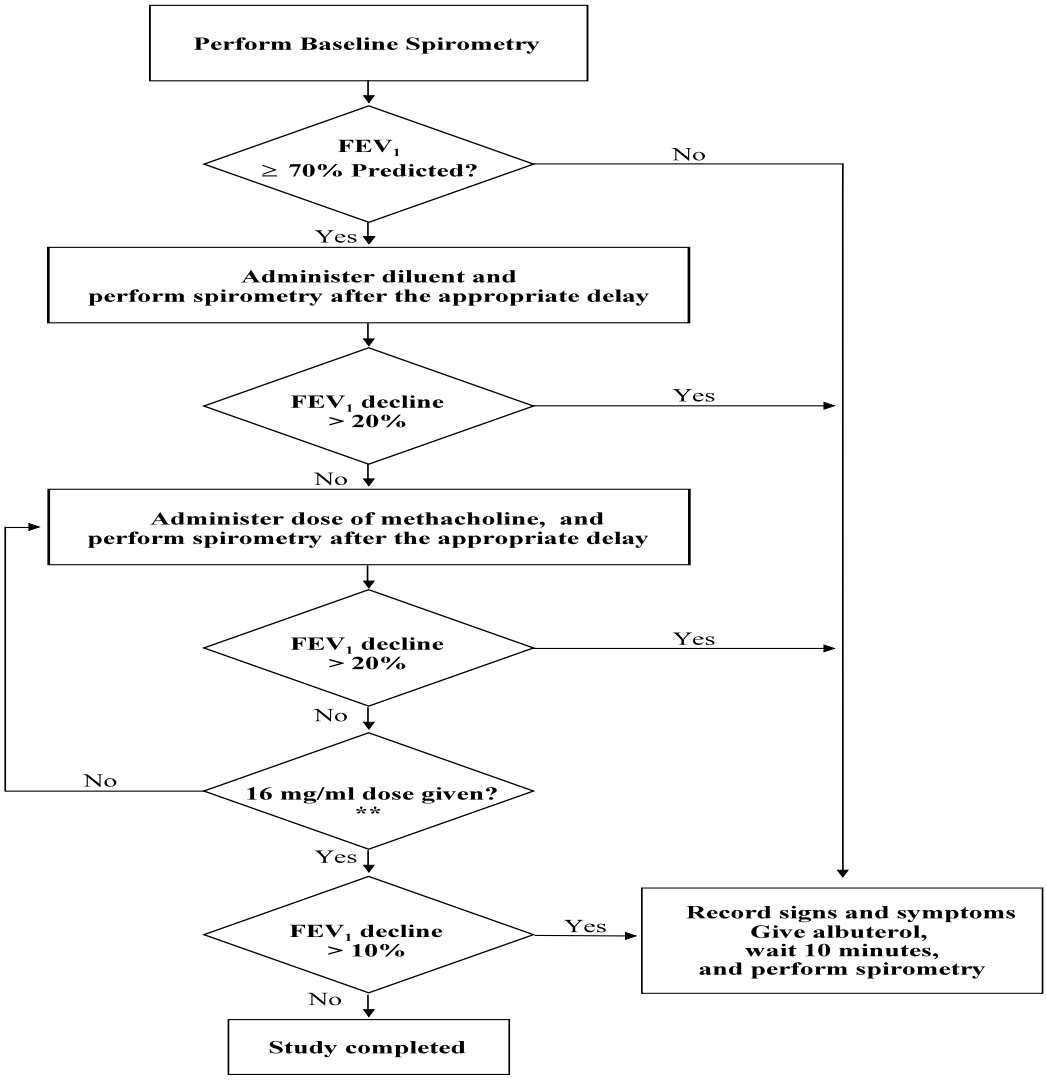
NOTE: The post diluent FEV1 will be considered the baseline for calculations of the PC20

8. 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
9. Follow procedure as outlined in #5-7 above
   - If the highest post methacholine FEV1 is > 80% of post diluent FEV1, proceed to the next dose (steps #5-7 above). **Note: even if one of the FEV1 measurements is ≤ 80% of post diluent FEV1 always base decision to proceed or terminate on highest FEV1 for that dose**
   - If the highest post methacholine FEV1 is ≤ 80% of the post diluent FEV1, terminate the challenge
10. Administration of bronchodilator
    - If the highest FEV1 from any dose is ≤80% of baseline (as found in Step #5) when the test is terminated or completed, administer 2 puffs bronchodilator (albuterol) by MDI with spacer. Wait 10 min and repeat spirometry. If post bronchodilator FEV1 is 90% or greater of baseline, the patient is finished and may leave the laboratory. If the post bronchodilator FEV1 is < 90% of baseline, administer 2 more puffs of albuterol, wait 10 min, and repeat spirometry
    - If FEV1 falls to < 90% of baseline FEV1 (as found in Step #5) when the test is terminated or completed, administer 2 puffs bronchodilator (albuterol) by MDI with spacer. Wait 10 minutes and repeat spirometry. If the post-bronchodilator FEV1 is < 90% of baseline, administer 2 more puffs of albuterol, wait 10 minutes and repeat spirometry

NOTE: Notify physician if post bronchodilator FEV1 remains < 90% of baseline

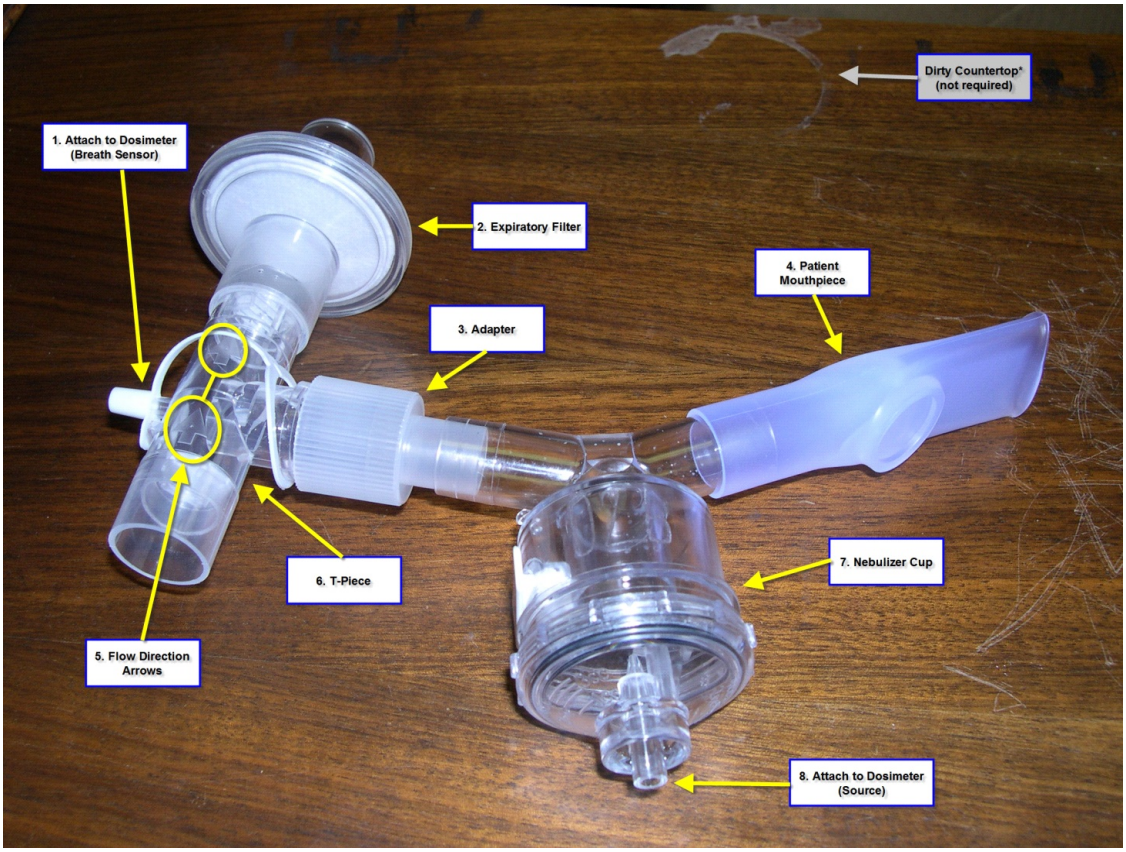
*unless your dosimeter/nebulizer has different requirements

3.7.13 ATS methacholine challenge testing sequence (flow chart)



3.7.14 Pictorial of equipment set-up

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 patient 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

3.8 Allergy skin testing

3.8.1 Purpose and timing

- To determine whether participant is atopic (allergic) so as to ascertain whether atopic status has an effect on response to nasal steroids
- Conducted at V2 unless contraindicated
- Tester must be ACRC certified for skin allergy testing - see section 3.8.6. Testers who were certified for MeCIS do not need to be re-certified.

3.8.2 Forms and supplies

Forms
- Allergy Skin Testing form (ST)
- Certification Skin Testing form (CS)
- (Participant) Instructions for Preparation of Allergy Skin Test (IAT) *distributed at V1*
- Greer Order Form (AO) - for ordering allergen extracts from Greer Laboratories

Supplied by the DCC
- MULTI TEST II training DVD
- MULTI TEST II devices (sterile, disposable, 8 head applicator; used to apply the allergens and simultaneously puncture the skin) aka 'caterpillars'
- 2 dipwell trays with covers
- Pre-printed labels for dipwell tray lids (one for certification tray and one for skin testing tray)
- Metric disposable rulers and plastic metric rulers
- Timer
- Transparent tape 5/8" wide or wider
- Fine point black felt tip pens for marking allergen test sites and outlining wheals on skin

Supplied by clinic
- Permanent marking pen for dipwell trays and dipwell tray labels
- Isopropyl alcohol swabs
- Cotton for blotting
- Tongue depressor to use to test for dermatographia
- Injectable epinephrine
- Elocon or other cortisone cream
- 16 'scratch test' allergen extracts
  - 12 core allergens
    Negative control
    Cockroach mix
    Rat epithelia

Alternaria alternata
Positive control
Standardized house dust mite mix
Mouse epithelia
Penicillium mix
Cladosporium herbarum
Dog epithelia
Standard cat hair
Aspergillus mix

– 4 local allergens chosen by clinical center (required)

Procedures for ordering scratch test mixtures from Greer Laboratories:

- If you do not already have an account with Greer, set up account:
  - Contact Greer at 800-378-3906 or customercare@greerlabs.com
  - Information needed:
    Doctor's name, medical liciense, and specialty
    Your name and contact information
    Billing address
    Shipping address
    Special information (e.g., if you and/or your shipping center are closed on certain days)
- Complete STAN Greer Order Form (AO) which is posted under forms on STAN webpage
  - 12 core allergen scratch test extracts are pre-entered
  - Write in four local allergen scratch test extracts - *to identify the item # and dilution of local allergens your PI has selected for your clinic, you will need to download the human catolog from Greer website:* http://www.greerlabs.com/index.php/human_allergy/catalog/
- Mail or fax form to Greer Labs:
  PO Box 800
  639 Nuway Circle NE
  Lenoir, NC 28645
  T: 800.378.3906
  F: 800.419.7302

Storage and information for 'scratch test' allergen extracts

- Store in refrigerator (4º C, approximately 39º F); never freeze
- Bacteriostatic and hygroscopic; will stay potent, stable, and free from evaporation in dipwell when properly stored
- Do not use after expiration date on extract bottle
- Use only for scratch testing (e.g., Multi-test II); do not use for intradermal testing

3.8.3 Contraindications

Absolute contradindications
Do not conduct test on participant if any of the following apply:

- Previous severe or systemic reaction to prick-puncture skin testing
- Use of a beta-adrenergic antagonist (beta blocker) *see section 3.8.8 for common beta blockers*
- Dermatographia (*condition in which lightly scratching the skin causes raised, red lines; skin cells are overly sensitive to minor injury, such as scratching*)

Relative contraindications
Permission from supervising physician required to proceed with test if participant has one of the following:

- Symptoms of an acute asthma exacerbation
- FEV1 below 70% predicted on day of test

3.8.4 Confounders

- Participant should have been asked to hold medication and herbal supplement as listed below. See section 3.8.9 for comprehensive list of medications in each category.
- Test should be conducted even if participant has not held medications/supplements
- Tricyclic and doxepin antidepressants also are confounders but participants will not be asked to hold these medications
- Data on confounders will be recorded on ST form

First-generation antihistamines *(eg, Actifed, Benadryl, Tavist, Theraflu, Triaminic, most allergy, cold or flu medications)*	3 days
H_2 antagonists *(eg, Axid, Pepcid, Tagamet, Zantac)*	3 days
Herbal supplements *(eg, astragalus, feverfew, green tea, licorice, milk thistle, saw palmetto, St. John's Wort)*	3 days
Topical nasal antihistamines *(eg, Astelin)*	5 days
Second-generation antihistamines *(eg, Allegra, Clarinex, Claritin, Zyrtec, Astelin)*	7 days

