

**Study of Soy Isoflavones in Asthma
(SOYA) Trial**

**Manual of Procedures
Version 1.1**

10 December 2010

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From

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SOYA MOP

Revision History

Version 1.0 (13 July 2010)

- Based on protocol 2.0 (26 March 2010)
- Posted on the SOYA website

Version 1.1 (10 December 2010)

- Based on PPMs subsequent to Version 1.0
- Incorporates revisions, clarifications and corrections to Version 1.0

<u>Section</u>	<u>Change/addition</u>
1.3	Study visit time windows and data collection schedule (<i>clarification</i>) <ul style="list-style-type: none"> • Added time window (weeks) and note about minimum time between visits to table
2.2	Screening (V1) (<i>clarification</i>) <ul style="list-style-type: none"> • Added instruction to register participant number in SOYA data system • Added information about meeting eligibility criteria at time of randomization
3.1.1	Clinical center staff certification (<i>PPM #6</i>) <ul style="list-style-type: none"> • Removed Spirometry Assurance Statement (SA) and Methacholine Challenge Test Assurance Statement (MA) from clinic coordinator certification requirements • Added Methacholine Challenge Test Assurance Statement (MA) to ACRC Center Director requirements
3.2	Study supplies (<i>PPM #13, #18 and clarification</i>) <ul style="list-style-type: none"> • Added section for Aerocrine so supplies can be obtained for the NIOX MINO • Added eNO and methacholine supplies that will be distributed by the DCC • Removed references to noseclips for EBC collection
3.6.1	Spirometry procedures <ul style="list-style-type: none"> • Removed references to inspiratory flow (<i>correction - SOYA does not measure inspiratory flow</i>) • Standardization of equipment: <ul style="list-style-type: none"> – Added KoKo spirometer using software version 4.11 (<i>PPM #8</i>) • Testing procedure: <ul style="list-style-type: none"> – 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 (<i>clarification</i>) • Pre and post bronchodilator procedures: <ul style="list-style-type: none"> – Removed FEV1 requirement for taking up to four puffs of albuterol (<i>correction</i>)
3.6.3	Spirometry over reading (<i>PPM #15</i>) <ul style="list-style-type: none"> • Added procedures for quality assurance reviews • Added instructions for filling out the QA report • Added instructions for reviewing submitted QA reports

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<u>Section</u>	<u>Change/addition</u>
	<ul style="list-style-type: none"> • Added information on spirometry tester certification
3.7.10	Preparation of methacholine solutions (<i>clarification</i>) <ul style="list-style-type: none"> • Storage of solutions: <ul style="list-style-type: none"> – Updated to reflect Vials I and J may be made and stored in the refrigerator less than 24 hours
3.7.11	Administration of methacholine challenge <ul style="list-style-type: none"> • Added equipment requirements (<i>revision - to reflect changes established for ACRC in MeCIS</i>) • Updated dosimeter instructions to include compressed air source at 35-60 psi, dose control in “Normal” mode and start duration of 0.5 seconds (<i>revision - to reflect changes established for ACRC in MeCIS</i>) • Updated baseline cutoff values (<i>correction</i>)
3.8.2.2	Specimen collection (<i>PPM #18 and clarification</i>) <ul style="list-style-type: none"> • Added note that nose clips are not required for EBC collection • Transferring EBC into aliquots: <ul style="list-style-type: none"> – Specified 250ml EBC will be pipetted into each of 3 cryovials for a total of 750ml
3.8.3	Exhaled NO <ul style="list-style-type: none"> • Equipment and supplies: (<i>PPM #13 and clarification</i>) <ul style="list-style-type: none"> – Added initial NIOX MINO test supply kit information – Removed number of tests sensor is good for – Added QC card and filter will be supplied by the DCC – Added clinics will provide replacement equipment • QC requirements for the NIOX MINO: (<i>clarification</i>) <ul style="list-style-type: none"> – Updated extended QC test to be performed at initial set up and every 7 days when a new sensor is used • Daily QC Test: (<i>revision - section revised to provide more detail</i>) <ul style="list-style-type: none"> – Added instruction for Normal Control tester to avoid nitrate rich food and exercise before test – Added instruction for Normal Control tester to not perform test in case of respiratory infection or acute seasonal allergies – Added steps for the daily QC test – Added instructions about the frequency of Weekly/Extended QC test – Added instructions for completing the Weekly/Extended QC procedure
3.8.3.1	Exhaled Nitric Oxide Comparison Substudy <ul style="list-style-type: none"> • When: <ul style="list-style-type: none"> – Updated visits where substudy occurs to V2, V4-V9 (<i>correction</i>) • Procedures: <ul style="list-style-type: none"> – Added note that the order of testing should be obtained from the data system at each study visit (<i>clarification</i>)
3.8.6	Eosinophil count (<i>clarification</i>) <ul style="list-style-type: none"> • Analysis arrangements:

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<u>Section</u>	<u>Change/addition</u>
	<ul style="list-style-type: none">- Added instruction that eosinophil count must be reported as cells/μL not as a percentage- Added instructions for converting % eosinophils to cells/μl
4.4.2.1	Overview <ul style="list-style-type: none">• Scoring: <i>(revision - instructions required to complete SI form)</i><ul style="list-style-type: none">- Added instructions for scoring the Sino-Nasal Questionnaire (SI)
Throughout	<ul style="list-style-type: none">• Various spelling and grammatical mistakes corrected

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1.1 Design and outcome measures

Title

Study of Soy Isoflavones in Asthma (SOYA)

Objective

To test the novel hypothesis that patients with symptomatic asthma have improved lung function when given a soy isoflavone dietary supplement as compared to patients given a placebo.

Type of study

- Randomized, double-masked, placebo-controlled, parallel group clinical trial
- Multicenter, 19 centers
- Fixed sample size, 380

Study drugs

- Soy supplement (Novasoy®) that contain 50mg of isoflavones (genistein, diadzein and glycitein)
 - ▶! 1 tablet PO twice daily
- Placebo tablets (Placebo, cellulose)
 - ▶! 1 tablet PO twice daily

Primary outcome

- Change in pre-bronchodilator forced expiratory volume in one second (FEV₁)

Secondary outcomes

- Biomarkers of airway inflammation
 - ▶! Exhaled nitric oxide (eNO)
 - ▶! Exhaled 8-isoprostane
- Measures of asthma symptoms
 - ▶! Change in Asthma Control Test (ACT) score
 - ▶! Asthma Symptom Utility Index Score (ASUI)
 - ▶! Daily asthma symptom scores
 - ▶! Asthma-specific Quality of Life (Marks AQLQ or CHSA)
 - ▶! Rate of Episodes of Poor Asthma Control (EPAC types 1* and 2†)
 - ▶! Nocturnal awakenings
 - ▶! Generic health-related quality of life (QOL)

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

- ▶ Decrease of $\geq 30\%$ 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

[1.1. Design and outcome measures](#)**Tertiary outcomes**

- Biomarkers of airways inflammation and oxidative stress
 - Peripheral blood eosinophil counts
 - Interleukin-6 (IL-6) levels
 - C-reactive protein (CRP) levels
 - Urinary LTE₄ levels
-

1.2 Eligibility criteria

The general goal of patient selection is to enroll adults and children with poor (e.g., inadequate) asthma control whom asthma physicians would consider need a change in or additional therapy to improve asthma control.

Inclusion criteria

Age

- 12 years or older

Asthma

- Physician diagnosed asthma
- FEV₁ equal to or greater than 50% predicted pre-bronchodilator
- At least one of the following from the previous 2 years:
 - At least 12% increase in FEV₁ 15–30 minutes after inhaling 2–4 puffs of albuterol, or
 - Positive methacholine challenge (20% fall in FEV₁ at less than 16 mg / mL)
- Currently taking daily controller asthma medication(s) (e.g., inhaled corticosteroids and/or leukotriene modifier)

Poor Asthma Control – defined by any one of the following at Visit 1 (screening):

- A score of 19 or less on the Asthma Control Test
- Use of beta-agonist for asthma symptoms two or more times per week on average over the past 4 weeks, or
- Nocturnal awakenings with asthma symptoms more than once per week on average over the past 4 weeks, or
- Two or more episodes of asthma symptoms in the past 12 months with each requiring at least one of the following: emergency department visit, unscheduled physician visit, prednisone course, hospitalization

Smoking status

- Non-smoker for 6 months or longer
- Less than 10 pack-year smoking history

Exclusion criteria

Pulmonary function

- FEV₁ less than 50% predicted pre-bronchodilator as measured at Visit 1

1.2. Eligibility criteriaOther major chronic illnesses

- Conditions which in the judgment of the study physician would interfere with participation in the study including but not limited to non-skin cancer, endocrine disease including insulin-dependent diabetes mellitus, coronary artery disease, congestive heart failure, stroke, severe hypertension, renal failure, liver disorders, malabsorption disorders, immunodeficiency states, major neuropsychiatric disorder
- History or physician diagnosis of chronic bronchitis, emphysema or COPD
- History or physician diagnosis of breast cancer, endometrial cancer or ovarian cancer.
- Active thyroid disease

Medication/supplement use

- Current consumption of soy isoflavone supplements
- Current or previous use of tamoxifen
- Oral corticosteroid use within the past 6 weeks
- Use of an investigational treatment in the previous 30 days

Supplement allergy

- Known adverse reaction to genistein, other phytoestrogens or soy products

Females of childbearing potential

- Pregnant or lactating – participants of appropriate age who might be pregnant at the time of Visit 2 (enrollment) will be screened and cannot participate if pregnant

Non-adherence

- Inability or unwillingness to provide consent or, in the case of children, inability or unwillingness of the child to provide assent
- Inability to swallow study supplement
- Inability to perform baseline measurements
- Inability to be contacted by telephone
- Intention to move out of the area within 6 months

Other

- Recent asthma exacerbation (within 6 weeks)
 - Recent upper respiratory infection (within 2 weeks)
 - Body weight less than 77 pounds (35 kg)
 - Intake of soy or soy-enriched foods 4 or more times in the past 30 days
 - Change in diet over the past month or expected change in diet (e.g., will initiate weight loss diet) during the study
-

1.3 Study visit time windows and data collection schedule

Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9
Time window (weeks)**	-4 to -2	0	***	2-6	6-10	10-14	14-18	18-22	22-26
Target (weeks)	-2	0	2	4	8	12	16	20	24
Consent, eligibility evaluation	•								
Methacholine challenge*	•								
Spirometry pre- and post-BD	•	•		•	•	•	•	•	•
Brief physical exam	•								•
Pregnancy Testing (if indicated)	•	•							
Instruction in diary, PEF, action plan	•	•	•	•	•	•	•	•	•
Return asthma diary		•		•	•	•	•	•	•
Randomization		•							
Treatment distribution		•		•	•	•	•	•	
Pill counts / Adherence Counseling				•	•	•	•	•	•
Interval Asthma / Health history		•	•	•	•	•	•	•	•
Adverse event screen			•	•	•	•	•	•	•
Block Soy questionnaire	•	•							•
Block Food Frequency Questionnaire		•							•
Asthma Control (ACT, ASUI)	•	•		•	•	•	•	•	•
Asthma Quality of Life (Marks AQLQ or CHSA)	•	•		•	•	•	•	•	•
SF-36 or CHQ-PF50 Questionnaire	•								•
Asthma in Females Questionnaire		•							
Smoke Exposure in Children Questionnaire		•							
Sino-Nasal Questionnaire (SI)		•							
CRP, IL-6 levels (blood)		•		•					•
Blood for genotype		•							
Genistein level (blood)		•		•					•
Eosinophil count (blood)		•		•					•
Urinary LTE ₄		•		•					•
Exhaled nitric oxide (eNO)		•		•	•	•	•	•	•
Exhaled breath condensate (EBC)		•		•					•

*Only if needed to meet eligibility criteria
PEF – Peak Expiratory Flow, V3 – phone visit

**Minimum of one week required between each visit after V2
***V3 conducted between V2 and V4

SOYA MOP**2. Study visits/contacts**

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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

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, collection of exhaled breath condensate, and spirometry can interfere with each other. Thus, it is critical that clinics perform these tests in a prescribed order. The tests below should be conducted in the order as listed:
 - Exhaled nitric oxide (eNO)
 - Exhaled breath condensate (EBC)
 - Spirometry, with or without bronchodilator

Note: All of these tests are not done at each visit.