3.8.5 Safety procedures

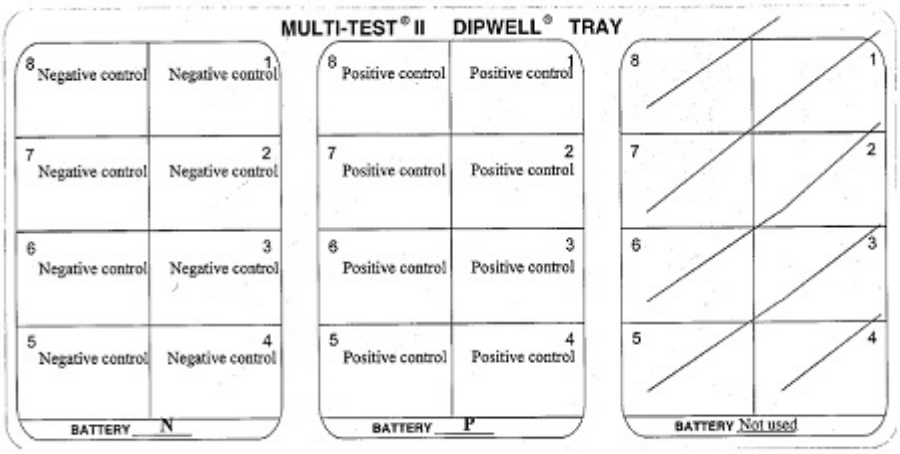
- Rarely, in very sensitive subjects, allergen skin testing can provoke a systemic-allergic reaction (anaphylaxis) resulting in urticaria, difficulty breathing and swallowing, asthma, and hypotension
- Anytime skin testing is performed the following are required
  - Injectable epinephrine - recommended dose is 0.3 cc of 1:1000 solution given subcutaneously or intramuscularly
  - Physician knowledgeable in anaphylaxis treatment readily available

3.8.6 Certification procedures

Certification requirements

- Watch the 15-minute Multi-Test II training DVD
- Complete certification practical exam sessions 1 and 2
- Send completed Certification Allergy Skin Testing form (CS) to CC certification coordinator

Dipwell tray setup for certification tests



- Supplies needed
  - Dipwell tray with lid, and instructions in sealed plastic pouch
  - Pre-printed lid label for CERTIFICATION provided by DCC
  - Permanent marking pen
  - Negative and positive control scratch test extracts
- Label the blue tray lid using the pre-printed ‘certification' label provided by the DCC (label goes over the words MULTI-TEST DIPWELL TRAY)
- Separate clear plastic tray from blue lid
- Orient blue lid so that you can read numbers
- Orient clear plastic well tray with ‘guideposts' toward top
- On the well tray below each group of 8 wells is a small etched square
  - Use permanent marker to label first group of 8 wells “N” and second group “P”
  - The third group of 8 wells will not be used
- Put negative control in each of the first set of 8 wells (N)
  - Fill dropper and while removing dropper from vial, wipe exterior surface of dropper against vial mouth to remove excess solution
  - Insert dropper into well and move tip of dropper to well bottom; squeeze bulb; withdraw dropper while continuing to squeeze bulb; while still squeezing bulb, place dropper back in vial to refill; this should be enough for 25 tests
  - For accurate testing, there must be at least 3 drops in well
- Put positive control in each of the second set of 8 wells (P)
- Store in refrigerator (4º C , approximately 39º F)

Certification practical exam

- Watch 15 minute MULTI-TEST training DVD prior to doing practical exam
- Assemble supplies
  - MULTI TEST II devices
  - Dipwell tray set up for certification test
  - Isopropyl alcohol swabs
  - Timer
  - Cotton for blotting
  - Disposible millimeter ruler or clear plastic metric ruler
  - Transparent tape 5/8" wide or wider
  - Fine point black felt tip pen
  - Elocon or other cortisone cream
  - Certification Allergy Skin Testing form (CS)
  - Injectable epinephrine

- Practical exam session 1
  - Objective: to demonstrate 100% negative controls
  - Obtain informed consent from volunteer per local institutional requirements
  - Screen volunteer for contraindications listed in section 3.8.3
  - Review medications holds (see section 3.8.9)

If volunteer has used a confounder within the recommended hold period, reschedule test or use another volunteer as it may not be possible to achieve an acceptable certification test

- Confirm that a physician capable of treating a systemic reaction is available
- Confirm that injectable epinephrine is at hand
- Cleanse the volunteer's forearm (inside surface) with alcohol
- Use Multi-Test II device to apply the "N" group (8 negative controls) to forearm
  - Dip MUTI-TEST II device (device) into first 8 allergen extracts in well tray ("N" group)
  - Orient device with the "T-bar" end up and press into forearm applying enough pressure to leave impression of point pattern from each test head
  - If test site is on rounded part of forearm, a gentle rocking motion may be required (end to end and side to side) to ensure penetration of all test head points
  - Bleeding should not occur and discomfort should be minimal
  - Discard used MUTI-TEST II device in accordance with local regulations
- Using felt tip pen, make an identification mark "N" on forearm at the top (‘T-bar end) of the testing site
- Blot off the drops carefully to avoid cross contamination
- Set timer for 20 minutes
- Do not leave volunteer alone during wait time
- After 20 minutes, outline each wheal (bump) with a fine point felt tip pen
- Transfer each outline to Certification Skin Testing (CS) form with a piece of transparent tape (one piece of tape per wheal)
  Use the CS form to guide you through the remaining steps
- Measure largest diameter and perpendicular diameter of each wheal. In examples below, the heavier line is the largest diameter and the lighter line is the perpendicular diameter (i.e., largest diameter perpendicular to the largest diameter)

- Calculate the mean diameter of each wheal by adding the largest diameter and perpendicular diameter and then dividing the sum by 2
- If any wheal has mean diameter equal to or greater than 3 mm at 20 minutes, the test has failed. Redo session 1 a new volunteer.
- If all wheals have a mean diameter less than 3 mm at 20 minutes
- Calculate the average mean diameter of all 8 tests (*add mean diameters of all 8 wheals and divide by 8*)
- Calculate 30% of the average mean diameter (*average mean diameter multiplied by .30*)
- If the mean diameters for all 8 tests are within 30% of the average mean, you have successfully completed session 1 of the practical exam

  - If the mean diameters for all 8 tests are not within 30% of the average mean, repeat session 1 with careful attention to the depth of the puncture. You may use the same volunteer or another volunteer. If you use the same volunteer, use volunteer's untested arm or if you want to use the same arm, wait several hours until skin has cleared on tested arm.

- Practical exam session 2
  - Objective: to demonstrate reproducibility
  - Obtain informed consent from volunteer per local institutional requirements
  - Screen volunteer for contraindications listed in section 3.8.3
  - Review medications holds (see section 3.8.9)

    If volunteer has used a confounder within the recommended hold period, reschedule test or use another volunteer as it may not be possible to achieve an acceptable certification test
  - Confirm that a physician capable of treating a systemic reaction is available
  - Confirm that injectable epinephrine is at hand
  - Cleanse the volunteer's forearm (inside surface) with alcohol
  - Use Multi-Test II device to apply the "P" group (8 positive controls) to forearm
  - Using felt tip pen, make an identification mark "P" on forearm at the top ('T-bar end) of the testing site
  - Blot off the drops carefully to avoid cross contamination
  - Discard used MUTI-TEST II device in accordance with local regulations
  - Set timer for 20 minutes
  - Do not leave volunteer alone during wait time
  - After 20 minutes, outline each wheal (bump) with a fine point felt tip pen
  - Transfer each outline to Certification Allergy Skin Testing (CS) form with a separate piece of transparent tape for each wheal

  Use the CS form to guide you through the remaining steps

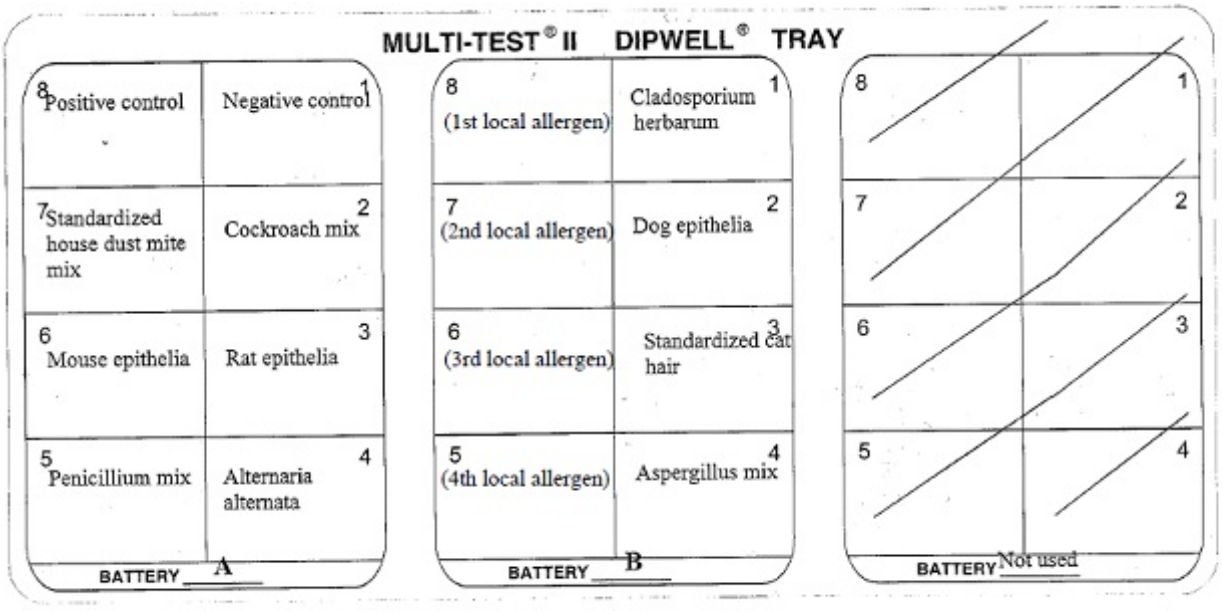
  - Measure the largest diameter and the perpendicular diameter (i.e., largest diameter perpendicular to the largest diameter)

  Calculate the mean diameter of each wheal

    - Calculate the average mean of all 8 tests (add means of all 8 means and divide by 8)
    - Calculate 30% of the average mean (average mean multiplied by .30)
    - If the mean diameter for all tests are all within 30% of the average, you have successfully demonstrated reproducibility and are finished with practical exam session 2
    - If the mean diameter for all tests are not all within 30% of the average mean, repeat the 8 tests with careful attention to the depth of the puncture and begin a new CS form. You may use the same volunteer or another volunteer. If you use same volunteer use untested arm or wait several hours until skin has cleared on tested arm.

3.8.7 Allergy skin test procedures

Dipwell tray set-up with allergen 'scratch test' extracts



- Supplies for dipwell tray setup
  - Dipwell tray with lid
  - Pre-printed label for dipwell tray lid with names of 12 core allergens (provided by DCC)
  - Permanent marking pen
  - 16 'scratch test' allergen extracts: 12 core allergen extracts and 4 local allergens identified by clinic
- Label the blue tray lid using the pre-printed label with 12 core allergens provided by the DCC as shown above
  - label goes on the blue lid surface over words " Multi-Test Dipwell Tray"
  - write the names of the four local allergens in 'well set B' numbers 5-8
- Separate clear plastic well tray from blue lid
- Orient clear plastic dipwell tray so that 'guideposts' are towards the top and you can read the numbers
- On the well tray below each group of 8 wells is a small etched square
  - Use permanent marker to label first group of 8 wells "A" and second group "B"
  - Third group of 8 wells will not be used
- Using the pre-printed label on the blue tray lid as your guide, proceed to put allergen extracts into corresponding wells

  - Fill dropper and, while removing dropper from vial, wipe exterior surface of dropper against vial mouth to remove excess solution
  - Insert dropper into well and move tip of dropper to well bottom; squeeze bulb and withdraw dropper while continuing to squeeze bulb; while still squeezing bulb, place dropper back in vial to refill. Repeating for a total of two times will give you enough extract for about 50 tests.
  - Never fill well higher than line at cap volume and always fill each well with equal amounts
- Store in refrigerator (4º C, approximately 39º F)
- Allergen extracts remain potent in well tray until their expiration date