- Spirometry (pre-bronchodilator only) to be conducted prior to methacholine challenge
- Albuterol is to be held prior to conducting spirometry - short acting should be held 4 hours prior to spirometry, long acting should be held 24 hours prior to spirometry

Required order for blood draws

- Collection of tubes should be conducted in the order as listed:
 - Blood for CRP and IL-6 (in red/gray top serum separator tube)
 - Blood for eosinophil count (in tube specified by local laboratory)
 - Blood for genistein and DNA (in lavender top tube)

Timing for pft testing and blood draws

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

2.2 Screening (V1)

Overview

- V1 consists of the initial screening visit, conducting the physical exam, and scheduling the methacholine challenge test, if needed 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

Equipment/materials

- Mini-Wright peak flow meters
- Participant binder, ACRC tote bag and magnet
- General asthma education materials

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 12-17 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 4.2.1)
 - Register participant number in SOYA data system
 - Place label in box on item 2 of Screening Form (SC)
- Complete Baseline Asthma and Medical History form (BA)
- Complete Participant Information Sheet (PI)
- 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
 - 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
 - If reversibility is $< 12\%$, schedule a methacholine challenge test to establish reversibility
- Conduct pregnancy test, if applicable
- Have participant complete questionnaires:
 - Asthma Control Test (TA)
 - Asthma Symptom Utility Index (AS)
 - Marks Asthma Quality of Life Questionnaire (MQ)

OR

 - Children's Health Survey for Asthma (PQ)

2.2. Screening (V1)

- Your Health and Well-Being MOS SF-36 v2 (MO)
OR
Child Health Questionnaire Parent Form 50 (CH)
- Block Soy Questionnaire (BS)
- 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 (eg. recent oral corticosteroid use), 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, do 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 randomization and methacholine challenge test (if applicable)
 - Recorded on Physical Exam (PE) form
- Schedule methacholine challenge test for eligibility, if necessary
 - Only for participants with $FEV_1 \geq 70\%$ predicted pre-bronchodilator at V1 who do not demonstrate 12% or greater increase in FEV_1 15-30 minutes after inhaling 2-4 puffs of albuterol.
 - Distribute and review Instructions for Preparation for Methacholine Challenge Test (IMC)
 - Conduct according to procedures detailed in MOP Section 3.7

Note: Methacholine challenge tests are required only for SOYA participants with FEV_1 70% predicted at the V1 initial screening, and who did not demonstrate either FEV_1 bronchodilator responsiveness $\geq 12\%$ or positive methacholine challenge test in the past 2 years. However, if on the day of the methacholine challenge the participant's $FEV_1 < 70\%$ predicted, the methacholine test may not be conducted. Instead, conduct post-bronchodilator spirometry. See SOYA Pulmonary Function/Methacholine Challenge Flowchart (MOP section 3.7.13), for further clarification.

- Distribute
 - Instructions for Measuring Peak Flow (IPF)
 - Instructions for Diary Cards (IDC)
 - Mini-Wright peak flow meter
 - Participant binder
 - Diary Cards
 - Complete item 1 (date) on Diary Cards
OR
 - Print out Diary Cards with pre-printed dates by clicking on appropriate link on the data system menu of SOYA 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 SOYA 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

2.2. Screening (VI)

- red zone: less than .50 of personal best
- o Fill in contact information
- Canvas bag with ACRC logo and ACRC magnet
- General Asthma Education Materials
- SOYA Schedule of Visits (SOV) with dates and times for all subsequent visits recorded
- Instructions for Preparation for Methacholine Challenge Test (IMC), if applicable
- 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 Pulmonary Function Testing form (PF) and Screening form (SC) into the data system immediately after visit. These 2 forms 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)
- Asthma Symptom Utility Index (AS)
- Block Soy Questionnaire (BS)
- Marks Asthma Quality of Life Questionnaires (MQ)
OR
Children's Health Survey for Asthma (PQ)
- Your Health and Well-Being MO SF-36 v2 (MO)
OR
Child Health Questionnaire Parent Form 50 (CH)

Information sheets (abbreviation)

- Instructions for Diary Cards (IDC)*
- Instructions for Preparation for Methacholine Challenge Test (IMC)*, if applicable
- Instructions for Measuring Peak Flow (IPF)*
- SOYA 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)
 - Asthma Symptom Utility Index (AS)
 - Children’s Health Survey for Asthma (PQ)
 - OR
 - Marks Asthma Quality of Life Questionnaire (MQ)
 - Block Soy Questionnaire (BS)
 - Block Food Frequency (BF)
 - OR
 - Block Kids Food Frequency (BK)
 - Asthma in Females (FQ)
 - Home Smoking Activity and Exposure to Tobacco Smoke Questionnaire (SQ) for participants age 12-17 only
 - Sino-Nasal Questionnaire (SI)
 - 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
 - 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 EBC and spirometry
 - Collect Specimen samples
 - Exhaled Breath Condensate (EBC) - must be conducted prior to spirometry
 - Serum for CRP and IL-6 levels - collect before other blood specimens
 - Plasma for genistein level
 - Packed blood cells for genotyping
 - Blood for eosinophil count
 - Urine for LTE₄ levels
 - Collect pulmonary function data, record on Pulmonary Function Testing form (PF):
 - Conduct peak flow procedure
 - Conduct pre- and post- bronchodilator spirometry procedures
 - Conduct pregnancy test (if applicable)
 - Review participant eligibility for study treatment using Randomization form (RZ)
- Note: Two forms must be data entered before randomization: Screening (SC), and Pulmonary Function Testing (PF) from V1.*
- If participant meets eligibility criteria, enter Randomization Form (RZ)
 - Obtain study supplement 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

2.3. Randomization (V2)

- Complete Asthma Action Plan card (AAP)
 - Fill in zone cut-offs and personal best peak flow calculated by data system
 - Remove Temporary Asthma Action Plan Sheet (TAP) from participant binder and put in participant's file
 - Review instructions for use of card
- Distribute SOYA Wallet Card
- Distribute assigned study supplement bottle from Kit ID assigned to participant
- Complete Study Kit Accountability Log (DA)
- Complete Tablet Dispensing and Counting Form (DD)
- 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 SOYA data system within 10 working days

Forms (abbreviation)

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

Questionnaires (abbreviation)

- Asthma Control Test (TA)
- Asthma Symptom Utility Index (AS)
- Marks Asthma Quality of Life Questionnaire (MQ)
- OR
- Children's Health Survey for Asthma (PQ)
- Asthma in Females (FQ)
- Home Smoking Activity and Exposure to Tobacco Smoke Questionnaire (SQ) - ages 12-17 only
- Sino-Nasal Questionnaire (SI)
- Block Food Frequency Questionnaire (BF)
- OR
- Block Kids Food Frequency Questionnaire (BK)
- Block Soy Foods Screener (BS)

Log/Administrative forms (abbreviation)

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

*not data entered

2.4 Telephone contact (V3)

Time frame

- Target – 2 weeks after Randomization (V2)
- Window – must be conducted between V2 and V4
- Duration of V3 – approximately 15 minutes

Tasks

- Conduct telephone interview using Phone Contact (PC) form

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

- Reinforce daily Diary Card completion
- 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 first followup visit (V4) and remind participant to bring:
 - All bottles of study supplement
 - Peak flow meter
 - Diary Cards

Form (abbreviation)

- Phone Contact (PC)
-

2.5 Followup visits (V4 to V8)

Time frame

- Targets – weeks 4, 8, 12, 16, 20 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)
 - Asthma Symptom Utility Index (AS)
 - Marks Asthma Quality of Life Questionnaire (MQ)
- OR
- Children's Health Survey for Asthma (PQ)
- Review returned Diary Cards and distribute additional Diary Cards (DC) as needed
- Conduct adverse event screening and interval asthma health history by completing Clinic Visit Form (CV)
- Collect exhaled Nitric Oxide (eNO) and complete Nitric Oxide form (NO) - must be conducted prior to EBC and spirometry
- Collect Exhaled Breath Condensate (EBC) (at V4) - must be conducted prior to spirometry
- Collect PFT data
 - Conduct peak flow procedure
 - Conduct pre- and post-bronchodilator spirometry procedures
- Collect serum for CRP and IL-6 levels (V4) – collect before other blood specimens
- Collect blood for eosinophil count (V4)
- Collect plasma for genistein levels (V4)
- Collect urine specimen for LTE₄ levels (V4)
- Review study supplements dispensed previously. Provide adherence counseling if necessary
 - If bottle has 4 or more tablets remaining, it should be returned to the participant
 - If less than 4 tablets remain in bottle, the clinic should retain the bottle. Record on Tablet Dispensing and Counting Form (DD)
 - Distribute additional study supplement if needed. Record newly distributed bottles on Tablet Dispensing and Counting Form (DD) and on Patient Bottle Accountability Log (PD)
- Key data as recorded on forms into SOYA data system within 10 working days of visit

Forms (abbreviation)

- Clinic Visit (CV)
- Diary Card (DC)
- Tablet Dispensing and Counting Form (DD)
- Nitric Oxide (NO)
- Pulmonary Function Testing (PF)
- Tablet Dispensing and Counting Form (DD)

Questionnaires (abbreviation)

- Asthma Control Test (TA)
 - Asthma Symptom Utility Index (AS)
 - Marks Asthma Quality of Life Questionnaire (MQ)
- OR
- Children's Health Survey for Asthma (PQ)

SOYA MOP

2. Study visits/contacts

2.5. Followup visits (V4 to V8)

Log/Administrative form (abbreviation)

- Patient Bottle Accountability Log (PD)*

*not data entered

2.6 Final visit (V9)

Time frame

- Target – week 24
- Window – weeks 22-26
- Duration of V9 – approximately 3 hours

Tasks

- Have participant complete self-administered questionnaires
 - Asthma Control Test (TA)
 - 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 - MOS SF-36 v2 (MO)
 - OR
 - Child Health Questionnaire Parent Form 50 (CH)
 - Block Food Frequency Questionnaire (BF)
 - OR
 - Block Kids Food Frequency Questionnaire (BK)
 - Block Soy Foods Screener (BS)
- Review returned Diary Cards
- Conduct interval asthma/health history and adverse event screening by completing Clinic Visit form (CV)
- Collect study supplement distributed previously. Count remaining tablets and record on Tablet Dispensing and Counting form (DD)
- Collect exhaled Nitric Oxide (eNO) and complete Nitric Oxide form (NO) - must be conducted prior to EBC and spirometry
- Collect Exhaled Breath Condensate (EBC) - must be conducted prior to spirometry
- Collect PFT data and record on Pulmonary Function Testing Form (PF)
 - Peak flow
 - Spirometry, pre- and post- bronchodilator
- Collect serum for CRP and IL-6 levels – collect before other blood specimens
- Collect blood for eosinophil count
- Collect plasma for genistein levels
- Collect urine specimen for LTE4 level
- Conduct exit interview using Exit Interview form (EI)
- Complete Treatment Termination form (TT), if appropriate
- Complete Unmasking form (UM), if appropriate
- Give participant exit envelope which includes
 - Patient exit letter (see prototype in Section 3.12.2)
 - Sealed treatment unmasking envelope
 - Copy of final spirometry results
- Send physician exit letter (see prototype in Section 3.4.3) to participant’s primary asthma care physician
- Key data as recorded on forms into SOYA data system within 10 working days, as applicable

2.6. Final visit (V9)**Forms (abbreviation)**

- Clinic Visit (CV)
- Tablet Dispensing and Counting Form (DD)
- Exit Interview Nitric Oxide form (NO) (EI)
- Nitric Oxide form (NO)
- Treatment Termination (TT)
- Pulmonary Function Testing (PF)
- Unmasking (UM)