Administering allergy skin test

- Person conducting test must be certified - see section 3.8.6
- Assemble supplies
  - Allergy Skin Testing form (ST)
  - MULTI TEST II devices (2 needed for each test)
  - Dipwell tray with allergen extracts
  - Isopropyl alcohol swabs
  - Timer
  - Cotton for blotting
  - Disposible metric ruler or clear plastic ruler
  - Transparent tape 5/8" wide or wider
  - Fine point black felt tip pen
  - Elocon or other cortisone cream
    - Injectable epinephrine
- Screen participant for contraindications (section 3.8.3)
- Review medications holds (see section 3.8.9) and record any confounders on ST from
  - Confirm that physician is readily available in the event of systemic reaction
  - Confirm injectable epinephrine is present
  - Clean inside surface of participant's forearm (palm side) with isopropyl alcohol and allow it to dry
  - Use Multi-Test II device to apply the "A" group of 8 allergens extracts to forearm
    - Dip MUTI-TEST II device into first 8 allergen extracts in well tray “A” group
    - Orienting MUTI-TEST II device with the "T-bar" end up, press into forearm applying enough pressure to leave impression of point pattern from each test head
    - If test site is on rounded part of forearm, a gentle rocking motion may be required (end to end and side to side) to ensure penetration of all test head points
    - Bleeding should not occur and discomfort should be minimal
  - Using felt tip pen, make an identification mark "A" on forearm at the top (‘T-bar end) of the testing site
  - Using a new MULT-TEST II device, apply "B" group of 8 allergens to another part of forearm and make an identification mark "B" on forearm at the top (‘T-bar end) of the testing site

- Gently blot the allergen drops with a cotton to remove excess fluid to avoid cross contamination
- Set a timer for 20 minutes; do not leave participant alone during wait time
- When timer goes off, gently wipe off the sites with alcohol and allow it to dry
- Outline each wheal with a fine point felt tip pen (wheal is the raised bump or welt)
- Transfer each outline to the corresponding box on Skin Testing (ST) form with a piece of transparent tape (one piece of tape per wheal)
- Use isopropyl alcohol to remove felt tip pen marks from participant's forearm
- If desired, apply Elocon or other cortisone cream to affected area

Interpretation

- Positive tests are those in which the application of an allergen produces a wheal (bump), with a flare, where the wheal has the mean diameter of at least 3 mm or more than the mean diameter from the negative control. *For example, if a participant has a mean diameter of 2 mm for the negative control, then a positive test for this participant would be defined as a reaction with a mean diameter of at 5 mm or greater.*

3.8.8 Common beta blockers

Use of a beta-blocker is an exclusion criteria for allergy skin testing for safety reasons.

Some of the common Beta-blockers	
Brand name	**Generic**
Atenolol	Tenormin
Betapace	sotalol
Blocadren	timolol
Cartrol	carteolol
Coreg	carvedilol
Corgard	nadolol
Corzide	nadol/ bendroflunetazide
Inderal	propranolol
Inderide	propranolol/HCTZ
Kerlone	betaxolol
Levatol	penbutolol

Some of the common Beta-blockers	
Brand name	**Generic**
Lopressor	metoprolol
Normodyne	labetalol
Sectral	acebutolol
Tenoretic	atenolol/HCTZ
Timolide	timolol/HCTZ
Toprol	metoprolol
Trandate	labetalol
Visken	pindolol
Zebeta	bisoprolol
Ziac	bisoprolol/HCTZ
Eye drops containing beta blockers	
Betagan	levobunolol
AK Beta	levobunolol
Betoptic	betaxolol
Optipranolol	metipranolol
Ocupress	carteolol
Timoptic	timolol

3.8.9 Medications to hold prior to allergy skin test

The following medications/supplements are known or suspected to interfere with skin testing.

If participant does not observe medication holds for the following medications, skin testing should still be conducted and the medications will be treated as confounders

Antihistamines

First-generation antihistamines - withhold 3 days before testing

4-way cold tablets

A.R.M.
Actifed
Actifed Cold & Allergy Tablets
Actifed Cold & Sinus Caplets
Allerest
Ambenyl cough syrup
Atarax
Atrohist
Benadryl
Benadryl Allergy Chewables
Benadryl Allergy Kapseal
Benadryl Allergy Liquid Medication
Benadryl Allergy Sinus Headache Caplets & Gelcaps
Benadryl Allergy Ultratabs Tablets
Benadryl Allergy/Cold Tablets
Benadryl Allergy/Congestion Liquid Medication
Benadryl Allergy/Congestion Tablets
Benadryl Dye-Free Allergy Liquid Medication
Benadryl Dye-Free Allergy Liqui-Gels Softgels
Bromfed
Children's Tylenol Allergy-D Liquid and Chewable Tablets
Children's Tylenol Cold Liquid and Chewable Tablets
Children's Tylenol Cold Plus Cough Suspension Liquid and Chewable Tablets
Children's Tylenol Flu Suspension Liquid
Children's Vicks NyQuil Cold/Cough Relief
Chlor- Trimeton Allergy Decongestant Tablets
Chlor- Trimeton Allergy Tablets
Codimal
Comhist
Comtrex
Contac Severe Cold & Flu Caplets Maximum Strength
Contact
Coricidin
Coricidin HBP Cold & Flu Tablets
Coricidin HBP Cough & Cold Tablets
Coricidin HBP Nighttime Cold & Flu Tablets
CTM
Deconamine
Dimetane- DC /DX
Dimetapp
Dimetapp Cold & Fever Suspension
Diphenhydramine HCL
Dristan
Drixoral Cold & Allergy Extended Release Tablets

Drixoral Cold & Flu Extended Release Tablets
Extendryl
Extra Strength Percogesic Aspirin-Free Coated Caplets
Fedahist
Hismanal (withhold 3 months)
Isoclor
Kronofed
Marax
Nolahist
Nolamine
Optimine
PBZ
PediaCare Cough-Cold Liquid
PediaCare NightRest Cough-Cold Liquid
Pediatric Vicks 44M Cough & Cold Relief
Percogesic
Percogesic Aspirin-Free Coated Tablets
Periactin Phenergan
Polaramine
Robitussin Nighttime Honey Flu
Rondec
Ru-Tuss
Ryna Liquid
Ryna-C Liquid
Rynatan
Sinarest
Singlet Caplets
Sinulin
Sinutab Sinus Allergy Medication, Maximum Strength Formula, Tablets & Caplets
Sudafed Cold & Allergy Tablets
Tacaryl
Tavist
Tavist Allergy 12-Hour Tablets
Teldrin
Temaril
TheraFlu Flu and Cold Medicine
TheraFlu Maximum Strength Flu and Cold Medicine for Sore Throat
TheraFlu Maximum Strength NightTime Flu, Cold & Cough Caplets
TheraFlu Maximum Strength NightTime Flu, Cold & Cough Hot Liquid
TheraFlu Maximum Strength Sore Throat and Cough Flu, Cold and Cough Hot Liquid
TheraFlu, Cold and Cough Medicine
Triaminic
Triaminic Cold & Allergy Soft chews
Triaminic Cold & Cough Soft chews

Triaminic Night Time
Triaminic Severe Cold & Fever
Triaminic Triaminicol Cold & Cough
Trinalin
Tussionex
Tylenol Allergy Sinus NightTime, Maximum Strength Caplets
Tylenol Allergy Sinus, Maximum Strength Caplets, Gelcaps, and Geltabs
Tylenol Cold Complete Formula, Multi-Symptom Tablets and Caplets
Tylenol Flu NightTime Maximum Strength Gelcaps
Tylenol Flu NightTime Maximum Strength Powder
Tylenol PM Pain Reliever/Sleep Aid, Extra Strength Caplets, Geltabs and Gelcaps
Tylenol Severe Allergy Caplets
Tylenol Sinus NightTime, Maximum Strength Caplets
Vicks 44M Cough, Cold & Flu Relief
Vistaril

Second-generation antihistamines - withhold 7 days before testing
Allegra (fexofenadine)
Clarinex (desloratadine)
Claritin (loratadine) – now over the counter
Zyrtec (cetirizine)
Topical nasal antihistamines (withhold 5 days before testing)
Astelin (azelastine)

H2 Antagonists - withhold 3 days before testing.
Axid (nizatidine)
Pepcid (famotidine)
Tagamet (cimetidine)
Zantac (ranitidine)

Herbal Supplements - withhold 3 days before testing.
Astragalus
Feverfew
Green Tea
Licorice
Milk Thistle
Saw Palmetto
St. John's Wort

Confounder medications not held

Antidepressants -

We will not ask participants to hold any antidepressants but use of these confounders needs to be reported on ST form. Except for doxepin, the following antidepressants should be reported as confounders if taken in the 3 days prior to skin testing. Doxepin should be reported if taken in the 7 days prior to testing.

Adapin (doxepin)
Amitriptyline
Anafranil (clomipramine)
Asendin (amoxapin)
Clomipramine
Desipramine
Desyrel
Doxepin
Elavil (amitriptyline)
Endep (amitriptyline)
Etrafon
Imipramine
Limbitrol
Ludiomil
Maprotiline
Norpramin
Nortriptyline
Pamelor
Pertofrane
Protriptyline
Sinequan (doxepin)
Surmontil
Tofranil
Triavil
Trimipramine
Vivactil

3.9 Exhaled NO measurement

Purpose

- Measure the fractional concentration of nitricoxide (NO) in exhaled breath (eNO) and ambient NO using the NIOX MINO®

When

- Visits V2 and V5 before spirometry and methacholine challenge testing

Whom

- eNO operators are not certified but do need to be trained by an Acrocrine representative or someone previously trained by Aerocrine

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.
- Ambient NO will also be measured using the same device.
- Participant empties lungs, and then inhales deeply through the filter to total lung capacity, followed by slow exhalation though the NIOX® filter until the continuous sound ceases and steady light is turned off.
- The measurement result is displayed on the display screen

Equipment and supplies

Equipment for Testing

NIOX MINO® unit (supplied by DCC)

The Initial NIOX MINO test supply kit (50 NIOX patient filters, one 50-test sensor, and two test cards)

NIOX MINO® test cards (blue)

- 2 cards formatted to STAN labeled STAN A and STAN B. Use one of these cards, e.g., STAN A, for STAN tests until DCC collects that test card to achieve tests at DCC. Then begin to use other card, e.g., STAN B.

NIOX® MINO patient filter

NIOX MINO® sensor

Replacement supplies

- Each ACRC NIOX MINO came with a 50 test kit (a 50 test sensor and 50 filters). The 50 test sensor is good for 50 tests, for 9 months after the sensor is placed in the MINO, or until the manufacturer's expiration date, whichever comes first. Once 50 tests have been conducted or 9 months have passed, clinical centers will need to purchase a new test kit from Aerocrine at the discounted price of $600 for a 50 test kit or $1200 for a 100 test kit. These costs should be covered by the SOYA capitation payments.

Note that the manufacturer's expiration date should not be the limited factor in the life of your sensor. *Contact the DCC if this should occur.*

- To ensure that you get the special ACRC price, please place your order by contacting Maryan Fahim and identifying yourself as part of the ACRC group. Do not order new sensors more than 2-3 weeks in advance of need, i.e., when the sensor will be placed in MINO.

  Maryan.fahim@aerocrine.com
  917.446.5429

  Note: Aeocrine staff track the expiration date of each QC filter and will send you a new filter at the appropriate time at no cost.

Equipment for Quality Control

- NIOX MINO® QC card (white) (supplied by DCC)
- NIOX MINO® QC filter for Weekly QC testing (supplied by DCC)

Quality Control requirements for the NIOX MINO®:

- Calibration by the user is not required
  The NIOX MINO® has standardized internal procedural controls that cannot be influenced by the user. Whenever a potential deviation is detected, the appropriate message is presented on the display making it impossible to continue the measurement or alternately, the procedure is aborted. A measurement result is only presented to the operator when the device handling and measurement processes are correctly executed.
- The QC test for the NIOX MINO® is a biologic control (Normal Control Tester).
- A "daily" QC test is required on the days when eNO testing is done.

- An extended/Weekly QC test should be performed at initial set-up, every 7 days, and when a new sensor is placed in the NIOX MINO.

Selection of Normal Control Testers for QC

- Identify staff members who will serve as the Biologic Control (Normal Control Tester) 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 sinonasal disease or asthma

Initial "Qualification" of Normal Control Tester

- Each Normal Control Tester should have a White QC card with their name written on it.
- With the White QC card inserted into the NIOX MINO, the selected staff member will perform a total of three eNO measurements.
- Only one eNO measurement should be performed per day and all three measurements should be completed within seven days.
- A mean value is calculated from the three measurements. If the mean value is between 5-40ppb it is considered acceptable and the Normal Control Tester is "Qualified".
- Subsequent QC test results from this Normal Control Tester must be within ± 10ppb of the mean value to be a PASS.
- Each normal control tester must perform a QC procedure (daily or extended/weekly) at least once every 28 days to maintain his/her qualification status.

Performing the QC tests:

- Before any QC measurement, the Normal Control Tester should:
  - Avoid nitrate rich food for 3 hrs
  - Avoid any strenuous exercise at least 1 hour
- A Normal Control Tester should not perform a measurement in case of:
  - Ongoing respiratory infection
  - Acute seasonal allergies

➢ **The "Daily" QC procedure**

- "Daily" is a misnomer; a Daily QC is required only on days the NIOX MINO is to be used for participant testing. *(A twinkling star next to the breathing cloud on the NIOX MINO screen indicates the Daily QC needs to be conducted.)*
- The Daily QC consists of a standard eNO test performed by a qualified Normal Control Tester with his/her White personal QC card inserted into the NIOX MINO.