Questionnaires (abbreviation)

- Asthma Control Test (TA)
- 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-MOS SF-36 v2 (MO)
OR
Child Health Questionnaire Parent Form 50 (CH)
- Block Food Frequency Questionnaire (BF)
OR
Block Kids Food Frequency Questionnaire (BK)
- Block Soy Questionnaire (BS)

Log/Administrative form (abbreviation)

- Patient Bottle Accountability Log (PD)*

*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)
 - phone contact (V3 only)
- Document missing Diary Cards since last visit as associated with the upcoming 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 V9 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 4, 5, and 6, and returned to the study during the time window for Visit 7, then a Visit 7 should be conducted)

Form (abbreviation)

- Missed Data (MD)
-

2.8 Rescreening and recycling

Rescreening

Purpose

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

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
- 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
- DO NOT delete original forms 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 name code and Pt ID assigned to 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

Form (abbreviation)

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

SOYA MOP**3. Procedures**

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3.1 Clinic certification

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3.1.1 Clinical center 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 SOYA
- Ensure consistent conduct of the trial over time within and across clinics so that findings from all clinics are comparable

When

- Before an ALA-ACRC clinical center and/or primary SOYA satellite center may enroll and treat patients for the Study of Soy Isoflavones in Asthma (SOYA)
- Prior to receiving study tablet kits

Tasks

- To be completed by main ACRC clinical center and satellites and all SOYA staff
- Acquisition of approval of protocol and consents from the clinical center's IRB
- Review of SOYA protocol and procedures
- Arrangements for facilities, equipment, and supplies that are needed to conduct SOYA procedures
- Completion of the Clinical Center Certification form (CC) by the main ACRC clinical center
- Completion of General Knowledge Assessment (GEN) and Personnel Assurance Statement (PA) by all staff members to be certified. 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 SOYA 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
 - Can be repeated unlimited number of times
- Additional clinic coordinator certification requirements
 - Entering of all staff members requiring 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 a sample Pulmonary Function Testing (PF) form (abstracted from a pulmonary test lab report from the clinical center) and online calculation of predicted FEV₁
 - Completion of Data System Operator requirements
- Additional requirements for ACRC Center Director
 - Completion of Spirometry Assurance Statement (SA)
 - Completion of Methacholine Challenge Test Assurance Statement (MA)
- Attendance by key study personnel at 10-11 February 2010 training meeting or other training authorized by the Data Coordinating Center
- Additional Data System Operator requirements
 - Completion of the certification data system tutorial (online, under Data System)
 - Completion of Data System Operator Knowledge Assessment (online, under Certification Materials)

3.1.1. Clinical center and staff certification

- Training of all personnel who did not attend formal SOYA training meeting in study procedures and form completion, as well as good clinical practice and research integrity
- Completion of online SOYA data entry tutorial for staff members who will be entering data into the SOYA database (see MOP section 3.1.2).
- It is recommended that the lead coordinator be certified for data entry as this certification is required to enter the Screening (SC) form and to randomize a participant online
- Submission of Clinical Center Certification form (CC), 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, and all other required approvals, materials and printouts to certification coordinator at Data Coordinating Center (**mailed or faxed**). (See Certification Checklist in MOP section 3.1.4)
- Receipt of a notification of clinical center and staff certification from the Data Coordinating Center (via e-mail)

Facilities

- Secure area for supplement 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 supplement supplies
- Pulmonary function, EBC, and eNO testing equipment

Equipment and materials required of clinical center

- Koko spirometer to measure FEV₁ and FVC
- Equipment to measure height and weight
- Equipment to measure eNO
- Pregnancy test kits
- Computer requirements for data entry and printing forms
 - Microsoft Windows (95, 98, ME, NT, 2000, XP, or Vista)
 - Microsoft Internet Explorer (5.5, 6.0, or 7.0)
 - Adobe Acrobat Reader 5.0 or above (available free from www.adobe.com)
 - Printer

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)
 - SOYA Personnel Assurance Statement (PA)
 - Methacholine Challenge Test Assurance Statement (MA)
 - Diary Card (DC)
 - Pulmonary Function Testing (PF)
 - Spirometry Assurance Statement (SA)
-

3.1.2 Data system certification

Access to the SOYA 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.

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 a SOYA 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 SOYA 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 SOYA 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 SOYA 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 SOYA web page at <http://www.jhcct.org/Secure/SOYA/SOYAHome.htm>. Access to any part of the SOYA 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, the system will assign a dummy password. This password must be changed the first time that user logs in to the data system.

*SOYA 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 SOYA. In this case, please note this when submitting other certification materials.

3.1.3 Consent statement checklist

Clinic: _____ Reviewer: _____ Date reviewed: _____

SOYA CONSENT CHECKLIST – based on Protocol version 2.0, 26 Mar2010

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 SOYA consent form in addition to statements required by your local IRB. Before submitting to your local IRB, be sure all items listed below are included. If you are unclear as to the inclusion of certain items in your consent, you may submit the completed checklist with your consent to the DCC for review prior to submission to your IRB. For SOYA certification, this completed checklist (noting the location in the consent where statement is found) must be submitted to the DCC along with your IRB-approved consent as part of your certification package.

Record page where item found in consent in left-hand space below

- _____ 1. Letter or stamp of approval from IRB with date approved and expiration of approval
- _____ 2. Full name of trial – Study of Soy Isoflavones in Asthma (SOYA)
- _____ 3. Sources of funding – ALA and NHLBI
- _____ 4. Participant encouraged to read the consent form carefully and ask questions
- _____ 5. Participation is voluntary; no penalty if quit study
- _____ 6. No access to test results during the study, but can be obtained if an emergency
- _____ 7. Participation in study not meant to replace usual care for asthma. Should tell your regular asthma doctor that you are in this research study. Also, we will send a letter to your asthma doctor to let them know that you are in this research study
- _____ 8. We may contact your physician during the study if you have poor asthma control and need additional care
- _____ 9. Asked to join study because you are being treated for asthma and are having some problems controlling your symptoms
- _____ 10. Purpose of the trial: to find out if soy isoflavones (chemicals found in soybeans) improve lung function and reduce asthma symptoms in patients with poorly controlled asthma
- _____ 11. Study treatment - soy supplement (Novasoy®) or placebo
 - _____ Soy supplement being tested as a treatment for asthma
 - _____ Use of soy supplement for asthma is investigational
 - _____ Approved by FDA as used for this study
 - _____ Provided by Archer Daniels Midland
- _____ 12. Number of participants -approximately 380
- _____ 13. To be conducted at network of 19 clinical centers around the United States

3.1.3. Consent statement checklist

- ____ 14. Participant to continue on current asthma medication
- ____ 15. Study drug dosing
 ____ Supplement and placebo in form of a tablet
 ____ To be taken twice daily
- ____ 16. General description of randomization
- ____ 17. Length of participation (6 months)
- ____ 18. Study supplement or placebo masked to participant and clinic staff
- ____ 19. General description of 8 study visits and 1 phone call – timeline
- ____ 20. Specific description of all procedures and questionnaires completed (spirometry, methacholine challenge, peak flow meter, asthma diary, questionnaires, and exhaled nitric oxide)
- ____ 21. Specific description of collected samples (exhaled breath condensate, blood draws, and urine samples)
- ____ 22. Use of blood for DNA testing is optional and not required for participation
- ____ 23. Females who have reached menarche to have pregnancy tests at screening and randomization visits, and before each methacholine challenge test
- ____ 24. Risks/Discomforts
- ____ Possible side effects of study supplement and procedures
- Allergic reaction to soy isoflavone supplement (skin rash, itching, difficulty breathing, difficulty swallowing, low blood pressure and passing out).
 - Isoflavones– none know at this time. Participants will be monitored for possible soy isoflavone side effects
 - Spirometry – chest soreness or lightheadedness from forceful blowing into spirometer
 - Albuterol – tremors, chest tightness, dizziness, nervousness, cough, headaches, sleeplessness, and, rarely, serious allergic reactions
 - Methacholine challenge – mild cough, shortness of breath or wheezing. Could include severe bronchoconstriction (like an asthma attack). Test will never be conducted on participants experiencing asthma symptoms, with low lung function at time of test, or has a known allergy to methacholine
 - Peak flow – chest soreness or lightheadedness if used standing up
 - Blood draw – discomfort, bruising; or, on rare occasions, infection or fainting
 - May be risks or side effects unknown at this time. Will be monitored for signs of possible adverse side effects from the soy supplement
- ____ Blood test for DNA - very small risk that results may be reviewed by an unauthorized person
- ____ Pregnancy - effect of soy supplement on sperm, egg, fetus, and new borns has not been studied. Also, safety of methacholine during pregnancy/nursing is unknown. Cannot participate if pregnant or breast feeding. If participant becomes pregnant during the study, they must inform study doctor immediately.

3.1.3. Consent statement checklist

25. Benefits
 No guaranteed health benefit
 Will receive an assessment of general health and asthma
 Results of the research may help understand how nutrition affects asthma
26. Payment/cost for participation
 No cost to participant
 Some financial compensation for completed procedures or visits
27. Voluntary nature of participation
 Participation is voluntary
 If decide not to participate, access to medical care at (site) will not be affected
 Participation in study may be discontinued early by participant or study doctor
 If decide to leave the study early, data collected to that point may be used for study purposes
28. HIPAA/Confidentiality – how personal data is handled
 Organizations such as governmental agencies, participating doctors and staff, processing labs, data coordinating center, and sponsors may see your health information
 Information collected includes contact information and personal health information from you or your child, and your doctor
 Use and disclosure of Information only as described in the consent and Notice of privacy
 Cannot participate if you choose not to share health information
29. Compensation for injury – the American Lung Association, Johns Hopkins Medical Institutions, and the federal government noted as not responsible. Participant and his/her insurance company are responsible for costs due to injury
30. Contact information
 At least one name and number (i.e., PI or coordinator) for questions or problems
 Person or group to contact if questions about rights as a participant
31. Ownership of data, blood, genetic material, and specimens
 Participant will not own the data, blood, and specimens given for the research
 Will not own product or idea resulting from the study
 No financial benefit from creation, use, or sale of products or ideas from study
32. Y/N Checkoff for blood draw use for DNA testing
33. Signing of consent – spaces for signature and date for participant, person obtaining consent witness (if required by IRB), and parent or legally authorized representative (if applicable)
34. Assent for children (if participant under age of 18) - as separate document or section of consent form
35. Information in consent explained to child in presence of parent/caretaker in language child could understand

3.1.4 Clinic and staff certification checklist

The following documents need to be completed and submitted to the Certification Coordinator at the DCC to obtain certification.