- The steps for the Daily QC test are as follows:
  - Remove the Blue Test card from the NIOX MINO device and insert the White personal QC card of the qualified Normal Control Tester doing the QC test.
  - The Normal Control Tester should conduct a standard exhalation test (see below for Test Procedures) and wait (1:40 min.) for the screen to display the result.
  - The screen displays the mean value (X) and the difference (▵) between the mean value and the day's QC test value.
  - If the difference (▵) is within ± 10 ppb of the Tester's mean value, then the test result is approved and the Daily QC procedure is complete.
    - Remove the White personal QC card and reinsert the Blue NIOX MINO test card
    - Press the return arrow for return to the menu screen.
  - *If the difference between the Tester's mean value and the day's QC test value is more than ±10 ppb, restart the QC procedure with another qualified tester*
  - *If the second testers result is not approved, do not proceed with eNO testing. Contact Aerocrine at service.US@aerocrine.com or call (866)275-6469.*

➢ **The Weekly/Extended QC test**

- The Weekly QC test, also known as the Extended QC procedure, needs to be done as part of the initial set-up, every 7 days, and when a new sensor is placed in the MINO. *(An alternating QC icon and breathing cloud on the MINO screen indicates a Weekly/Extended QC procedure needs to be conducted.)*
- The Weekly/Extended procedure consists of:
  - A normal control measurement completed by a qualified normal tester (as done for the daily QC)
  - A measurement of a nitric oxide free sample using the NIOX MINO QC filter *(The NIOX MINO® QC filter produces a nitric oxide free sample. When the instrument completes its analysis of this sample, it should display a result below the detection limit (< 5 ppb) of the instrument.)*
    - After completing the procedure for the "daily" QC test as above, without removing the White personal QC card, attach the QC filter to the NIOX MINO patient filter opening, then attach the NIOX filter to the QC filter.
    - Touch the display screen to activate the instrument.
    - Perform an exhalation test (see below for Test Procedures) and wait (1:40 min.) for the result.
    - If the reading is < 5 ppb, the extended/weekly QC test is complete.
      - Remove the QC filter and the White Personal care from the NIOX MINO.
      - Insert the Blue NIOX MINO card.
      - If the reading is not < 5 ppb, the QC has failed and you need to contact Aerocrine at service.US@aerocrine.com or call (866)275-6469.

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.

Participant preparation:

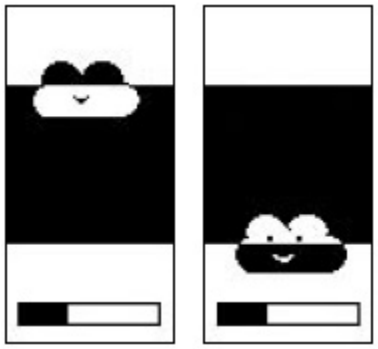
- Study participants should be instructed to avoid any food or drink for one hour prior to eNO testing.
- Study participants also should avoid any strenuous exercise or smoking for one hour prior to eNO testing.
- If possible, participants should avoid bronchodilator use for 2 hours before eNO testing
- eNO measurement should be done before spirometry and methacholine challenge testing
- If the participant has an acute upper and/or lower respiratory infection, note this on the NO form.
- If participant used inhaled or oral corticosteroids on the day of the test, record time of most recent use on NO form.
- Do NOT use nose plugs.

Test Procedures:

- KEEP DEVICE POWERED AT ALL TIMES (including overnight).
- Make sure the NIOX MINO® sensor is in place.
- Insert the Blue test card into the unit.
  - Each clinical center has been provided with 2 formatted ACRC blue test cards
  - Choose one card and continue to use it for all participant tests until the DCC asks you to send in this "active" card. At this point, you will start using the second card for all participant tests.
  - The DCC will download the test data from the "active" (first) test card and return the empty test card to you for use the next time the DCC collects the "active" test card for download.
- Insert a NIOX MINO® patient filter into the unit.
- Make sure the patient is seated during the entire procedure.
- Touch the display screen. When the top light on the unit is lit, the unit is ready for measurement of eNO.
- The participant empties the lungs first, and then inhales deeply through the filter to total lung capacity. The cloud on the display is inflated and the top light is turned off during inhalation. Next, the participant exhales slowly through the NIOX® filter. Visual guidance is provided by the top light and there is also a continuous sound to guide the participant. The participant can also view the display using a mirror.
  You can instruct the patient as follows;
  - First empty your lungs by breathing out as much as possible
  - Next inhale deeply through the filter to total lung capacity
  - Then exhale slowly through the NIOX MINO® filter

As the patient exhales, listen to the sound signals and watch the top light - a continuous sound and a steady light means the test is OK.

Correct exhalation display



Exhalation too hard (left or too low (right)

- When the exhalation is approved, the sound ceases with a click, and the top light turns off.
- Wait (1:40min.) for the result to be displayed on the screen.
- Record the result on the Nitric Oxide (NO) form.
  - If result of eNO <5 ppb, record "0" ppb.
- Repeat the test and record results from second test on NO form
- If results are not consistent between tests, note this on NO form and comment on possible problems.

Proceed to measure the ambient NO

- Select the "information menu" on the display screen, and then select "Ambient measurement". It takes about 3.5 minutes to measure the Ambient NO.
- Record the Ambient NO value on the Nitric Oxide (NO) form.

Forms (abbreviation)

- Nitric Oxide form (NO)

Exhaled Nitric Oxide Comparison Sub-study

Purpose

- To assess the device -to-device variability and repeatability of eNO measurements using the NIOX MINO®.

When

- Visits V2 and V5 before spirometry and methacholine challenge testing

Where

- Selected ACRC clinics that have two NIOX MINO® devices.

3.9. Exhaled NO measurement

Equipment and supplies (supplied by clinic)

- Two NIOX MINO® units. For identification purposes, please label the units as MINO "A" and MINO "B".
- NIOX MINO® test supplies
- Clinics participating in the substudy were provided with 2 test cards labeled "ACRC B". Use one of the ACRC B tests cards for the substudy. The DCC will collect the test cards periodically to archive the tests. At that point you will use the other "ACRC B" card for the substudy tests.

Overview

- A convenience sample including 10-20 individuals from each center participating in the sub-study.
- Participants will have replicate measurements of eNO using two NIOX MINO® devices (MINO "A" and MINO "B").
- To ensure that there is no bias created by testing order, the order in which the devices are tested will be randomly assigned at each clinic visit.
- Ambient NO will also be measured with each unit and recorded on NO form

Procedures

- Log on to the STAN data system: http://www.jhcct.org/Secure/STAN/DataSystem/STANMenu.asp
- Click on "STAN eNO Comparison Sub-study Randomization", enter the participant information, click "yes" to "randomize eNO instrument testing order", click "done"
- The data system will provide you with order of testing this needs to be done at each clinic visit. Enter this information on the NO form (item #14). **Note that the order of testing should be obtained from the data system for each study visit.**
- Have the study participant perform two eNO tests on the first NIOX MINO® (as per the testing order) and then two eNO tests on the second NIOX MINO®.
- Measure the Ambient NO using each unit and record the values for each unit on the NO form

Forms (abbreviation)

- Nitric Oxide form (NO)

3.10 Specimen collection

3.10.1 Overview of specimen collection schedule

- **Visit 2**
  - Blood draw for ecp, eotaxins and DNA
  - Nasal lavage
- **Visit 5**
  - Blood draw for ecp and eotaxins
  - Nasal lavage

3.10.1. Overview of specimen collection schedule

Visits	Specimen	Collection tube	Label	Processing	Action
V2	Packed blood cells for Pharmacogenetic analysis (DNA)	- 4 mL purple top vacutainer	Vacutainer: Designated label from Vacutainer Label Sheet	• Centrifuge 5 minutes at 2000g, 4°C • Immediately remove plasma from vacutainer and discard plasma • Replace vacutainer top and freeze packed cells at -70°C	• Batch ship (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
V2, 5	Blood serum for eotaxins and ecp levels	- 3.5 mL red/grey top serum separator vacutainer - Two 1.2 mL cryovials	Vacutainer: Designated label from Vacutainer Label Sheet Cryovials: Designated labels from Cryovial Label Sheet	• Collect 3.5 mL blood in a serum separator vacutainer • Invert tube 10 times • Clot at room temperature for 30 minutes • Centrifuge at 1000g for 15 minutes within one hour of collection • Transfer serum into two 1.2 mL cryovials and immediately place on ice • Freeze at -70°C	• Batch ship (frozen) priority overnight to : Jayanthi Garudathri Vermont Lung Center at UVM HSRF 227 149 Beaumont Avenue Burlington, VT 05405 Upon shipment, send email to: jayanthi.garudathri@uvm.edu
V2, 5	Nasal lavage	- Sterile 3-4oz specimen cup - Falcon polypropylene conical centrifuge tube (50cc) -Five 1.2 mL cryovials	Cryovials: Designated labels from Cryovial Label Sheet	• Pour content of 3-4oz specimen cup into Falcon polypropylene conical centrifuge tube • Centrifuge at 2500g at 4°C for 15 minutes • Aliquot into five 1.2 mL cryovials • Store at -20°C	• Batch ship (frozen) priority overnight to: Jayanthi Garudathri Vermont Lung Center at UVM HSRF 227 149 Beaumont Avenue Burlington, VT 05405 Upon shipment, send email to: jayanthi.garudathri@uvm.edu

3.10.2 Blood draw for ECP and Eotaxins

Purpose:
- To collect serum for eotaxin and eosinophil cationic protein

When
- Visits 2 and 5

Preparation

Supplies for Collection and Processing
- Supplied by DCC
  - 5 mL serum separator clot activator tube (red/gray tops)
  - Two 1.2 mL cryovials
  - Labels from Vacutainer Label Sheet
  - Labels from Cryovial Label Sheet (see section 3.9.6 for example)
  - Transfer pipette

- Supplied by clinic
  - Lab marking pen
  - Needle (appropriate gauge for age of participant)
  - Needle holder
  - Gloves
  - Swabs for cleaning blood draw site
  - Band-Aids
  - Emergency supplies readily available
  - *EMLA cream acceptable for pediatric patients, if approved by individual IRB*

Collection

Collection Tasks
- Prepare labels with marking pen. Fill in Participant ID and Visit ID
- Affix vacutainer label onto serum separator
- Draw 5 mL blood into labeled Serum separator tube
- Gently invert tube 10 times
- Allow to clot at room temperature for 30 minutes
- Centrifuge at 1000g for 15 minutes within one hour of collection
- Transfer serum with pipette into each cryovial and immediately place on ice
- Affix cryovial label with Participant ID and Visit ID to each cryovial, covering with a piece of scotch tape
- Immediately place cryovial tubes in -70° C freezer and hold specimens for batch shipment at a later date.

3.10.2. Blood draw for ECP and Eotaxins

If -70° C freezer is unavailable, samples may be stored at -20° C for up to one week.

Shipping supplies

- Supplied by DCC
  - Styrofoam box with outer cardboard box
  - Plastic biohazard specimen bag
  - Absorbent sheet
  - Dry ice label
  - UN3373 label
- Supplied by clinic
  - Dry ice
  - FedEx air bill

Shipping Tasks

- Samples may be batched and shipped every 3 months
- Make sure clinic staff members preparing shipments
  - are up-to-date with current IATA and DOT regulations regarding Category B and dry ice shipments
  - have completed compliance training
- Specimens must remain frozen throughout the packaging and shipping process
- Cryovials
  - Organize cryovials in cryovial box and record positions on specimen storage grid (Section B) on Specimen Transmittal Sheet (TS)
  - Place cryovial box and absorbent sheet in plastic specimen bag (8" x 8"); press lock
  - Place completed Specimen Transmittal Sheet (TS) into sleeve of specimen bag. Retain copy of ST form
  - Place specimen bag in styrofoam box
- Add a generous amount (at least 10 pounds) of dry ice to box and fill remaining space with padding (bubble wrap is acceptable)
- Affix proper labels on outside of cardboard box
  - UN3373 label
  - Dry ice label (with weight of dry ice and shipper/consignee name and addresses)

3.10.2. Blood draw for ECP and Eotaxins

- Complete air bill and ship to:

Jayanthi Garudathri
Vermont Lung Center at UVM
HSRF 227
149 Beaumont Avenue
Burlington, VT 05405
Phone: (802) 656 9984

  - Use FedEx account number: 4895-1772-8
  - Ship on Monday, Tuesday, or Wednesday only, and not within 3 days of a holiday
  - Ship Priority Overnight
  - For item #6, Special Handling, indicate “Yes, Shipper’s Declaration not required”
  - For item #6, Special Handling, check "Dry Ice" and fill in weight of dry ice in kilograms (3 pounds = 1.5 kg)
  - Shipment does not contain dangerous goods (only specimens for diagnostic purposes)

- Immediately upon shipment of specimens notify the lab with tracking information by sending an email to:

Email: jayanthi.garudathri@uvm.edu

Form (abbreviation)

- Specimen Transmittal Sheet (TS)

3.10.3 Blood draw for DNA

Purpose:
- To collect packed blood cells for DNA analysis

When
- Visits 2

Note: Do not save DNA specimen without participant consent. Item 29 on the Randomization Form (RZ) must be marked as yes to donate and store DNA.