Primary Certification form

- Clinical Center Certification (CC) form (completed by Lead Coordinator and signed by Principal Investigator)

Study documents

- IRB notice of approval of SOYA protocol
- IRB approved Consent Statement with IRB stamp or notice of approval
- IRB approved Assent Statement with IRB stamp or notice of approval
- Consent checklist - noting page where each item is found in the consent

All staff

- SOYA General Knowledge Assessment (GEN) – printout of online test result
- SOYA Personnel Assurance Statement (PA)

Additional Main ACRC Clinic Director requirements

- SOYA Methacholine Challenge Test Assurance Statement (MA)
- Sign off on Clinical Center Certification (CC) form

Additional Coordinator requirements

- Sample SOYA Diary Cards (DC)
- Sample Pulmonary Function Testing (PF) form with printout of online calculator results and anonymized patient pulmonary function test results report from which the PF form was completed
- Sample Methacholine Challenge Testing (MC) form (if not previously certified for this)

Additional data system operator requirements

For new data system operator not previously certified for ACRC data entry

- Certification Data System (CD)
 - Data system operator knowledge assessment (DSO) - printout of online test
-

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 SOYA website (<http://www.jhcct.org/Secure/SOYA/SOYAhome.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 kits or \$1200 for 100 test kits
 - Sensors alone are the same price as the kits
- For sensor/filter kits for substudy contact the DCC

Data Coordinating Center will distribute the following:

- 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 Educational Materials
 - SOYA Wallet Cards
 - ACRC appointment cards
 - 1" participant binders with SOYA cover
- Questionnaires (hard copy)
 - Block 2005 Food Frequency Questionnaire (BF)
 - Block 2004 Kids Food Frequency Questionnaire (BK)
 - Block Soy Screener (BS)
 - Serving Size choices sheet
 - Forms and other questionnaires will be posted on the SOYA website
- Specimen collection supplies (supplies with asterisk (*) are not distributed automatically at study start-up, but are available on request)
 - EBC (exhaled breath condensate)
 - RTube™ (disposable plastic collection tube and mouth piece) for EBC collection
 - 1.2 mL conical cryovials, white top
 - Micropipettor tips
 - Cooling sleeve with insulated cover*
 - Plunger*
 - Freezer bags for cooling sleeve*
 - Micropipettor (1 per clinic)*

3.2. Study supplies

- Urine for LTE₄ levels
 - Urine specimen collection cup
 - 2.0 mL cryovials, red top
- Blood for genistein levels and DNA
 - Vacutainers, 10 mL, lavender top
 - 2.0 mL cryovials, orange top
- Serum for CRP and IL-6
 - Vacutainers, 10 mL red/gray top, serum separator
 - 1.2 mL cryovials, white top, external thread
- eNO supplies
 - NIOX MINO unit
 - Start-up test supply kit containing 50 patient filters, 50 sensors
 - Quality control equipment
 - White QC card
 - QC filter for weekly QC testing
- Methacholine testing supplies
 - Mouthpieces for nebulizer cups
 - Expiratory filters for T-piece
 - Step down adapters
 - T-pieces
 - Syringe filter for transferring MeCI solution to nebulizer cup
 - Calibrated nebulizer cups
- Other SOYA supplies
 - Pre-printed Vacutainer Label Sheet
 - Pre-printed Cryovial Label Sheet
- ACRC general supplies
 - Marking pens for labels
 - Disposable transfer pipettes
 - Cardboard boxes for cryovial storage in freezer and shipping
- ACRC shipping supplies
 - Styrofoam shippers
 - Plastic biohazard specimen bags
 - Absorbent sheets
 - Dry ice label (UN 1845)
 - UN3373 label

Ordering additional supplies from Data Coordinating Center

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

Clinical Centers will provide

- Vacutainers for eosinophil analysis (per local hospital's instruction)
- Blood collection supplies (needles, tourniquet, etc)
- Dry ice
- Scotch tape

3.2. Study supplies

- FedEx mailing labels
- Packing material (bubble wrap, “peanuts,” or crumpled newspaper)
- Study forms and questionnaires (downloaded from SOYA website <http://www.jhct.org/Secure/SOYA/SOYAHome.htm>)
- Pregnancy test kits
- Nose clips for spirometry
- Insulated gloves for handling aluminum cooling sleeve (EBC) and/or dry ice
- Scrubbers and disposable mouthpieces, if applicable

Forms (abbreviation)

- Methapharm Order Form (MP)
 - Peak Flow Meter Order Form (PO)
 - SOYA Supply order form (YO)
 - ACRC General Supply order form (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 SOYA cover
- Labels, ML-1000

Instructions and materials included

- Information label - on front of inside pocket. Use ML-1000 labels provided by DCC. For each clinical center 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 SOYA data system page (<http://www.jhcct.org/Secure/SOYA/SOYAHome.asp>)
 - 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 1 (date) 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 left of the form (optional)
- Spare Diary Cards - include 4-5 blank cards
- Temporary Asthma Action Plan Sheet (TAP)

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

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3.4.1 Prototype: Physician introduction letter

Dear Dr. _____:

Your patient, _____, was recently enrolled in the clinical trial, the Study of Soy Isoflavones in Asthma, or SOYA. This study is designed to test the hypothesis that, patients (12 and older) with symptomatic asthma have improved lung function when treated with a soy isoflavone dietary supplement. This randomized, double-masked, placebo-controlled trial involves 19 clinical centers in the United States and will enroll approximately 380 patients whose asthma has been poorly controlled on at least one controller medication such as an inhaled corticosteroid and/or leukotriene and may benefit from a change in or additional therapy to improve asthma control. After initial tests and questionnaires to determine eligibility followed by a 2 to 8 week run-in period, patients who meet eligibility criteria will be randomized to one of two treatment groups:

- Soy supplement (Novasoy®) that contains 50mg of isoflavones (genistein, daidzein and glycitein), twice daily
- OR
- Matching placebo twice daily

Patients will receive the study treatment in addition to their regularly prescribed asthma medication. Treatment will last approximately 24 weeks with 6 follow-up clinic visits during the trial period. The trial will collect information concerning demographics, medical history, lung function results, as well as asthma symptoms and diet (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 supplements 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 and spirometry results. 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 provider

RESEARCH SUBJECT CONSENT TO RELEASE BREATHING TEST RESULTS FORM

Title: The Study of Soy Isoflavones in Asthma (SOYA)

Protocol No.: xxxxxxxxxxx

Sponsor: National Heart, Lung, and Blood Institute (NHLBI)/The American Lung Association (ALA)
Bethesda, Maryland/New York, New York
United States

Investigator: Robert A. Wise, M.D.
Johns Hopkins University
5501 Hopkins Bayview Circle
Baltimore, MD 21224
(410) 550-0545
(410) 905-5688 (24-hour pager)

Site(s): Johns Hopkins University
Bloomberg School of Public Health
ACRC Coordinating Center
Johns Hopkins Center for Clinical Trials
615 North Wolfe Street, Room W5010
Baltimore, MD 21205

**STUDY-RELATED
PHONE NUMBER(S):** Research study questions
Janet Holbrook, MPH, Ph.D.
410-955-0930

Research-related injury
Robert Wise, M.D.
410-550-0545
443-287-5791 (24-hours)

SOYA MOP

3. Procedures**3.4.2. Prototype participant release to send spirometry results to asthma care provider****SUB-INVESTIGATOR(S):** Janet Holbrook, MPH, Ph.D.**Permission to Notify Physician:**

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

 Printed Name of Subject

 Date

 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 the clinical trial, the Study of Soy Isoflavones in Asthma, or SOYA. This study was designed to test the hypothesis that, patients (12 and older) with symptomatic asthma have improved lung function when treated with a soy isoflavone dietary supplement. This randomized, double-masked, placebo-controlled trial involved 19 clinical centers in the United States and enrolled approximately 380 patients whose asthma has been poorly controlled on at least one controller medication such as an inhaled corticosteroid and/or leukotriene and may benefit from a change in or additional therapy to improve asthma control. Patients who met eligibility criteria were randomized to one of two treatment groups:

- Soy supplement (Novasoy®) that contains 50mg of isoflavones (genistein, daidzein and glycitein), twice daily
OR
- Matching placebo twice daily

Patients received the study treatment in addition to their regularly prescribed asthma medication. Treatment lasted approximately 24 weeks with 6 follow-up clinic visits during the trial period.

Your patient has now stopped taking the study treatment 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 test. 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 more times to obtain 3 readings. Record the highest of the 3 readings on the diary card.
 - 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 Temporary Asthma Action Plan (TAP)

Note: Personal best for Temporary Asthma Action Plan (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 SOYA data system upon data entry of the Randomization form (RZ). 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)

[3.5. Peak flow procedures](#)**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

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3.6.1 Spirometry procedures

Purpose

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

When

- Visits 1, 2, 4-9

Standardization of equipment

- 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 SOYA pulmonary function calculator. To access the online calculator go to the SOYA website: <http://www.jhcct.org/Secure/SOYA/SOYAHome.htm> and follow the link to the SOYA data system page and then to the SOYA 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

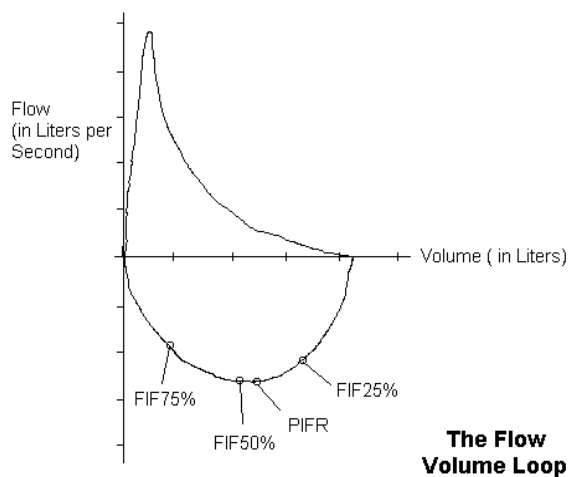
- Test performed at least 4 hours after last dose of short-acting bronchodilator and at least 12 hours after the last dose of long-acting bronchodilator
- Participant is seated with feet flat on floor
- Participant is wearing nose clips
- Restrictive clothing is loosened

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 FV 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 (FEV₁ 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

3.6.1. Spirometry procedures

- 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 **FEV₁** 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
 - **FEV₁:** The second largest FEV₁ should be within .2 L of the largest acceptable FEV₁
- 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 FEV₁ 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.



- Print out the individual curves, if the equipment allows. Otherwise, whatever quality assurance values are obtained should be noted (this depends on equipment)
- Note quality assurance values: time to peak flow, back extrapolation volume, and total expiratory time to help assess the quality of each maneuver and overall test session
- Calculate FEV₁ percent predicted value:
 - Use SOYA online calculator from SOYA website:
<http://www.jhcct.org/Secure/SOYA/SOYAHome.htm>
 Follow link to data system page and then to the SOYA calculator
 - OR**
 - Manually calculate using predicted FEV₁ value per Hankinson (formula in Table 3.6.2) and the following formula:
 Percent predicted = $FEV_1 / \text{predicted } FEV_1 \times 100$

3.6.1. Spirometry procedures

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 SOYA 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 FEV₁ (item 13 on PF form)
- Administer bronchodilator
 - Administer 2 puffs of metered dose inhaler (MDI) albuterol
 - Wait 15 - 30 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 FEV₁
- Calculate pre- and post-bronchodilator percent predicted FEV₁
 - Use the following formula:
Percent Predicted = FEV₁ / predicted FEV₁ x 100
 - Percent predicted pre-bronchodilator FEV₁
 - Calculated using pre-bronchodilator FEV₁
 - Percent predicted post-bronchodilator FEV₁
 - 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: $PFT = Z + A(\text{Age}) + B(\text{Age}^2) + C(\text{Height}^2)$

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.

3.6.3 Spirometry over reading

Summary

- SOYA will conduct spirometry quality assurance to include over-reading by a “Spirometry Reading Center” (SRC) to evaluate the performance of spirometry sessions and to provide feedback to ACRC Centers about the quality of their spirometry testing. Clinics will submit an ACRC spirometry Quality Assurance (QA) report after each spirometry session at their clinic.

Certification

- A staff member will be “provisionally certified” as a spirometry tester for SOYA after they have submitted a satisfactory Pulmonary Function Testing (PF) form along with results from a KoKo spirometer using software version 4.11. With provisional certification staff members may perform spirometry on SOYA participants.
- After a staff member has submitted 5 acceptable QA reports they will become fully certified to administer spirometry for ACRC studies.

Procedures for Quality Assurance Reviews

- The results of all spirometry sessions for SOYA **must** be submitted for quality assurance review using the customized “ACRC Spirometry Quality Assurance (QA) report.”
- The report for each session may be submitted in any of the following ways:
 - QA Report is saved directly as a PDF file within the KoKo software (“Save PDF Report”) and emailed to the SRC at spiro@jhct.org
 - QA Report is printed on paper and faxed to the SRC at 443-817-0610
 - QA Report is printed on paper and then scanned to PDF format and emailed to the SRC at spiro@jhct.org
- The SRC will review the report to evaluate all aspects of spirometry testing, including maneuver acceptability (rapid start, end-of-test, no coughing, etc.), repeatability of FEV₁ and FVC, and number of maneuvers attempted. The SRC will assign grades and provide an assessment of the overall session as follows.

3.6.3. Spirometry over reading

- The SRC will assign grades for flow (FEV₁) and volume (FVC) and will provide an assessment of the overall session as follows:

FVC and FEV₁:

Grade	Criteria
A	Repeatability 0.00L - 0.10L
B	Repeatability 0.11L - 0.15L
C	Repeatability 0.16L - 0.20L
D	Repeatability >0.20L

Session Assessment:

Assessment	Criteria
Excellent	At least 3 acceptable maneuvers; two repeatable (i.e., grade of A or B for both FVC and FEV ₁)
Good	8 maneuvers attempted if unacceptable or not repeatable
Fair	Fewer than 8 maneuvers attempted but at least 1 acceptable
Unacceptable	0 acceptable maneuvers

Instructions for filling out the QA report:

- Fill in all required fields at the top of the QA Report. Be aware of special instructions for the following:
 - ID:** Add SOYA participant ID. For a provisional certification report use a number from 900 to 999 for your clinic. (For example, BCM would use YA900, DUKE would use YB990, YB991, etc)
 - Tech** (technician): Use spirometry tester's ACRC PIN (note: the KoKo carries over the name of the last technician to use the machine if this field is not updated)
 - Comments/Visit ID:** Add "Visit Vx" where "x" is the number of the visit. Use V0 for certification. Also include any other important information, such as "participant was ill and couldn't perform well," "participant unable to complete all testing," etc.

3.6.3. Spirometry over reading

Instructions for reviewing submitted QA reports:

- From the SOYA data system main page, select the option “SOYA Spirometry Review System”
- After a spirometry report has been submitted it will be categorized as either “pending” (waiting to be graded by the SRC), “graded” (waiting for clinic review), or “completed” (graded and reviewed). In order to see the status of your report, select one of these options.
- After a clinic reviews a graded report they can mark it as “completed” by clicking anywhere in the row, reviewing the grades and comments, entering their own comments if desired, and clicking the “Save Review” button.

Spirometry tester certification

- All staff administering spirometry for SOYA must be certified by the DCC. Spirometry testers must obtain provisional certification to begin testing and then will become fully certified after 5 acceptable QA report on ACRC participants have been submitted and graded. Each clinic must have at least one provisionally certified spirometry tester to begin SOYA activities.
 - For provisional certification staff should submit the following to spiro@jhct.org or to fax number 443-817-0610:
 - “ACRC Spirometry Quality Assurance (QA)” report from a demonstration spirometry session. The spirometry session must have been performed in 2010 or later. The spirometry sample can be from a co-worker or participant in an ACRC trial, however, if the spirometry for provisional certification was done on a co-worker, it will not count towards the 5 required spirometry tests for official certification. Spirometry **for provisional certification** can contain both pre- and post-bronchodilator, or just pre-bronchodilator by itself. All fields in the report must be properly filled out.
 - A printout showing correct KoKo settings for the demonstration session. Spirometry testers who have already received provisional certification should submit a printout to show the correct KoKo setting.
 - The submitted QA report for provisional certification will be graded and must receive a session assessment of “Excellent” or “Good.” After receiving the required grade the DCC will notify the tester that they are provisionally certified and they may begin administering spirometry for SOYA.
 - When a spirometry tester has submitted five acceptable (session assessment of “Excellent” or “Good” and performed on an ACRC participant) spirometry QA reports during the trial, they will be officially certified as a spirometry tester for ACRC trials. The DCC will notify the tester and this certification can transfer to future trials, such as STAN.
-

3.7 Methacholine challenge

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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 FEV₁ by 20% from post-diluent baseline (PC₂₀). All participants with FEV₁ \geq -70% predicted at V1, and who did not demonstrate either FEV₁ bronchodilator responsiveness \geq 12% or positive methacholine challenge in the past 2 years, will need a MeCI test.

3.7.2 Purpose and schedule

Purpose

- To measure airway reactivity to establish eligibility

When

- V1 – For participants who have not demonstrated 12% reversibility or a positive MeCI test within the last 2 years. The test will be conducted after the physical exam and spirometry tests on participants who demonstrate FEV₁ greater than or equal to 70% of predicted
-

3.7.3 Requirements for personnel administering the methacholine challenge

The methacholine challenge administered by an ACRC clinic will be performed according to the methacholine protocol as outlined in section 3.7.11 of the MOP and posted on the SOYA website (<http://www.jhcct.org/Secure/SOYA/SOYAHome.asp>). The SOYA methacholine protocol is based on ATS recommendations. The test is to be conducted either: (1) by ACRC staff with experience conducting methacholine challenge tests at clinical center facility, or (2) by non-ACRC staff at a pulmonary testing lab in the clinical center's facility or institution, or (3) by non-ACRC staff at an outside pulmonary testing lab that has been identified by clinical center staff.

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

- All centers must use the KoKo spirometer, the external KoKo dosimeter, and characterized nebulizer cups. The nebulizer cups are supplied by the DCC.
 - The Principal Investigator must complete the Methacholine Challenge Test Assurance Statement (MA)
 - 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 SOYA methacholine challenge tests conducted at or for the clinical center and any affiliated clinical sites. The statement asserts the following:
 - All methacholine challenge tests conducted at the clinical center and satellite clinics will be conducted in accordance with the SOYA 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 (clinic staff and affiliated or outside lab technicians) must complete certification requirements approved by the DCC before they may conduct methacholine challenge tests.
-

3.7.4 Contraindications

Absolute contraindications

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

- FEV₁ < 70% predicted or < 1 L (using Hankinson predicted equations, or using the SOYA online calculator).
- Myocardial infarction or stroke within last 3 months
- Known arterial aneurysm
- Uncontrolled hypertension (ie, SBP > 200, DBP > 100)
- Positive pregnancy test or breast feeding (For women of child-bearing potential a negative pregnancy test is required before every methacholine challenge)
- 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.

3.7.5 Medication holds prior to methacholine challenge

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

Short-acting β -agonists	at least 6 hours
Medium-acting β -agonists	24 hrs
Long-acting β -agonists	24 hrs
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
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.

3.7.6 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.

3.7.7 Patient instructions

- Two to three days before the test, remind patient
 - to hold medications as detailed in Section 3.7.5
 - to abstain from caffeine, cola drinks, and chocolate on the day of the test
 - to abstain from exercise and smoking for 6 hours before his/her methacholine challenge appointment
- Instructions prior to 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).

3.7.8 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
-

3.7.9 Equipment and supplies

- Concentrations of methacholine solution (described in MOP section 3.7.10)
- KoKo External Dosimeter
- Step down adapter*
- T-pieces*
- Characterized nebulizer(s)* (other nebulizers not acceptable)
- Mouth pieces for nebulizer cups*
- KoKo Spirometer (with nose clip, mouthpiece)
- Timer
- Oxygen
- Stethoscope, sphygmomanometer, pulse oximeter
- Resuscitation equipment
- Emergency medications including albuterol (MDI and for nebulization) and atropine
- Expiratory filters for T-piece*
- Compressed air tank
- Syringe for methacholine solutions
- Syringe filters for transferring methacholine solution to nebulizer*

Methacholine testing supplies and equipment not noted as supplied by DCC 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

†Contact DCC for list of suppliers

3.7.10 Preparation of methacholine solutions

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)
- **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)

3.7.10. Preparation of methacholine solutions

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.

3.7.11 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 \geq 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 \geq 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 \leq 80% of baseline FEV1, terminate challenge

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

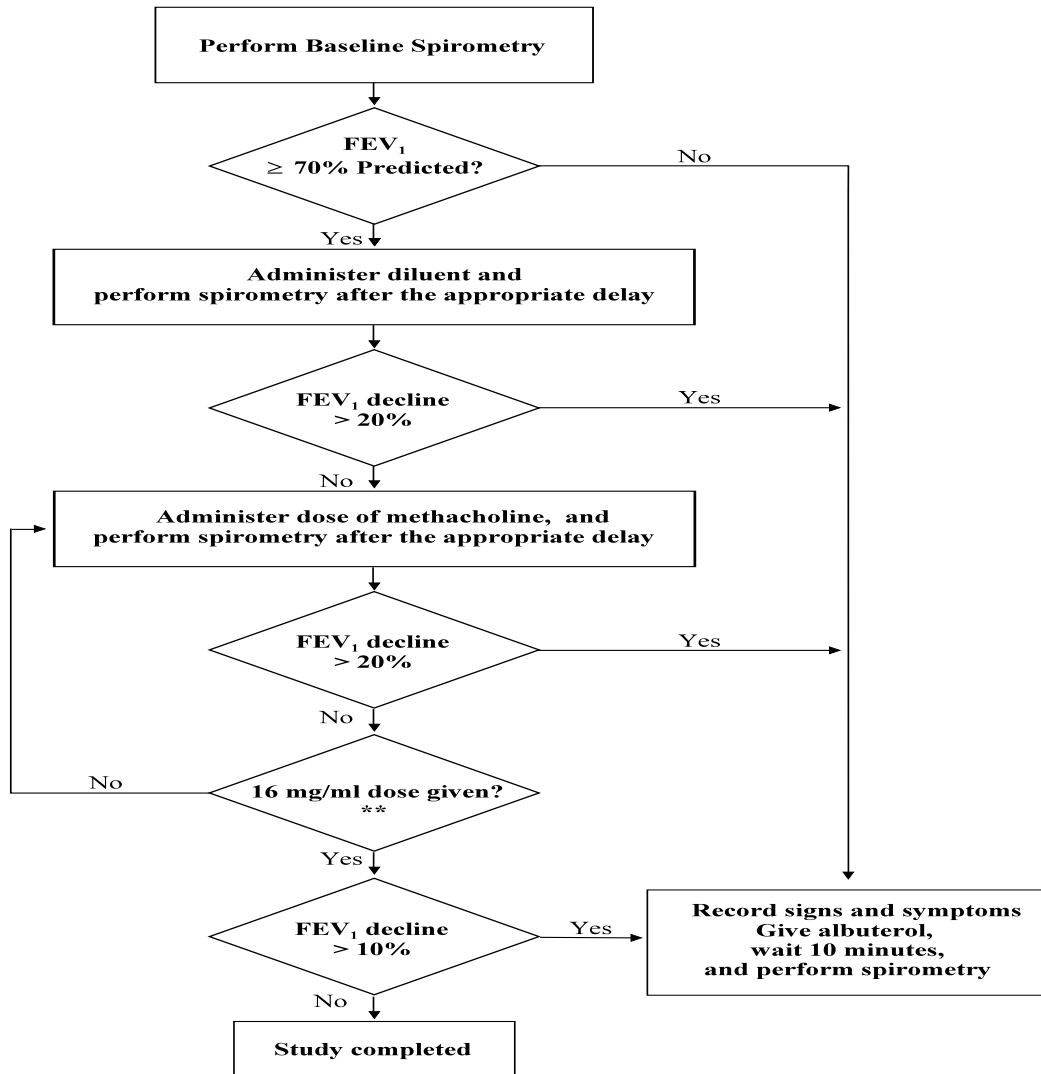
8. Empty nebulizer by shaking excess fluid into sink. Trigger the dosimeter once to dry the nebulizer nozzle. Withdraw 2 mL of first methacholine dose and place in same nebulizer
9. Follow procedure as outlined in #5-7 above
 - If the highest post methacholine FEV1 is $>$ 80% of post diluent FEV1, proceed to the next dose (steps #5-7 above). **Note: even if one of the FEV1 measurements is \leq 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 \leq 80% of the post diluent FEV1, terminate the challenge