Supplies for Collection and Processing
- Supplied by DCC
  - 4 mL EDTA vacutainer (lavender top)
  - Label from Vacutainer Label Sheet (see section 3.10.5. for example)
- Supplied by clinic
  - Lab marking pen
  - Needle (appropriate gauge for age of participant)
  - Needle holder
  - Gloves
  - Swabs for cleaning blood draw site
  - Band-aids
  - Scotch tape
  - Emergency supplies readily available

Collection Tasks
- Prepare label with marking pen. Fill in Pt ID and Visit ID
- Affix vacutainer label lengthwise onto vacutainer. Place Scotch tape lengthwise over the label so that the tape completely covers the label and adheres to the tube on either side.
- Draw 4 mL of blood into labeled vacutainer
- Gently invert tube 10 times
- May store at 4° C for up to 30 minutes
- Centrifuge at 2000g for 7 minutes at 4° C
- Remove the plasma (upper layer) with a transfer pipette. Discard plasma.
- Replace top on vacutainer tube
- Immediately place vacutainer in -70° C freezer. Lay the tube horizontal in the freezer for 20 min prior to storing it upright, otherwise expansion of ice crystals may crack the tube.

Shipping supplies

- Supplied by DCC
  - Styrofoam box with outer cardboard box
  - Plastic biohazard specimen bag
  - Absorbent sheet
  - Dry ice label (UN 1845)
  - UN3373 label

- Supplied by clinic
  - Dry ice
  - FedEx air bill

Shipping Tasks

- Batch ship frozen within three months of collection
- Make sure clinic staff members preparing shipments
  - are up-to-date with current IATA and DOT regulations regarding Category B and dry ice shipments
  - have completed compliance training
- Specimens must remain frozen throughout the packaging and shipping process
- Place frozen specimens and an absorbent sheet in plastic specimen bag (8" x 8"); press lock
- Place completed DNA Specimen Transmittal Sheet (DT) into sleeve of specimen bag. Retain copy of ST form
- Place specimen bag in styrofoam box
- Add a generous amount (at least 3 pounds) of dry ice to box and fill remaining space with padding (bubble wrap is acceptable)
- Affix proper labels on outside of cardboard box
  - UN3373 label
  - Dry ice label (UN 1845) with weight of dry ice and shipper/consignee name and addresses
- Complete air bill and 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

- Use FedEx account number: 4895-1772-8
- Ship on Monday, Tuesday, or Wednesday only, and not within 3 days of a holiday
- Ship Priority Overnight
- For item #6, Special Handling, indicate "Yes, Shipper's Declaration not required"
- For item #6, Special Handling, check "Dry Ice" and fill in weight of dry ice in kilograms (3 pounds = 1.5 kg)
- Shipment does not contain dangerous goods (only specimens for diagnostic purposes)

• Immediately upon shipment, notify lab by sending email to:
emougey@nemours.org

Form (abbreviation)

• DNA Specimen Transmittal Sheet (DT)

3.10.4 Nasal lavage

Purpose
- To collect lavage fluid for analysis of eotaxins and eosinophilic cationic protein (ecp)

When
- Visits V2 and V5

Supplies for collection and processing
- Chux pad
- Sterile specimen cups (3-4oz)
- Lab marking pen
- Patient gown
- Gloves
- Paper tissues
- Sterile normal saline, warmed to body temperature
- 10 mL slip tip syringe
- Five 1.2 mL cryovials
- 50cc conical centrifuge tube
- Labels from Cyrovial Label Sheet (see section 3.9.6. for example)

Preparation for conduct of nasal lavage
1. Gather supplies
2. Place Chux pad on preparation surface

Participant preparation
1. Have subject wear a patient gown during procedure. Gown can go over their clothes
2. Have subject in sitting position
3. Explain procedure to subject
4. Don gloves
5. Have patient gently blow their nose
6. Instruct patient to take a deep breath and perform a Valsalva manoeuvre.

Instruct patient to tilt head back-extended 30 degrees ("Look at the ceiling") and close their soft palate to prevent saline from draining down the back of their throat - instruct them to pull tongue to back of mouth, push against palate and hold breath

Specimen Collection
For Adult patients:
1. Instill 10 mL normal saline warmed to body temperature into one nostril. Have subject keep head extended back for 10 seconds after nostril is filled

2. Have subject bring their head forward and let the saline drip from nostril into sterile specimen cup. Then blow lightly to maximize saline recovery.
3. Repeat entire procedure in opposite nostril (can collect in same specimen cup)

For Children:

1. Instill 5 mL normal saline warmed to body temperature into one nostril. Have subject keep head extended back for 10 seconds after nostril is filled
2. Have subject bring head forward and let the saline drip from nostril into sterile specimen cup. Then blow lightly to maximize saline recovery.
3. Repeat entire procedure in opposite nostril (can collect in same specimen cup)

Processing

- Centrifugation
  - Pour content of the specimen cup into 50cc conical centrifuge tube. Collect about 5-15ml for adult and 2.5-8 mL for child.
  - Centrifuge sample at 2500g at 4°C, for 15 minutes.
  - Aliquot into 1.2 mL labeled cryovials (of liquid for assay), prepare **up to** 5 aliquots depending on return, then store at -20°C.

Shipment of Nasal Lavage samples

Shipping Tasks

- Samples may be batched and shipped every 3 months
- Make sure clinic staff members preparing shipments
  – are up-to-date with current IATA and DOT regulations regarding Category B and dry ice shipments
  – have completed compliance training
- Specimens must remain frozen throughout the packaging and shipping process
- Cryovials
  – Organize cryovials in cryovial box and record positions on specimen storage grid (Section B) on Specimen Transmittal Sheet (TS)
  – Place cryovial box and absorbent sheet in plastic specimen bag (8" x 8"); press lock
  – Place completed Specimen Transmittal Sheet (TS) into sleeve of specimen bag. Retain copy of ST form
  – Place specimen bag in styrofoam box
- Add a generous amount (at least 10 pounds) of dry ice to box and fill remaining space with padding (bubble wrap is acceptable)

- Affix proper labels on outside of cardboard box
  - UN3373 label
  - Dry ice label (with weight of dry ice and shipper/consignee name and addresses)
- Complete air bill and ship to:

Jayanthi Garudathri
Vermont Lung Center at UVM
HSRF 227
149 Beaumont Avenue
Burlington, VT 05405
Phone: (802) 656 9984

  - Use FedEx account number: 4895-1772-8
  - Ship on Monday, Tuesday, or Wednesday only, and not within 3 days of a holiday
  - Ship Priority Overnight
  - For item #6, *Special Handling*, indicate “Yes, Shipper’s Declaration not required”
  - For item #6, *Special Handling*, check "Dry Ice" and fill in weight of dry ice in kilograms (3 pounds = 1.5 kg)
  - Shipment does not contain dangerous goods (only specimens for diagnostic purposes)
- Immediately upon shipment of specimens notify the lab with tracking information by sending an email to:
  jayanthi.garudathri@uvm.edu

Forms (abbreviation)

- Specimen Transmittal Sheet (TS)

STAN

Vacutainer Label Sheet

– Cut through blank row; place labels in participant file; affix labels to vacutainers –

Visit 2

Vacutainer - red/gray
STAN Serum
Pt ID: __ __ __ __ __
Visit ID: __ __

Vacutainer - lavender
STAN DNA
Pt ID: __ __ __ __ __
Visit ID: __ __

Visit 5

Vacutainer - red/gray
STAN Serum
Pt ID: __ __ __ __ __
Visit ID: __ __

Visit 2

Vacutainer - red/gray
STAN Serum
Pt ID: __ __ __ __ __
Visit ID: __ __

Vacutainer - lavender
STAN DNA
Pt ID: __ __ __ __ __
Visit ID: __ __

Visit 5

Vacutainer - red/gray
STAN Serm
Pt ID: __ __ __ __ __
Visit ID: __ __

Visit 2

Vacutainer - red/gray
STAN Serum
Pt ID: __ __ __ __ __
Visit ID: __ __

Vacutainer - lavender
STAN DNA
Pt ID: __ __ __ __ __
Visit ID: __ __

Visit 5

Vacutainer - red/gray
STAN Serum
Pt ID: __ __ __ __ __
Visit ID: __ __

STAN Cryovial Label Sheet

Each column contains all necessary cryovial labels for one participant for V2 and V5

STAN serum #1

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN serum #2

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN lavage #1

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN lavage #2

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN lavage #3

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN lavage #4

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN lavage #5

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN serum #1

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN serum #2

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN lavage #1

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN lavage #2

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN Lavage #3

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN Lavage #4

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN Lavage #5

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN Serum #1

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN Serum #2

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN lavage #1

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN lavage #2

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN lavage #3

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN lavage #4

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN lavage #5

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN Serum #1

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN Serum #2

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN lavage #1

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN lavage #2

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN lavage #3

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN lavage #4

Pt ID: __ __ __ __ __

Visit ID: __ __

STAN lavage #5

Pt ID: __ __ __ __ __

Visit ID: __ __

3.11 Randomization

Purpose

- Assign participant to a study nasal spray treatment
- Avoid or minimize bias in treatment assignments
- Marks official enrollment into trial
- Random assignment to 1 of 2 treatment groups

When

- V2, after all screening and eligibility procedures are completed, and all baseline data are collected
- SC form from V1 must be entered before randomization

Tasks

- Review screening and baseline procedures for eligibility
- Have eligibility confirmed by clinic investigator
- Key RZ form into STAN data system while participant is physically in the clinic
- Data system will assign a Kit ID and treatment dose
- Upon data entry of RZ form, data system will calculate peak flow cut-off values for Asthma Action Plan; record these values on Asthma Action Plan card
- Print randomization page and attach to RZ form; store in participant's file
- Dispense assigned Kit
  - Fill in required information on kit labels
  - Complete DD form (see MOP section 3.11.2)
- If assigned Kit ID is not available at clinical center, contact DCC immediately

Forms (abbreviation)

- Randomization (RZ)
- Drug Dispensing and Counting Form (DD)
- Screening Form (SC)

3.12 Study drug administration and accountability

3.12.1 Study drug description, procurement, and storage

Note: Clinics should use the Drug Dispensing and Counting Form (DD) to record dispensing, counting, and destruction of study drug kits packaged in bottles. Receipt, issuance, and destruction of study drug kits packaged in bottles should be recorded on the Study Kit Accountability log (DA) and the Patient Bottle Accountability log (PD). Please contact the DCC with questions.

Treatment groups

- Intranasal mometasone (Nasonex®) spray
- Intranasal placebo spray (Schering-Plough/Merck)

Study drug administration

- Depending on participant age at randomization, one or two sprays of nasal steroid or matching placebo are to be taken once daily in the morning
- Participants less than 12 years of age at randomization administer one spray per nostril once a day in the morning (ie, total of 2 sprays)
- Participants age 12 years and older at randomization administer two sprays per nostril once a day in the morning (ie, total of 4 sprays)

Study drug packaging

- Study drug is packaged in a box called a "kit"
- Each kit has its own unique Kit ID
- Participants are assigned by the data system to a specific Kit ID
- Each kit box contains 7 nasal spray bottles (3 bottles and 4 spares for participants less than 12 years; 6 bottles and 1spare for participants 12 or older)
- Each nasal spray bottle contains 17 grams of Nasonex or matching placebo

Procurement of randomization kits

- Randomization kits are automatically supplied to clinics
  - Upon clinic certification, DCC will notify STAN Drug Distribution Center to send initial supply of four kits
  - Data-entering a Randomization (RZ) form will automatically generate a notice to Drug Distribution Center to send another randomization kit to clinic
- Randomization kits may be manually ordered by the clinic *only in unusual circumstances*; i.e., two or more randomizations expected within one week

Procurement of replacement kits

- The randomization kit is designed to supply a participant with an adequate amount of nasal spray for the entire trial
- If a nasal spray bottle is lost or destroyed, there should be spare bottles in the randomization kit, however, should there be a need a clinic can order a replacement kit using the STAN Drug Distribution System

- Replacement kits will arrive at the clinic with the participant ID already recorded on the kit label

To access STAN Drug Distribution website for drug orders:

- To order study drug manually, a coordinator must be certified for data entry
- Go to http://www.jhcct.org/Secure/STAN/STANHome.asp
- Under "Data System," click on "Data Entry System (real data entry)"
- Log-in using clinical center ID, coordinator PIN, and personal password (see MOP section 3.1.2 for more details)
- Click on "STAN Drug Distribution system"
- To place an order for randomization kits (only in unusual circumstances; randomization kits are automatically supplied)
  - Click on "Order Randomization Kit"
  - Follow instructions to place order as indicated and confirm
  - Contact DCC with any problems or special requests
- To place an order for a replacement randomization kit
  - Click on "Order Replacement Randomization Kit(s)"
  - Enter the Participant ID, namecode, clinic ID, and randomization kit ID from the participant's original randomization kit (assigned by the randomization system at V2)
  - Kit ID must be entered in this format: N-XXXX
  - Click on "Continue" and follow instructions to place order as indicated and confirm
- Clinics generally will receive kit(s) 3 to 4 days after receipt of order by the STAN Drug 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

Receipt and storage

- Upon receipt of study drug, sign packing slip and fax to STAN Drug Distribution Center
- Record receipt, dispensing, and transfer of study drug on Drug Accountability Log (DA)
- Maintain one Drug Accountability Log for all kits
- Maintain a separate DA log for each site where drug is stored or used. Satellites do not store study kits but should maintain a separate DA log to document receipt and assignment of kits
- Maintain one Patient Bottle Accountability worksheet (PD) for each participant
- Store drug in a secure, locked location with limited public access
- Store kits separately; e.g., store the kits on designated shelf - away from drugs for other trials
- Store at controlled room temperature, 59°- 86°F
- Do NOT store study drug returned by patients with unused drug; drug that has been dispensed to a patient cannot be returned and re-dispensed

3.12.1. Study drug description, procurement, and storage

Note: Randomization kits should only be stored at main site for STAN because it will not be known at which site the next participant will be randomized. After randomization occurs and Kit ID assignment is known, Randomization Kit should be shipped by Lead Coordinator to satellite.

Log/Administrative forms (abbreviation)

- Study Kit Accountability Log (DA)
- Patient Bottle Accountability Log (PD)

3.12.2 Dispensing and compliance monitoring

Note: Clinics should use the Drug Dispensing and Counting Form (DD) to record dispensing and counting of study drug kits and spray bottles. Receipt, issuance, and destruction of study drug kits and spray bottles should be recorded on the Drug Accountability log (DA) and the Patient Bottle Accountability log (PD). Please contact the DCC with questions.

Purpose

- Distribute assigned study drug to participants
- Evaluate compliance to study drug assignment

When

- Dispense study drug at Randomization (V2)
- Dispense additional study drug at follow-up visits (V3,V4) as needed
- Monitor compliance at each clinic visit

Supplies

- Kits with unique Kit ID

Study Drug Overview

- Study drug is packaged in a box called a "kit" containing 7 nasal spray bottles. Each spray bottle contains 17g of Nasonex or placebo
- Depending on participant age at randomization, one or two sprays of study drug or matching placebo will be administered per nostril once daily in the morning.
  - Participants less than 12 years of age at randomization take one spray per nostril once daily in the morning
  - Participants greater than or equal to12 years of age at randomization take two sprays per nostril once daily in the morning
- Once a participant is assigned to a kit ID, they may only be dispensed drug from that individual kit box

Dispensing (V2,V3, V4-if applicable)

- Participants are assigned to an individual kit (box) ID
  - At randomization (V2) this kit ID is provided by the online randomization system and corresponds to a randomization kit in stock at the center
  - At other times, if necessary, the Drug Distribution Center may send a replacement kit if original RZ kit will expire. These replacement kits will arrive at the clinic with the participant ID written on the label
- Remove kit with assigned kit ID from stock
- Record kit ID as “assigned” to the participant on the Drug Accountability (DA) Worksheet
- Record kit ID, expiration date, visit ID, and date dispensed on the Patient Bottle Accountability Worksheet (PD)

- Fill in labels on the outside of the kit box:
  - Record dosage information (1 or 2 sprays per nostril daily, depending on participants age at V2)
  - Record the Participant ID, name, issue date, emergency contact information (physician name and phone number) for your clinic
- Remove the tear-off label attached to kit and affix to DD form
- Break seal and open kit box. Fill in information on all 7 nasal spray bottles:
  - Record dosage information on inside panel of nasal spray bottle
  - Record Participant ID and Kit ID on outside label of each nasal spray bottle
  - Label bottom of bottle (using a permanent marker) A through G and record which bottles are distributed on the DD form
  - If two family members are participating in the study at the same time, write participant name somewhere on each bottle
- Dispense individual nasal spray bottles over time. **Do not** dispense the entire kit box of 7 nasal spray bottles to the participant at one time
  - Be sure to dispense enough study drug to meet the participants dosage requirements until next clinic visit. *Remember there is a **2 month** period between V3 and V4 and a **3 month** period between V4 and V5*
- Spare bottle(s) may be issued to the participant or retained in the clinic at the discretion of the coordinator
- Complete Patient Bottle Accountability Worksheet (PD)
  - Record the Visit ID and date dispensed for the appropriate bottles(s)

  Complete a Drug Dispensing and Counting (DD) form
  - If not done already, remove tear-off label attached to kit and affix to DD form
  - Record the sequence letters of all dispensed to the participant that day
- Instruct participant to:
  - Use nasal spray once daily in the morning and take dose indicated on the bottle
  - Contact study personnel if side effects occur
  - Bring in all study drug (empty and partially used) to each clinic visit

Compliance Monitoring (V3-V5)

- **At all clinic visits and phone contact**
  - Discuss compliance
  - Record compliance information on Phone Contact (PC) or Clinic Visit Form (CV), as applicable
- Participants must bring in all nasal spray bottles (including empties) to each clinic visit

- **Returned study drug should be stored until the end of the study**
  - The DCC will notify clinics when it is okay to destroy returned study drug.
  - Drug should be destroyed per local institutional guidelines
  - When bottles are retained by the clinic, record information on bottle on the Drug Dispensing and Counting Form (DD)
  - Destruction of study drug kits must be recorded on the Drug Accountability Log (DA) and Patient Bottle Accountability log (PD)
  - Never put study drug returned by a participant back into study drug stock

Forms (abbreviation)

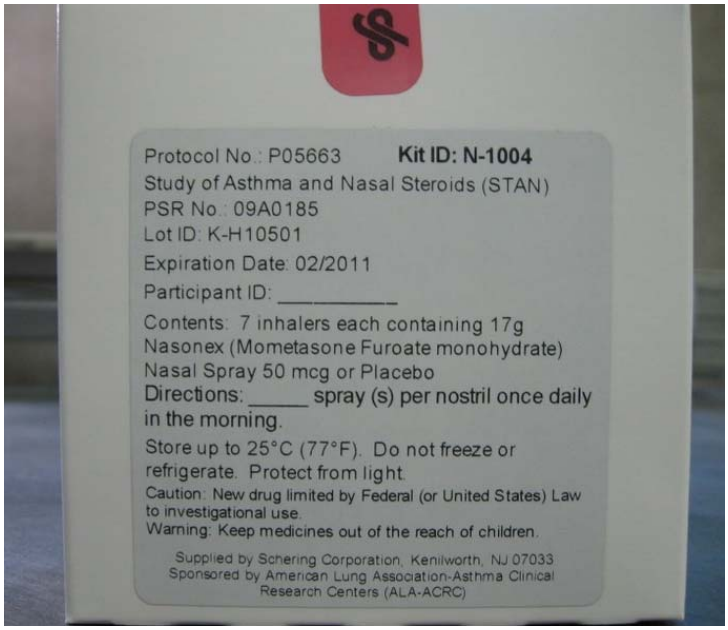
- Clinic Visit (CV)
- Drug Dispensing and Counting Form (DD)
- Phone Contact (PC)

Log/Administrative form (abbreviation)

- Drug Accountability Log (DA)
- Patient Bottle Accountability Worksheet (PD)

3.12.3 Study drug labels

Nasal spray bottle label



Study Kit label

ALA-ACRC (STAN) Study Medication **Kit ID: N-xxxx** **Exp Date: Feb 2011** **FCS IC#: yyyyyy**	*Detach and affix this portion to DD form* **ALA-ACRC (STAN) Study Medication** **Kit ID: N-xxxx** **Exp Date: Feb 2011** **FCS IC#: yyyyyyy**

Tear off label located on top of Study Kit

Study Kit Accountability Log

Purpose: Account for study kit stock at a specific clinical center or satellite.
When: An entry should be made to the log whenever study kits are received and whenever a study kit is assigned to a participant or to a satellite.
Instructions: Maintain one log for all STAN study kits. **Satellite clinics must maintain a separate supplement log from the main clinical center.** The first entry should be your initial shipment of study kits from Drug Distribution Center or from the main clinical center. Use as many continuation pages as necessary. **Use one entry for each Kit ID.**

- **Column b**: Specify where the kit was received from; place a checkmark if a supplement shipment was received from STAN Drug Distribution Center or specify the clinical center, or satellite as applicable. Specify the date received.
- **Column c**: Specify how study kit was disposed of - assigned to a participant, sent to another clinic/satellite, or other; place a checkmark if kit was destroyed.

Clinical center ID: D C C ___

Satellite name *(if appropriate)*: _____

a. Kit ID			b. Received			c. Assigned/Sent/Destroyed					
			Specify Source			Specify Recipient					
Entry	Kit ID	Exp Date	Drug Distr Center	Center/ Satellite Name	Date Rec'd	Participant ID	Name Code	Center/ Satellite Name	Other *(explain)*	Destroyed	Date
1	N-1122	FEB 2011	✓		20 Sep 10	NZ101	SJROE				23 Sep 10
2	N-1403	FEB 2011	✓		20 Sep 10	NZ102	AAKIR				24 Sep 10
3	N-1354	FEB 2011	✓		04 Oct 10			SPH			06 Oct 10
4	N-2424	FEB 2011	✓		04 Oct 10	NZ103	ELBRO				07 Oct 10
5	N-2191	FEB 2011	✓		11 Oct 10	NZ 104	ECCAS				14 Oct 10
6	N-2145	FEB 2011	✓		11 Oct 10	NZ 105	KEMOS				15 Oct 10
7	N-3246	FEB 2011	✓		11 Oct 10			SPH			15 Oct 10
8	N-3433	FEB 2011	✓		15 Oct 10	NZ 106	LRESH				18 Oct 10
9	N-3210	FEB 2011	✓		15 Oct 10	NZ 107	HLDAV				20 Oct 10

Patient Bottle Accountability Worksheet – 12 years and older

Purpose: Optional worksheet to account for study bottles for a participant.
When: An entry should be made to the log whenever a bottle from a participant's study kit is assigned, dispensed, or returned.
Instructions: Maintain one log for each STAN participant. Record the date and visit dispensed, returned, and/or destroyed for each bottle.

Clinical center ID: DCC

Participant ID: NZ101

Satellite name *(if appropriate)*: _____

STAN Kit ID : N-1122

Expiration date: FEB 2011

a. Bottle	b. Dispensed/Returned/Destroyed					
	Dispensed		Returned		Destroyed	
	Visit ID	Date Dispensed	Visit ID	Date Used Bottle Received	Date Destroyed	Comments
A	V2	23 Sep 10				Spare
B	V2	23 Sep 10	V3	21 Oct 10		
C	V3	21 Oct 10	V4	30 Dec 10		
D	V3	21 Oct 10	V4	30 Dec 10		
E	V4	30 Dec 10				
F	V4	30 Dec 10				
G	V4	30 Dec 10				

Patient Bottle Accountability Worksheet -6-11 years

Purpose: Optional worksheet to account for study bottles for a participant.
When: An entry should be made to the log whenever a bottle from a participant's study kit is assigned, dispensed, or returned.
Instructions: Maintain one log for each STAN participant. Record the date and visit dispensed, returned, and/or destroyed for each bottle.