3.7.11. Administration of methacholine challenge**10. Administration of bronchodilator**

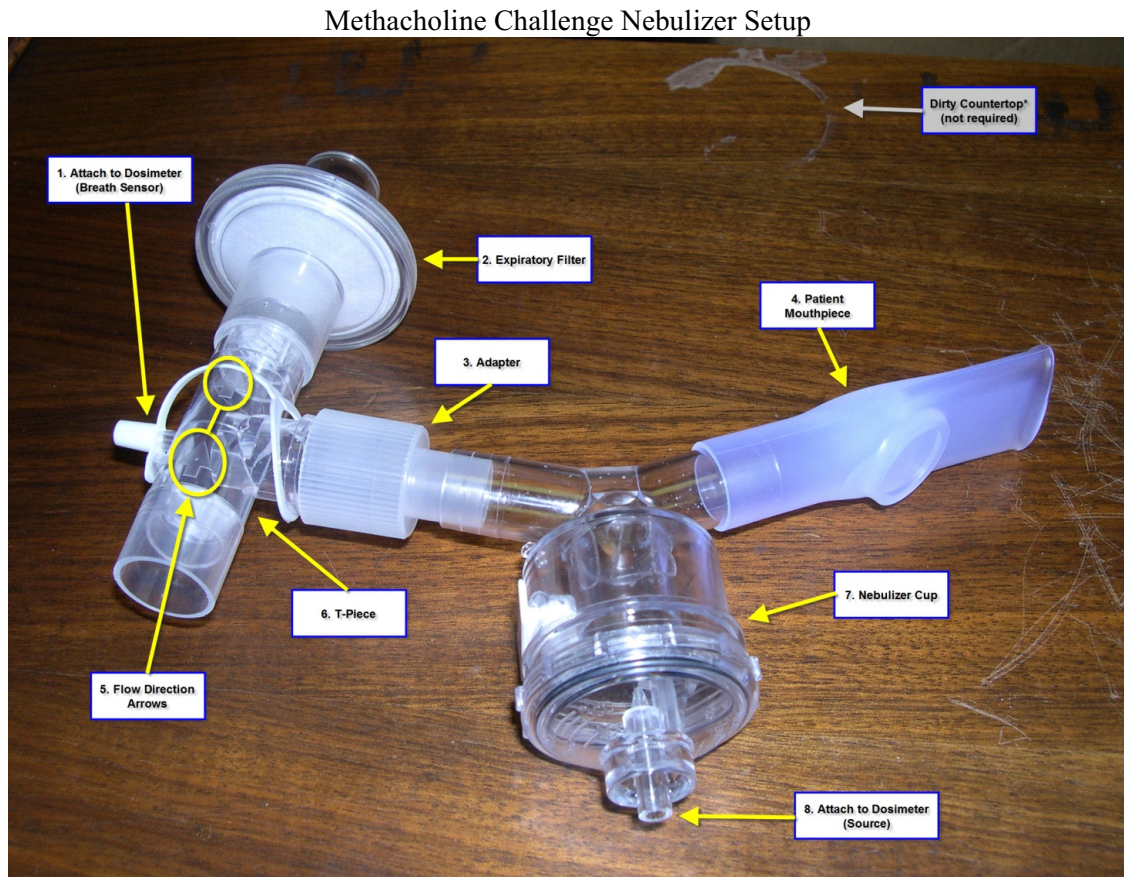
- If the highest FEV1 from any dose is $\leq 80\%$ of baseline (as found in Step #5) when the test is terminated or completed, administer 2 puffs bronchodilator (albuterol) by MDI with spacer. Wait 10 min and repeat spirometry. If post bronchodilator FEV1 is 90% or greater of baseline, the patient is 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

3.7.12 ATS methacholine challenge testing sequence (flow chart)



3.7.13 Pictorial of equipment set-up



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 Specimen collection

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3.8.1 Overview of specimen collection schedule

- **Visit 2**
 - Blood for DNA, genistein level, CRP, IL-6, and eosinophil count
 - Exhaled breath condensate (EBC) for 8-isoprostane
 - Urine for leukotrienes
- **Visit 4**
 - Blood for genistein level, CRP, IL-6, and eosinophil count
 - Exhaled breath condensate (EBC) for 8-isoprostane
 - Urine for leukotrienes
- **Visit 9**
 - Blood for genistein, CRP level, IL-6, and eosinophil count
 - Exhaled breath condensate (EBC) for 8-isoprostane
 - Urine for leukotrienes

3.8.1. Overview of specimen collection schedule

Visits	Specimen	Collection tube	Label	Processing	Action
V2, 4, 9	IL-6 and CRP (collect first)	10 mL red/gray top Vacutainer tube	Designated labels from <i>Cryovial Label Sheet</i> Aliquots 1-4	<ul style="list-style-type: none"> Let blood sit in serum separator tube for at least 30 min at room temperature Centrifuge for 15 min at >1500xg Aliquot serum into four 1.2 ml cryovials (white top) Store at -70°C 	Batch, ship (frozen) priority overnight to: Dr. Lewis J. Smith Northwestern Memorial Hospital Clinical Research Unit Core Laboratory 251 E. Huron, Feinberg 10-754 Chicago, IL 60611 Upon shipment, send email to: j-franzen@northwestern.edu
	Genistein levels and DNA	10 ml lavender top Vacutainer (EDTA)	Designated label on <i>Vacutainer Label Sheet</i> Cryovial: Genistein level label from <i>Cryovial Label Sheet</i>	<ul style="list-style-type: none"> Centrifuge for 7 min at 2000g, 4°C Immediately remove plasma from Vacutainer tube and place in two (2.0 mL) cryovial (orange top) Freeze cryovials and Vacutainer at -70°C At V2 only, replace vacutainer top and freeze packed cells for DNA analysis 	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
	eosinophil count (whole blood)	as specified by local lab		<ul style="list-style-type: none"> as specified by local lab 	-send for local analysis within time period specified by local lab - record results on CV form
	Exhaled breath condensate (EBC)	RTube™	RTube™ pre-affixed label Cryovials: EBC labels from <i>Cryovial Label Sheet</i> • Aliquot 1-3	<ul style="list-style-type: none"> Remove RTube™ from cooling sleeve Remove mouthpiece Plunge tube and transfer specimen into three 1.2 mL cryovials (white top) Freeze at -70°C 	Batch, ship (frozen) priority overnight to: Dr. Lewis J. Smith Northwestern Memorial Hospital Clinical Research Unit Core Laboratory 251 E. Huron St., Feinberg 10-754 Chicago, IL 60611 Upon shipment send email to: j-franzen@northwestern.com
	Creatinine and leukotrienes (spot urine)	Urine collection cup	Cryovials: urine labels from <i>Cryovial Label Sheet</i>	<ul style="list-style-type: none"> Fill four 2.0 mL cryovials (red top) to 1.8 line and freeze at -70°C 	Batch, ship (frozen) priority overnight to: Dr. Lewis J. Smith Northwestern Memorial Hospital Clinical Research Unit Core Laboratory 251 E. Huron St., Feinberg 10-754 Chicago, IL 60611 Upon shipment send email to: j-franzen@northwestern.edu

3.8.2 EBC

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3.8.2.1 Preparation

Purpose

To collect liquid condensate from exhaled breath for analysis of 8-isoprostane levels

When

- V2, V4, and V9
- Before spirometry (PFT)
- After eNO testing

Supplies for collecting, aliquoting, and storing

Provided by DCC

- RTube (disposable plastic collection tube and mouthpiece)
- Three 1.2 mL cryotubes, white top
- Micropipettor tips
- Labels for Cryovial Label Sheet (SOYA EBC #1, 2, and 3) [see section 3.8.9 for example]
- Cryovial box for storing specimens in freezer and shipping
- Aluminum cooling sleeve*
- Blue insulated cover for cooling sleeve*
- Evacuation plunger*
- Plastic freezer bag (to hold cooling sleeve)*
- 250 μ L micropipettor*

Provided by Clinic

- Insulated gloves for handling chilled RTube and/or dry ice

Participant preparation

- No food and beverages for one hour prior to EBC collection
- eNO collection must be done prior to EBC collection
- Spirometry must be done after EBC collection

Equipment preparation

- **Check valve operation on RTube**
 - If the RTube has been stored for longer than 6 months or stored in a warm environment the valve inside the tube may stick
 - To eliminate potential difficulty, verify proper operation before using by following instruction appended to the end of this section (basically look into tube at valve slit, very gently squeeze outside of tube with thumb and forefinger perpendicular to valve slit and see if valve opens)

3.8.2.1. Preparation

- **Chill aluminum cooling sleeve**
 - Remove blue insulation cover from aluminum cooling sleeve
 - Place cooling sleeve in a plastic bag to prevent moisture from freezing to the inside of the sleeve and contaminating the sample
 - Put cooling sleeve in a -20°C or -70 freezer for one to two hours to chill. Alternatively, put cooling sleeve in a cooler with dry ice for 15 minutes.
 - If transferring cooling sleeve over long distances, store in an ice chest filled with ice or frozen packets

- **Assemble Cooling sleeve and RTube**
 - Fill out label on collection tube (Pt ID, name code, date, and time)
 - Orient Rtube with valve pointing upward, away from mouthpiece
 - Put on insulated gloves and remove chilled aluminum cooling sleeve from freezer
 - Place blue insulation cover over cooling sleeve to protect hands
 - Place insulated cooling sleeve over plastic collection tube

* Provided upon request. Most clinics will already have supplies with asterisk from previous trials

3.8.2.2 Specimen collection



- Begin 10 minute collection period immediately after cooling sleeve and plastic RTube are assembled
- Participant is seated; if necessary, provide a support for arm holding RTube™
- RTube™ is held upright; up arrow is pointing upward
- Instruct participant to breathe normally in and out through the mouthpiece.
If participant has a shallow breathing pattern, encourage participant to exhale hard enough "to hear breath flowing through the top of the tube". If participant hyperventilates, encourage participant to breathe normally.
- If you cannot hear breath going through the R-tube, valve may be stuck. Have participant blow hard into the tube for force the valve open. If this doesn't fix the problem, you may need to use another R-tube. Please let the DCC know about the defective R-tube.
- Monitor participant
 - If participant gets tired, s/he may take short breaks
 - If an extended break is needed, it may be necessary to change to a fresh chilled cooling sleeve
 - Regardless of breaks, actual time breathing through RTube should add up to 10 minutes and RTube must remain upright at all times.
- Note: nose clips are not required for EBC collection

Transferring EBC into aliquots

- After 10 minute collection period, remove mouthpiece from collection tube; dispose of mouthpiece
- Use evacuation plunger to gather sample near top of collection tube
 - Orient collection tube with the arrow on side of tube pointing up, and exhalation valve (pointed valve inside tube) pointing up
 - Place collection tube on evacuation plunger
 - Pull collection tube down over evacuation plunger; the exhalation valve inside of the tube will move up the tube collecting the sample near the top of the tube
- Fill in labels from peel-off Cryovial Label Sheet and place labels on cryovials
- Using 250 µL micropipettor, immediately transfer 250µL EBC into each of 3 cryovials (i.e. a total of 750µl divided each of into 3 cryovials)
- Immediately place cryovials on ice and freeze at 70° C until shipping

Cleaning plunger

- Wear gloves
 - Firmly grip plastic collection tube and gently pull off plunger
 - Dispose of plastic collection tube
 - Wash plunger with soap and water or wipe down with alcohol
 - Allow plunger to dry before next use
-

3.8.2.2. Specimen collection



Procedure to Verify Proper Operation Before Use

i If stored in a warm environment for an extended period of time, the RTube may offer increased resistance upon the first attempt to use. This is due to minor adhesion internal to the duckbill valve. This is expected and normally has no effect, but in rare cases it can be enough to impair usage of the RTube. Apply this procedure prior to using RTube to verify proper operation and eliminate any potential impairment.