Clinical center ID: DCC

Participant ID: NZ102

Satellite name *(if appropriate)*: _____

STAN Kit ID : N-1403

Expiration date: FEB 2011

a. Bottle	b. Dispensed/Returned/Destroyed					
	Dispensed		Returned		Destroyed	
	Visit ID	Date Dispensed	Visit ID	Date Used Bottle Received	Date Destroyed	Comments
A	V2	24 Sep 10				Spare
B	V2	24 Sep 10	V3	08 Oct 10		
C	V3	22 Oct 10	V4	17 Dec 10		
D	V4	17 Dec 10				
E	V4	17 Dec 10				
F						
G						

3.12.5 Temporary withdrawal or termination of study drug

Purpose

- To set criteria for the temporary withdrawal or termination of study drug administration

When

- Anytime after completion of Randomization Visit (V2) when study drug is temporarily or permanently stopped due to adverse event, participant request, lost to followup, pregnancy, or other reason
- At end of study period

Tasks

- **Unscheduled temporary drug termination**
  - Record information relating to the hiatus in study drug treatment on the Clinic Visit form (CV)
  - Complete an Unusual Event (UE) form or Serious Adverse Event Report (SR) as appropriate

- **Unscheduled permanent drug termination before end of study**
  - 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 drug
    - Study physician will determine if study drug 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 3.13)
    - Regardless of severity, all potential side effects should be recorded on Clinic Visit form (CV), items 30-33
  - Complete Treatment Termination (TT) form
  - Collect all study drug (including all unused nasal spray bottles) from participant
  - Complete Drug Dispensing and Counting (DD) form
  - Continue to follow participant for all study visits (i.e., continue all relevant study procedures) through Visit 5
  - If early unmasking is necessary refer to MOP Section 3.12.6

- Drug termination at end of study
  - Complete Treatment Termination (TT) form
  - Collect all study drug (including all unused nasal spray bottles) from participant
  - Complete Drug Dispensing and Counting (DD) form
  - Conduct exit procedures as detailed in MOP Section 3.14

Forms (abbreviation)

- Drug Dispensing and Counting Form (DD)
- Treatment Termination (TT)

3.12.6 Unmasking

Purpose

- Reveal treatment assignment to participant after the participant completes the study (i.e., after Exit Interview at V5)
- 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 Interview and last study visit, V5
- Early unmasking
  - An acute, severe reaction suspected to be related to the study drug where knowledge of treatment assignment will help to determine treatment
  - An overdose of study drug by participant or someone else
  - Request by physician or participant

Supplies

- Participant exit letter (see MOP Section 3.14.2)
- Sealed Treatment Assignment Envelope provided by DCC with participant randomization kit

Procedures for scheduled unmasking after Exit Interview

- Give participant exit letter and Treatment Assignment Envelope. Refer to MOP Section 3.14 for exit procedure details
- Complete Treatment Termination (TT) and Unmasking (UM) forms

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
  - If Data Coordinating Center staff cannot be reached, clinic personnel should access website to be unmasked
    - To access Unmasking website:
      - Go to http://www.jhcct.org/Secure/STAN/STANHome.asp
      - Click on Data System link
      - Click on STAN Unmasking link

Note: Access to this site is monitored by DCC

  - If web system is unavailable, open the sealed Treatment Assignment Envelope. Report tracking number on envelope to DCC

3.12.6. Unmasking

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 alaacrc@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)

- Treatment Termination (TT)
- Unmasking (UM)

3.13 Serious adverse event reporting

Purpose

- To report an occurrence of a serious adverse event

Definition

- A serious adverse event (SAE) is an adverse event that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Also, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent any of the outcomes previously listed in this definition

Note: Pregnancy must also be reported as an SAE

By whom

- Identification of a serious adverse event as study drug related is the responsibility of the study physician

When

- As needed whenever a serious unexpected adverse event associated with study drugs or placebo is first reported or whenever a followup report is documented

Tasks

- Report a serious adverse event to the DCC by telephone (443-287-3170) within 4 working days
- Fax a completed Serious Adverse Event Report (SR) form to the DCC at 775-871-4030. Confirm receipt of fax. To update report complete a new form
- Key Serious Adverse Event Report (SR) forms within 5 working days of learning of the event
- A followup report should be filed when the serious adverse experience is resolved, or if there has been a significant change in the patient's condition or the physician's judgment about the experience since the previous report was filed. 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, other asthma treatment) should be determined per best medical judgement of the study physician
- Record event on CV form, item #33

Forms (abbreviation)

- Clinic Visit (CV)
- Serious Adverse Event Report (SR)

3.14 Exit procedures

3.14.1 Exit tasks

Purpose

- Notify participant of study treatment via sealed treatment envelope after participant completes Visit 5

Timeframe

- Conducted at Visit 5
- If participant does not return to clinic for Visit 5, conduct exit interview over the phone and mail written materials

Materials

- Patient exit letter (may need to be reviewed and approved by local IRB before it is used)
- Sealed treatment assignment envelope

Tasks

- Conduct interview and record on Exit Interview (EI) form
- Complete Treatment Termination (TT) form, if appropriate
- Give the participant
  - Patient exit letter signed by study physician (see prototype in MOP Section 3.14.2)
  - Sealed treatment assignment envelope
  - Copy of final spirometry results
- Complete Unmasking form (UM)
- Review contents of the exit letter with participant
- Send physician exit letter
- Key forms into STAN data system within 5 working days

Forms (abbreviation)

- Exit Interview (EI)
- Treatment Termination (TT)
- Unmasking (UM)

3.14.2 Prototype Participant exit letter

Dear _____,

Thank you for participating in the clinical trial, "Study of Asthma and Nasal Steroids (STAN)". The purpose of the trial is to determine if the addition of treatment with nasal steroids improves asthma control. The treatment to which you were assigned is listed in the enclosed, sealed envelope. We have also enclosed the results of your final pulmonary function 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 pulmonary function test. Be sure to follow the guidelines on your Asthma Action Plan card. If you have problems with your asthma, or need a new prescription of asthma medication before you see your asthma care provider, you can call our clinic at: XXX-XXX-XXXX.

There are other participants in the study, enrolled after you, who are still being treated and followed in the study. 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 those participants. 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 STAN.

Sincerely,

Principal Investigator
Institutions Name

Enclosures: Treatment Assignment envelope
Results of final pulmonary function tests

3.14.3 Prototype Parent/Guardian exit letter

Dear _____ ,

Thank you for letting your child participate in the clinical trial called the "Study of Asthma and Nasal Steriods (STAN)". The goal of the trial is to determine if the addition of treatment with nasal steroids improves asthma control in individuals with chronic sinusitis and/or rhinitis. There is a sealed envelope included with this letter that has the treatment assignment for your child. This is the study drug that your child was taking during the study. We have also included the results of your child's final pulmonary function (or breathing) test.

You should arrange to see your child's regular asthma care provider within the next three weeks. We suggest that you show your child's asthma care provider the treatment assignment, and the results of your child's final pulmonary function (or breathing) test. Be sure to follow the guidelines on your child's Asthma Action Plan card. If your child has problems with his/her asthma before he/she sees his/her asthma care provider, call our clinic at: XXX-XXX-XXX.

There are other particpants in the study who are still being treated and followed. It is important that both you and your child do not tell me, the other study staff, or other participants in the study what study drug your child was taking. We make it a point not to know what study drug people in the study are taking so it does not affect our judgement about how well the drug worked or influence the data we are collecting.

Again, thank you for letting your child participate in STAN.

Sincerely,

Principal Investigator
Institution Name

Enclosures: Treatment assignment envelope
Results of final pulmonary function test

4. Data collection and forms completion

4.1 List of forms and logs

Form/Log name	Abbreviation	Data entered
Data forms		
Baseline Asthma and Medical History	BA	✓
Clinic Visit Form	CV	✓
STAN Diary Card	DC	✓
Exit Interview	EI	✓
Methacholine Challenge Testing	MC	✓
Methacholine Challenge Worksheet	MW	✓
Missed Data	MD	✓
Patient Screening Log	PD	✓
Phone Contact	PC	✓
Physical Exam	PE	✓
Pulmonary Function Testing	PF	✓
Participant Information	PI	No
Randomization Form	RZ	✓
Screening Form	SC	✓
Serious Adverse Event Report	SR	✓
Allergy Skin Test	ST	✓
Treatment Termination	TT	✓
Unusual Event	UE	✓
Unmasking	UM	✓
Questionnaires		
Asthma Symptom Utility Index	AS	✓
Asthma in Females Questionnaire - English	FQ	✓
Child Health Questionnaire - Parent Form 50	CH	✓
Your Health and Well-Being (Medical Outcomes Study SF-36)	MO	✓
Marks Asthma Questionnaire	MQ	✓
Children's Health Survey for Asthma	PQ	✓
SNOT-22 (Sino Nasal Outcome Test-22)	SN	✓
SN-5 Sinus and Nasal Quality of Life Survey	SV	✓
Smoking Questionnaire - English	SQ	✓
Sino-nasal Questionnaire - English	SI	✓
Sinus Symptom Score	SS	✓
Asthma Control Test - Adult	TA	✓
Asthma Control Test - Child	TP	✓

4.1. List of forms and logs

Form/Log name	Abbreviation	Data entered
Logs/Administrative forms		
ACRC General Order Form	GO	No
Drug Distribution Form	DD	No
Exhaled Nitrix Oxide Test (eNO) Supply Order Form	NS	No
Greer Order Form	AO	No
Nitric Oxide Form	NO	✓
NO Senor Log	NL	No
Peak Flow Meter Order Form	PO	No
Patient Screening Log	PS	✓
Patient Bottle Accountability Worksheet	PD	No
Shipment Receipt	SH	No
SOYA/STAN Methapharm Orders	MP	No
Specimen Transmittal Sheet	TS	No
Study Kit Accountability Log	DA	No
Information sheets		
Instructions for Allergy Skin Test	IAT	No
Instructions for Measuring Peak Flow	IPF	No
Instructions for Methacholine Challenge Test	IME	No
Instructions for STAN Diary Cards	IDC	No
Methacholine Worksheet	MW	No
Patient Information for Methacholine Challenge Testing	IMT	No
Schedule of Visits	SOV	No
Temporary Asthma Action Plan - Visit 1	TAP	No
Certification forms		
Certification Allergy Skin Test	CS	No
Clinical Center Certification	CC	No
Satellite Center Certification	CT	
STAN Methacholine Challenge Test Assurance Statement	MA	No
STAN Personnel Assurance Statement	PA	No
STAN Spirometry Test Assurance Statement	SA	
Other		
Consent Statement	–	No

4.2 ID codes

Codes

- Reference #
- Participant ID
- Namecode
- Visit
- 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 center alphanumeric code taken sequentially from the sheet of Clinic Labels
- Distributed to the clinical center by the Data Coordinating Center (see example in MOP Section 132)
- Unique # assigned to each potential participant who starts the Screening Visit (V1)
- All participant forms will be identified by that #

Namecode

- 5 character code, unique for every participant enrolled at a site
- Assigned by coordinator at participant registration
- Suggested assignment scheme
  - First letter of code is the first letter of the participant's first name
  - Second letter is the first letter of the participant's middle name
  - Third-fifth letters are the first 3 letters of the participant's last name
  - Use "X" to substitute for any missing letters
- Examples
  - John L. Doe = JLDOE
  - John Doe = JXDOE
  - Don Ho = DXHOX
- If two participants at a site have the same namecode, substitute an "X" for one of the letters, use last letter of the last name, or substitute a number
  - Jane W. Smith = JWSMI
  - Joseph W. Smithe = JXSMI or JWSME
  - John W. Smile = JWSMX or JWSM 2

Visit

- 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
- Assigned by DCC
- Staff members must be "registered" by being entered in the online directory for a PIN to be generated

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
North Shore/Long Island Jewish Health System	LIJ
Illinois Consortium	IC
Indiana University, Asthma Clinical Research Center	IU
Louisiana State University Health Sciences Cent, 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

Clinic Label Sheet

STAN

Clinical Center Z: **TEST**

To assign participant ID:
Attach next sequential label to
#2 on Screening Form (SC)

NZ100	NZ101	NZ102
NZ103	NZ104	NZ105
NZ106	NZ107	NZ108
NZ109	NZ110	NZ111
NZ112	NZ113	NZ114
NZ115	NZ116	NZ117
NZ118	NZ119	NZ120
NZ121	NZ122	NZ123
NZ124	NZ125	NZ126

4.4 Completing forms

4.4.1 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 space should have only one letter or digit per space
- All forms must be signed off by a study physician or clinic coordinator who is certified for the study
- Numeric responses are to be right justified with all spaces completed. Use lead zeros as necessary. Example: 0 0 3 2
- Alpha or alphanumeric responses are to be left justified. If blank spaces remain, leave them blank. Example: P 1 2 __; D C C _
- Data on forms should always match database

4.4.2 Error correction

- Do not obliterate erroneous responses
- Never use write-out or erase a response
- Draw a single line through incorrect response and indicate correct response clearly, above or next to the erroneous response
- Use a different color ink; e.g., green or red, to make edits
- Staff member making changes to a form should initial and date change in the margin and provide a short explanation for the change; e.g., “error”, “participant changed mind”
- Update database with revised information

4.4.3 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 are never to be added 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 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: Do not round responses unless the number of digits in a response field requires it. Otherwise, record data as collected.

If there are more whole integer digits than the response field allows, contact the Data Coordinating Center.

4.5 Description of study forms

4.5.1 Data forms

Purpose

- Record study data on standardized data collection instruments
- Guide data collection and visit procedures

Tasks/Timeframe

- **Baseline Asthma and Medical History (BA)** - completed at Clinic Visit 1 to establish asthma history, asthma treatment, and smoking history
- **Clinic Visit Form (CV)** - completed at Clinic Visits 2-5 to record information about diary cards, asthma symptoms, and interim medications
- **Drug Dispensing and Counting Form - Nasal Spray Bottles (DD)** Used to record dispensing, counting, and return of study nasal spray bottles
- **Exit Interview (EI)** - completed at Clinic Visit 5 to obtain the participant's impression of the treatment received
- **Methacholine Challenge Testing (MC)** form - used to record the results of testing at Clinic Visit 1 and Clinic Visit 5 for participants who qualify for methacholine challenge
- **Missed Data (MD)** form - used to record information about visits/contacts or procedures that were missed by an enrolled participant
- **Nitric Oxide Form (NO)** - completed at Clinic Visit 2, and Clinic Visit 5 to record eNO levels
- **Participant Information (PI)** - completed at Clinic Visit 1 to record patient location and contact information. This form is kept in the participant's folder located at the clinic
- **Phone Contact (PC)** form - completed for the phone interview conducted at Phone Contact 1-3 to assess compliance, side effects, and asthma control
- **Physical Exam (PE)** form - completed by study physician at Clinic Visit 1 and Clinic Visit 5 to assess participant's general health and note any abnormalities
- **Pulmonary Function Testing (PF)** form - completed at Clinic Visits 1-5 to record the results of pulmonary function tests, including peak flow and spirometry
- **Randomization (RZ)** - completed and entered into the database at Clinic Visit 2 after all other forms and activities for that visit have been completed. Once the form is data entered, treatment assignment should be recorded on the form
- **STAN Diary Card (DC)** - completed by the participant on a daily basis to record peak flow, asthma medication use, and severity of asthma episodes. Participants should bring completed diary cards to each clinic visit
- **Screening Form (SC)** - completed at Clinic Visit 1 after initial forms and procedures are completed. This form checks preliminary eligibility and provides the participant with a pass code to access web information about STAN
- **Serious Adverse Event Report (SR)** - completed if an event deemed reportable according to Section 3.13 of the MOP occurs. The form must be faxed to the DCC within 4 working days and keyed to the database within 10 working days

4.5.1. Data forms

- **Allergy Skin Test (ST)** - completed at Clinic Visit 2 to determine whether an individual is atopic (allergic).
- **Treatment Termination (TT)** form - completed when study treatment is terminated either before the participant completed the study or when the participant completes the study
- **Unmasking (UM)** form - completed when the participant is unmasked either before the end of the study or at the end of the study
- **Unusual Event (UE)** form - completed to report protocol deviations, events that do not rise to the level of a serious adverse event, and communications that need to be recorded which are not captured on other data forms

4.5.2 Logs/administrative forms

Purpose

- Provide record of the disposition of study nasal spray, patients screened for the trial, transmission of specimens, and supplies ordered

Tasks/Timeframe

- **Drug Kit Accountability Log (DA)** - filled out whenever study nasal spray shipments are received, whenever nasal spray stock is destroyed, whenever study nasal spray kits are issued to a participant, and whenever study nasal spray kits are transferred to a satellite. A log should be maintained at each specific clinic that stocks nasal spray including satellite clinics (See Section 3.12.4 of MOP)
- **Patient Bottle Accountability Worksheet**
- **General Supplies Order Form**
- **Greer Allergen Order Form (AO)** - used each time allergen vials for allergy skin tests are ordered from the Greer Labs
- **ACRC General Order Form** - order form for general ACRC supplies
- **Methapharm STAN Order Form (MP)** - used each time methacholine is ordered from Methapharm, Inc.
- **Peak Flow Meter Order Form (PO)** - used each time peak flow meters are ordered from Bay View Medical Inc.
- **Patient Screening Log (PS)** - used to keep a record of demographic information and disposition of all patients screened for the trial
- **Shipment Receipt (SH)** - initiated at the Data Coordinating Center and accompanies supplies. Upon receipt of supplies, the Shipment Receipt is to be completed and faxed to the Data Coordinating Center
- **Specimen Transmittal Sheet (TS)** - to accompany transmittal of specimens
- **STAN Supply Order Form (ZO)** - order form for supplies specific to STAN

4.5.3 Participant information sheets

Purpose

- Provide instructions about study procedures for participants

Tasks/Time frame

- **Asthma Action Plan Card (AAP)** - given to participants at randomization (V2). Clinic staff should fill out the card with the participant at V2 and instruct the participant in the appropriate use of the card
- **General Asthma Educational Materials** - general patient information on asthma distributed at screening (V1)
- **Instructions for Allergy Skin Test (IAT)** - given to participants at V1; provides information on medication holds before allergy skin test at V2
- **Instructions for Measuring Peak Flow (IPF)** - reviews procedures for participants and should be distributed at V1. Staff may use this sheet while instructing participants how to use the Peak Flow Meter. A copy should be included in the Participant Binder
- **Instructions for Preparation for Methacholine Challenge Test (IMC)** - reviews procedures and conduct of a Methacholine Challenge Test conducted at V1
- **Instructions for STAN Diary Cards (IDC)** - given to participants at V1. Staff should use this sheet to review Diary Card procedures with a participant. A copy should be included in the Participant Binder
- **STAN Schedule of Visits (SOV)** - highlights visit procedures and future appointments. This sheet can be used as a reference for participants and should be included in the Participant Binder
- **STAN Wallet Card** - wallet size card with contact information for study and primary asthma physician
- **Temporary Asthma Action Plan Sheet (TAP)** - given to participants at screening (V1) for use between V1 and V2. Clinic staff should fill in the blank items on the sheet and instruct the participant on the appropriate use of the sheet

4.5.4 Certification forms and consents

Certification forms

Purpose

- To assure that all necessary facilities, equipment, personnel, and approvals are in place before STAN is open to participants

Task/Timeframe

- **Clinical Center Certification (CC)** form - to be completed by the Lead ACRC Coordinator and signed by the Center Director after all arrangements for the conduct of STAN are in place
- **Satellite Certification (CT) Form** - to be completed by main coordinator at the satellite center and counter signed by Lead Coordinator at main clinic
- **STAN Personnel Assurance Statement (PA)** - to be signed by all personnel requesting certification and a PIN to conduct STAN. Signed statement sent to DCC and copy kept by clinic
- **STAN Methacholine Challenge Test Assurance Statement (MA)** - to be signed by ACRC Clinical Center Director and Co-PI of satellite(s) [if applicable] as assurance that methacholine challenge test is being conducted per STAN protocol. Signed statement sent to DCC and copy kept by clinic
- **STAN Spirometry Test Assurance Statement (SA)** - to be signed by ACRC Clinical Center Director and Co-PI of satellite(s) [if applicable] as assurance that spirometry testing is being conducted per STAN protocol. Signed statement sent to DCC and copy kept by clinic.
- **Certification Allergy Skin Test (CS)** - to be completed as part of practicals for allergy skin test certification
- **FDA Conflict of Interest form (Form 3455)**: to be completed by Principle Investigator at main site and CO-PI at satellite.

Consents

- **Research Subject Information and Consent Form** - Read and signed by Participant. Co-signed by person obtaining consent and PI (if different than person obtaining consent).
- **Research Subject Assent Form** - Signed by participant less than 18 years of age and by staff member conducting assent discussion. This may be part of the main consent.

4.5.5 Distributed data entry

Online data system background

- Distributed data entry for the ALA-ACRC STAN 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 usernames stored in the STAN 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 (Treatment assignment consists of Kit ID)
- To track participant activity
- To monitor clinical center performance

Tasks/Timeframe

- Clinical center staff will log into the data entry system on the STAN web site at http://www.jhcct.org/Secure/STAN/STANHome.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 patient
  - Enter/edit data for an existing patient
  - View reports for their clinic
  - Get treatment assignments (consisting of Kit ID)
- Patients must be registered before any forms can be entered for that patient; registration consists of creating a record for a new patient including his/her STAN ID and namecode
- RZ (Randomization) forms must be keyed in real-time, while the participant remains in the clinic, in order to receive a treatment assignment (Kit ID)
- MD (Missed Data) 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
- 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)
- 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

5. Quality assurance

5.1 ACRC Clinical Center responsibilities

- A clinical center is composed of one main ACRC Clinical Center which may have additional satellite clinics associated with it
- Primary clinical center staff must include a Principal Investigator, lead clinic coordinator, and a Data System Operator. Additional staff members are recommended
- Study drug is distributed by the STAN Drug Distribution Center to the main ACRC Clinical Center only. The main ACRC Clinical Center is to designate one specified staff member at one address for receipt of study drug kits. The main ACRC Clinical Center must record distribution of study drug kits to satellite centers on the Drug Accountability Log (DA) for the primary clinical center
- The main ACRC Clinical Center is responsible for distributing supplies to satellites
- The Lead Coordinator at the main ACRC Clinical Center is responsible for keeping current the ALA-ACRC web-based directory for that clinical center and its 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 other ACRC staff members at their 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 their clinical center and satellite clinic(s) as appropriate
- The main ACRC Clinical Center is responsible for ordering all peak flow meters from Bay View Medical, Inc (the peak flow meter distributor)
- The main ACRC Clinical Center is responsible for ordering methacholine or methacholine from Methapharm, Inc.

5.2 Satellite clinics

- Satellite clinics are an adjunct to their main (or primary) clinical center (see end of MOP Section 4.2 for list of clinical centers, and respective ID codes)
- Each satellite clinic is to have a coordinator who is responsible to lead coordinator at the main (or primary) clinical center
- Other study personnel (e.g. study investigator, data system operator) are optional and at the discretion of the satellite clinic and primary clinical center
- Study drugs are received from, and returned to, the primary clinical center
- Forms for study visits conducted at a satellite clinic are to be completed and maintained at the satellite
- All functions performed by a satellite clinic must conform to the protocol and Manual of Operations (MOP)
- Drug Accountability Logs (DA), separate from that of the primary center, are to be maintained at the satellite clinic

5.3 Data checks

Data for the study will be entered from data forms into an internet-based data system. The data system works with Microsoft's Internet Explorer, versions 5.0, 5.5, and 6.0, running on personal computers with any version of Microsoft Windows (95/98/ME/NT/2000/XP). The user interface employs standard web page controls and does not require any additional software to be installed, but 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 insure 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.

5.4 Data audits and data quality queries

On-going data audits

- Periodically during and after the clinical phase of the trial, the DCC will audit clinics
  - DCC will send an email to a clinic requesting copies of forms for a particular participant(s)
  - Within 2 weeks clinics should send copies of the requested forms (STAN Fed Ex number: 4895-1772-8)
  - The DCC will review the data on the paper form and compare it to entries in the data system

Data Quality (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 in a form
  - All DQQs will be posted on the DQQ Management System. To get to the DQQ page go to the STAN website, http://www.jhcct.org/Secure/STAN/STANHome.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 MOP Section 4.4 Completing forms
- 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

Drug Accountability Audits

- Periodically, the DCC will request materials from centers to audit STAN study drug supplies
- 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 Drug Accountability (DA) logs
  - List of kit IDs of all kits currently at the clinic

First randomization audits

- The full set of forms for V2 will be audited for the first patient randomization completed by a coordinator
- If problems are identified, forms from the second and possibly third randomization completed by the coordinator may be audited

6. Asthma medications

6.1 Controller medications

Inhaled anti-inflammatory agents

- Non-steroidal
  - Cromolyn Sodium (Intal)
  - Nedocromil Sodium (Tilade)
- Inhaled corticosteroids
  - Beclomethasone (e.g., Beclovent, Vanceril, Vanceril Double Strength, QVAR)
  - Budesonide (Pulmicort, Symbicort component*)
  - Ciclesonide (Alvesco, Omnaris)
  - Flunisolide (Aerobid)
  - Fluticasone (Flovent, Advair component*)
  - Mometasone (Asmanex)
  - Triamcinolone (Azmacort)

Oral corticosteroids

- Prednisone (e.g., Deltasone, Orasone Prednicen-M, Sterapred)
- Prednisolone (e.g., Pediapred, Prelone)
- Methylprednisolone (Medrol)

Long-acting beta-agonists

- Salmeterol (e.g., Serevent inhalation aerosol, Serevent Diskus inhalation powder, Advair component*)
- Formoterol (Foradil, Symbicort component*)
- Arformoterol (Brovana®)

Long-acting anticholinergics

- Tiotropium (Spiriva)

Methylxanthines

- Theophylline, sustained-release (e.g., Slo-Phyllin, Uniphyl, Theo-Dur, Slo-Bid, Theolair, Theo-24)

Oral antileukotrienes

- Montelukast (Singulair)
- Zafirlukast (Accolate)
- Zileuton (Zyflo)

Immunologlobulin E blockers (for subcutaneous injection)

- Omalizumals (Xolair)

*Combination drug of which generic drug noted is a component

6.2 Rescue medications

Inhaled short-acting beta2-agonists

- Albuterol (e.g., Proventil, Proventil HFA, Ventolin, ProAir HFA)
- Bitolterol (Tornalate)
- Pirbuterol (e.g., Maxair Autohaler, Maxair Inhaler)
- Terbutaline (Breathaire)
- Levalbuterol (Xopenex)
- Metaproternol (Alupent, Metaprel)

Anti-cholinergic

- Ipratroprium bromide (Atrovent, Combivent component*)

*Combination drug of which generic drug noted is a component