<p>①</p> <p>Remove from package and set cap aside.</p>	<p>②</p> <p>Look down into top of RTube and note the orientation of the apex of the duckbill valve. This is the visible peak of the valve running all the way across.</p>	<p>③</p> <p>Grasp the RTube between your thumb and forefinger such that the apex of the valve is in line with finger placement. Note that valve orientation varies normally. Adjust finger position accordingly and gently squeeze the RTube.</p>	<p>④</p> <p>Look for the opening of the valve as shown. Proceed to use RTube.</p>	<p>⑤</p>
<p>If valve does not open, ensure proper position of fingers and try again. If on successive attempts the valve does not open, do not use.</p>				

3.8.2.3 Shipment of EBC specimens

Shipping

- Government regulations require that personnel have job-specific training before offering a Dangerous Goods (including dry ice) shipment to FedEx or another air carrier. Personnel should receive training from their institution or make outside arrangements for a training session.
- These instructions for shipping follow guidelines for Category B, Infectious Substances, as requested by the receiving laboratory at Northwestern University
- Batch ship frozen cryovials within two months of collection
- DO NOT ship on Friday, Saturday, or day before a national holiday

Shipping supplies provided by DCC

- Cryovial box used for storing and shipping specimens
- Styrofoam box with outer cardboard box
- Plastic specimen bag (8" x 8")
- Absorbent sheet
- UN3373 label
- Dry ice label (UN1845)

Shipping supplies provided by clinic

- Dry ice
- FedEx air bill

Shipping Tasks

- Specimens must remain frozen throughout the packaging and shipping process
- Organize cryovials in cryovial box and record positions on specimen storage grid (Section B) of Specimen Transmittal Sheet (ST)
- Place cryovial box and an absorbent sheet in plastic specimen bag
- Seal bag, insert copy of completed ST form in pocket and place bag in Styrofoam cooler
- Add generous amount (at least 3 pounds) of dry ice and fill remaining space with padding (bubble wrap is acceptable)
- Affix proper labels on outside of box
 - UN3373 label
 - Dry ice label (with weight of dry ice and shipper/consignee name and address)
- FedEx air bill
 - Shipping address:

Lewis J. Smith, MD
Northwestern Memorial Hospital
Clinical Research Unit Core Laboratory
251 E. Huron St.
Feinberg 10-754
Chicago, IL 60611
Ph: 312-926-3194
 - Use FedEx account number: 4895-2708-1
 - Ship Priority Overnight
 - For item #6, *Special Handling*, check Dry Ice and fill in weight of dry ice in kilograms (3 pounds = 1.5 kg)
 - For item #6, *Special Handling*, check Yes, Shipper's Declaration not required
- Immediately upon shipment, notify lab by sending email to:

j-frazen@northwestern.edu

Form (abbreviation)

- Specimen Transmittal sheet (ST)
-

3.8.3 Exhaled NO

Purpose

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

When

- Visits V2 and V4-V9 before spirometry, methacholine challenge testing, or EBC collection.

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 through 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

NIOX MINO® unit (supplied by DCC)



3.8.3. Exhaled NO

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

NIOX® patient filter



NIOX MINO® sensor



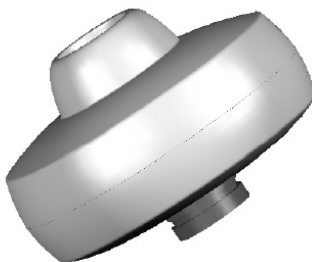
NIOX MINO® test card (blue)

- 2 cards are provided for each clinical center.

Equipment for Quality Control

NIOX MINO® QC card (white) (supplied by DCC)

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



3.8.3. Exhaled NO**Replacement equipment:**

- Clinics will provide replacements

QC 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 is required and 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

Identify the 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 allergies (except seasonal, see below) 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 ± 10 ppb 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

3.8.3. Exhaled NO**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 (Δ) between the mean value and the day’s QC test value.
 - If the difference (Δ) 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.

3.8.3. Exhaled NO**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, methacholine challenge testing, and exhaled breath condensate (EBC) collection.
- 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.

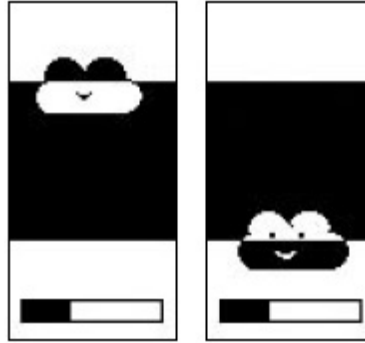
Test Procedures:

- 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.

3.8.3. Exhaled NO

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)

3.8.3.1 Exhaled Nitric Oxide Comparison Substudy

Purpose

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

When

- Visits V2 and V4-V9 before spirometry, methacholine challenge testing, or EBC collection.

Where

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

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
- Nitric Oxide form (NO)

Overview

- A convenience sample including 10-20 individuals from each participating center.
- 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.
- Ambient NO will also be measured with each unit and recorded on NO form

Procedures

- Log on to the SOYA data system: <http://www.jhcct.org/Secure/SOYA/DataSystem/SOYAMenu.asp>
- Click on “SOYA eNO Comparison Substudy 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. 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)
-

3.8.4 Blood draw for genistein level and DNA

Purpose:

- To collect packed cells for pharmacogenetics (DNA) and plasma for genistein levels

When

- Genistein – Visits 2, 4 and 9
- DNA – visit 2

Note: Do not save DNA specimen without participant consent. Item 20 on the Randomization Form (RZ) must be marked as “yes” to donate and store DNA.

Supplies for Collection and Processing

- Supplied by DCC
 - 10 mL EDTA vacutainer (lavender top)
 - Two 2 mL cryovials, orange top
 - Transfer pipette
 - Label for vacutainer tube (see section 3.8.8 for example)
 - Labels for 2 cryovials (SOYA genistein #1 and 2) [see Section 3.8.9 for examples]
- 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 labels with marking pen. Fill in Pt ID and Visit ID
- Affix vacutainer label lengthwise onto vacutainer. Place Scotch tape on vial to cover label and go completely around vial.
- Draw at least 8 mL of blood into labeled vacutainer
- Gently invert tube 5 times
- May store at 4° C for up to 30 minutes
- Centrifuge at 2000g for 7 minutes at 4° C
- Transfer plasma (upper layer) to cryovials. Fill to 1.8 mL line.
- Replace vacutainer top and keep packed cell pellet (only if visit 2 and participant consented to donate DNA)
- Immediately place cryovials and vacutainer (if applicable) in -70° C freezer and hold specimens for batch shipment at a later date. Lay Vacutainer tube horizontal in freezer for 20 minutes prior to storing upright, otherwise expansion of ice crystals may crack the tube.

Shipping supplies

- Supplied by DCC
 - Cryovial box for storing and shipping specimens
 - Styrofoam box with outer cardboard box
 - Plastic biohazard specimen bag
 - Absorbent sheet

3.8.4. Blood draw for genistein level and DNA

- Dry ice label (UN 1845)
- UN3373 label
- Supplied by clinic
 - Dry ice
 - FedEx air bill

Shipping Tasks

- Batch ship frozen cryovials and vacutainers within two 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
- Cryovials (plasma for genistein)
 - Organize cryovials in cryovial box and record positions on specimen storage grid (Section B) on Specimen Transmittal Sheet (ST)
 - Place cryovial box and an absorbent sheet in plastic specimen bag (8" x 8"); press lock
 - Place completed Specimen Transmittal Sheet (ST) into sleeve of specimen bag. Retain copy of ST form
 - Place specimen bag in styrofoam box
- Vacutainers (packed cells for DNA)
 - Place frozen Vacutainers and an absorbent sheet in plastic specimen bag (8" x 8"); press lock
 - Place completed Specimen Transmittal Sheet (ST) into sleeve of specimen bag. Retain copy of ST form
 - Place specimen bag in styrofoam box
- Add generous amount (at least 3 pounds) of dry ice to styrofoam box and fill remaining space with padding (bubble wrap is acceptable)
- 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: 4895-2708-1
- 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)
- Shipments do not contain dangerous goods (only specimens for diagnostic purposes)
- Immediately upon shipment, notify lab by sending email to:
emougey@nemours.org

Form (abbreviation)

- Specimen Transmittal Sheet (ST)
-

3.8.5 Blood draw for CRP level and IL-6 level

Purpose:

- To collect serum for IL-6 and CRP levels

When

- Visits 2, 4, and 9
- Specimens should be collected at the same time of day for visits 2, 4, and 9, due to diurnal variation with IL-6
- Collect before other blood specimens
- Collect within 1 minute of applying tourniquet
- Draw blood via venipuncture – do not use indwelling catheter

Supplies for Collection and Processing

- Supplied by DCC
 - 10 mL red/gray top serum separator vacutainer tube
 - Four 1.2 mL cryovials, white top, external thread
 - Label for vacutainer tube
 - Disposable transfer pipette
 - Labels for 4 cryovials (SOYA serum #1, 2, 3 and 4) [see section 3.8.9 for examples]
- 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

Collection Tasks

- Prepare labels with marking pen. Fill in Pt ID and Visit number
- Affix cryovial label to vials, covering with a piece of Scotch tape that extends around entire diameter of vial
- Draw 10 mL of blood into serum separator vacutainer
- Let blood sit in tube for at least 30 minutes at room temperature
- Centrifuge for 15 minutes at $> 1500 \times g$
- Aliquot serum into four 1.2 mL cryovials. Do not fill higher than 1.0 line
- Place on ice and freeze at -70°C until batch shipment at a later date

Shipping supplies

- Supplied by DCC
 - Cryovial box for storing and shipping specimens
 - 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

- Batch ship frozen cryovials within two 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
- Organize cryovials in cryovial box and record positions on specimen storage grid (Section B) of Specimen Transmittal Sheet (ST)
- Place cryovial box and an absorbent sheet in plastic specimen bag (8" x 8"); press lock
- Place completed Specimen Transmittal Sheet (ST) 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 (with weight of dry ice and shipper/consignee name and addresses)
- Complete air bill and ship to

Dr. Lewis J. Smith
 Northwestern Memorial Hospital
 Clinical Research Unit Core laboratory
 251 E. Huron Street, Feinberg 10-754
 Chicago, IL 60611
 (312) 926 - 3194

- Use FedEx account number: 4895-2708-1
- 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)
- Shipments do not contain dangerous goods (only specimens for diagnostic purposes)
- Immediately upon shipment, notify lab by sending email to:
j-franzen@northwestern.edu

Form (abbreviation)

- Specimen Transmittal Sheet (ST)

3.8.6 Eosinophil count

Purpose

- To collect blood for quantitative eosinophil count (Eosinophils are a blood marker of inflammation)

Analysis arrangements

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

$$\frac{1\% \text{ eosinophils} \times 5,000 \text{ white blood cells}/\mu\text{L}}{50 \text{ eosinophil cells}/\mu\text{L}}$$
- Obtain collection and processing/storage instructions from lab

When

- Visits 2, 4, and 9

Supplies provided by clinic

- Vacutainer as specified by local lab
- Lab marking pen
- Needle, 21 G
- Needle holder
- Gloves
- Swabs for cleaning blood drawing site
- Band-aids
- Emergency supplies readily available

Tasks

- Collect blood as specified by local lab
- Send for local analysis
- Record results, cells per μL on Clinic Visit Form

Forms (abbreviation)

- Clinic Visit (CV)
-

3.8.7 Urine specimen for urinary LTE₄ level

Purpose:

- To collect urine sample for determination of leukotriene levels and creatinine

When:

- Visits 2, 4, and 9

Collection Supplies:

- Supplied by DCC:
 - Urine collection cup
 - Four 2.0 mL cryovials, red top
 - Labels for 4 cryovials (SOYA urine #1, 2, 3 and 4) [see section 3.8.9 for examples]
 - Transfer pipette
- Supplied by clinic:
 - Label marking pen
 - Gloves
 - Scotch tape
 - Disposable transfer pipette

Collection tasks:

- Fill out Pt ID, and Visit ID on labels and affix to cryovials. Place Scotch tape on vial to cover label and go completely around the vial.
- Provide participant with labeled urine collection cup
- Instruct participant to collect about 10 mL of urine. It may be helpful for the coordinator to mark the 10 mL line on the collection cup with a marker.
- Using transfer pipette, fill four 2.0 mL cryovial to the 1.8 line and place on ice immediately
- Freeze at -70°C
- Batch specimens and ship to lab within two months of collection

Shipping Supplies:

- Supplied by DCC:
 - Thermosafe Styrofoam shipper with outer cardboard box
 - Cryovial box for storing and shipping specimens
 - Plastic biohazard specimen bag
 - Absorbent sheet
 - Dry ice label (UN1845)
 - UN 3373 label
- Supplied by clinic:
 - Dry ice
 - Packing material (bubble wrap, “peanuts,” or crumpled newspaper)
 - Fed Ex air bill

Shipping tasks:

- Make sure clinic staff:
 - Are up-to-date with current IATA and DOT regulations regarding exempt human specimen and dry ice shipments
 - Have completed compliance training
- Batch ship frozen urine specimens within 2 months of collection
- Specimens must remain frozen throughout the packing and shipping process

3.8.7. Urine specimen for urine LTE4 level

- Organize cryovials in cryovial box and record positions on specimen storage grid (Section B) of Specimen Transmittal Sheet (ST)
- Place cryovial box and an absorbent sheet into a plastic biohazard bag; press to lock and seal bag
- Place completed Specimen Transmittal Sheet (ST) into sleeve of specimen bag. Retain copy of ST form.
- Place biohazard bag with frozen specimen into styrofoam shipper
- 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 box:
 - UN 3373 label
 - Dry ice label (with weight of dry ice and shipper/consignee name and address)
 - Use FedEx account number: 4895-2708-1
 - 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)
 - Shipments do not contain dangerous goods (only specimens for diagnostic purposes)
- After completing air bill, and ship to:

Dr. Lewis Smith
 Northwestern Memorial Hospital
 Clinical Research Unit Core laboratory
 251 E. Huron Street, Feinberg 10-754
 Chicago, IL 60611
 312-926-3194

- Ship on Monday, Tuesday or Wednesday only, and not within 3 days of a holiday
- Immediately upon shipment of specimens, notify lab by sending an email to:
j-franzen@northwestern.edu

Form (abbreviation):

- Specimen Transmittal Sheet (ST)

SOYA

Vacutainer Label Sheet

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

Visit 2	Vacutainer - red/gray SOYA CRP/IL6 Pt ID: _____ Visit ID: ____	Vacutainer - lavender SOYA DNA/genistein Pt ID: _____ Visit ID: ____
Visit 4	Vacutainer - red/gray SOYA CRP/IL6 Pt ID: _____ Visit ID: ____	Vacutainer - lavender SOYA genistein Pt ID: _____ Visit ID: ____
Visit 9	Vacutainer - red/gray SOYA CRP/IL6 Pt ID: _____ Visit ID: ____	Vacutainer - lavender SOYA genistein Pt ID: _____ Visit ID: ____
spares	Vacutainer - red/gray SOYA CRP/IL6 Pt ID: _____ Visit ID: ____	Vacutainer - lavender SOYA genistein Pt ID: _____ Visit ID: ____
Visit 2	Vacutainer - red/gray SOYA CRP/IL6 Pt ID: _____ Visit ID: ____	Vacutainer - lavender SOYA DNA/genistein Pt ID: _____ Visit ID: ____
Visit 4	Vacutainer - red/gray SOYA CRP/IL6 Pt ID: _____ Visit ID: ____	Vacutainer - lavender SOYA genistein Pt ID: _____ Visit ID: ____
Visit 9	Vacutainer - red/gray SOYA CRP/IL6 Pt ID: _____ Visit ID: ____	Vacutainer - lavender SOYA genistein Pt ID: _____ Visit ID: ____
spares	Vacutainer - red/gray SOYA CRP/IL6 Pt ID: _____ Visit ID: ____	Vacutainer - lavender SOYA genistein Pt ID: _____ Visit ID: ____

SOYA Cryovial Label Sheet

Each sheet contains all
necessary cryovial labels for
one participant.

Visit 2
(V2)

SOYA serum #1

Pt ID: _____

Visit ID: ____

SOYA serum #2

Pt ID: _____

Visit ID: ____

SOYA serum #3

Pt ID: _____

Visit ID: ____

SOYA serum #4

Pt ID: _____

Visit ID: ____

SOYA EBC #1

Pt ID: _____

Visit ID: ____

SOYA EBC #2

Pt ID: _____

Visit ID: ____

SOYA EBC #3

Pt ID: _____

Visit ID: ____

SOYA genistein #1

Pt ID: _____

Visit ID: ____

SOYA genistein #2

Pt ID: _____

Visit ID: ____

SOYA urine #1

Pt ID: _____

Visit ID: ____

SOYA urine #2

Pt ID: _____

Visit ID: ____

SOYA urine #3

Pt ID: _____

Visit ID: ____

SOYA urine #4

Pt ID: _____

Visit ID: ____

Visit 4
(V4)

SOYA serum #1

Pt ID: _____

Visit ID: ____

SOYA serum #2

Pt ID: _____

Visit ID: ____

SOYA serum #3

Pt ID: _____

Visit ID: ____

SOYA serum #4

Pt ID: _____

Visit ID: ____

SOYA EBC #1

Pt ID: _____

Visit ID: ____

SOYA EBC #2

Pt ID: _____

Visit ID: ____

SOYA EBC #3

Pt ID: _____

Visit ID: ____

SOYA genistein #1

Pt ID: _____

Visit ID: ____

SOYA genistein #2

Pt ID: _____

Visit ID: ____

SOYA urine #1

Pt ID: _____

Visit ID: ____

SOYA urine #2

Pt ID: _____

Visit ID: ____

SOYA urine #3

Pt ID: _____

Visit ID: ____

SOYA urine #4

Pt ID: _____

Visit ID: ____

Visit 9
(V9)

SOYA Serum #1

Pt ID: _____

Visit ID: ____

SOYA Serum #2

Pt ID: _____

Visit ID: ____

SOYA Serum #3

Pt ID: _____

Visit ID: ____

SOYA Serum #4

Pt ID: _____

Visit ID: ____

SOYA EBC #1

Pt ID: _____

Visit ID: ____

SOYA EBC #2

Pt ID: _____

Visit ID: ____

SOYA EBC #3

Pt ID: _____

Visit ID: ____

SOYA genistein #1

Pt ID: _____

Visit ID: ____

SOYA genistein #2

Pt ID: _____

Visit ID: ____

SOYA urine #1

Pt ID: _____

Visit ID: ____

SOYA urine #2

Pt ID: _____

Visit ID: ____

SOYA urine #3

Pt ID: _____

Visit ID: ____

SOYA urine #4

Pt ID: _____

Visit ID: ____

Spares

SOYA Serum #1

Pt ID: _____

Visit ID: ____

SOYA Serum #2

Pt ID: _____

Visit ID: ____

SOYA Serum #3

Pt ID: _____

Visit ID: ____

SOYA Serum #4

Pt ID: _____

Visit ID: ____

SOYA EBC #1

Pt ID: _____

Visit ID: ____

SOYA EBC #2

Pt ID: _____

Visit ID: ____

SOYA EBC #3

Pt ID: _____

Visit ID: ____

SOYA genistein #1

Pt ID: _____

Visit ID: ____

SOYA genistein #2

Pt ID: _____

Visit ID: ____

SOYA urine #1

Pt ID: _____

Visit ID: ____

SOYA urine #2

Pt ID: _____

Visit ID: ____

SOYA urine #3

Pt ID: _____

Visit ID: ____

SOYA urine #4

Pt ID: _____

Visit ID: ____

3.9 Randomization

Purpose

- Assign participant to a study 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
- After the following V1 forms have been data entered: SC, and PF

Tasks

- Review screening and baseline procedures for eligibility
- Have eligibility confirmed by clinic investigator
- Key RZ form into SOYA data system while participant is physically in the clinic
- Data system will assign a Kit ID
- Record Kit ID on RZ form
- Upon data entry of RZ form, data system will calculate peak flow cut-off values for Asthma Action Plan; record these values on RZ form
- Print randomization page and attach to RZ form; store in participant's file
- Complete Study Accountability Log (DA)
- Dispense bottle from kit box
 - Fill in required information on kit and bottle labels
 - Complete DD form
 - Complete a Patient Bottle Accountability Log (PD)
- Kit box should remain at clinical center
- If assigned Kit ID is not available at clinical center, contact DCC immediately

Forms (abbreviation)

- Randomization (RZ)
 - Tablet Dispensing and Counting (DD)
 - Study Accountability Log (DA)
 - Patient Bottle Accountability Log (PD)
-

3.10 Study supplement administration and accountability

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3.10.1 Study supplement description, procurement and storage

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

Treatment groups

- Soy supplement (Novasoy®) or matching placebo

Study tablet administration

- One tablet of soy supplements or matching placebo is to be taken twice daily (total 100 mg/day)

Study tablet packaging

- Study tablets are packaged in a box called a “kit”
- Each kit has its own unique Kit ID
- Participants are assigned to a Kit ID
- Each kit box contains 6 bottles of tablets
- Each bottle contains 70 tablets

Procurement of randomization kits

- Randomization kits are automatically supplied to clinics
 - Upon clinic certification, DCC will notify SOYA Supplement Distribution Center to send initial supply of two kits
 - Data-entering a Randomization (RZ) form will automatically generate a notice to SOYA Supplement 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 tablets for the entire trial
- If tablets are lost or destroyed, a clinic can order a replacement kit using the SOYA Drug Distribution System
- Replacement kits will arrive at the clinic with the participant ID already recorded on the kit label

To access SOYA Drug Distribution website for kit orders:

- To order study kits, a coordinator must be certified for data entry
- Go to <http://www.jhcct.org/Secure/SOYA/SOYAHome.htm>
- 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 “SOYA 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 the DCC with any problems or special requests
- To place an order for a replacement randomization kit
 - Click on “Replacement RZ Kit”

3.10.1. Study supplement description, procurement and storage

- Enter the Participant ID, Name code, 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: Y-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 SOYA Supplement 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 kits, sign packing slip and fax to SOYA Supplement Distribution Center
- Record receipt, dispensing, and transfer of study tablets on Study Kit Accountability Log (DA) and Patient Bottle Accountability Log (PD)
- Maintain one DA log for all kits
- Maintain a separate DA log for each site where kits are stored; i.e., satellites that store additional kits for randomized participants must maintain separate DA logs
- Maintain one Patient Bottle Accountability (PD) Log for each participant
- Store tablets 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 tablets returned by patients with unused tablets; tablets that have been dispensed to a patient cannot be returned and dispensed to another patient
- Study kits can be transferred between sites as long as it has been appropriately stored

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

Log/Administrative forms (abbreviation)

- Study Kit Accountability Log (DA)
 - Patient Bottle Accountability Log (PD)
 - Randomization form (RZ)
-

3.10.2 Dispensing and compliance monitoring

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

Purpose

- Distribute assigned study tablets to participants
- Evaluate compliance to study tablet assignment

When

- Dispense study tablets at Randomization (V2)
- Dispense additional study tablets at follow-up visits (V4-V8) as needed
- Monitor compliance at each clinic visit

Supplies

- Kits with unique Kit ID

Study Tablet Overview

- Study tablets are packaged in a box called a "kit" containing 6 bottles of tablets. Each bottle contains 70 tablets.
- One tablet of soy supplements or matching placebo is to be taken twice daily (total 100 mg/day)
- Once a participant is assigned to a kit ID, they may only be dispensed tablets from that individual kit box

Dispensing (V2, V4-V8)

- 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
- Remove kit with assigned kit ID from stock
- Record kit ID as "assigned" to the participant on the Study Kit Accountability (DA) Log
- Record kit ID, expiration date, visit ID, and date dispensed on the Patient Bottle Accountability (PD) Log
- Fill in labels on the outside of the kit box:
 - Record the Participant ID, and name
- Break seal and open kit box. Fill in information on all six bottles:
 - Record Participant ID, Participant name, Issue date, and emergency contact information (physician name and phone number) on outside label of each bottle. All six bottles will be labeled with a Bottle ID ending with the letter A through F
- Dispense individual bottles over time (DO NOT dispense the entire kit box of 6 bottles to the participant at one time)
 - Be sure to dispense enough tablets (one bottle contains 70 tablets) to meet the participant's dosage requirements for at least 30 days
 - Dispense a new tablet bottle at each clinic visit even if there are still tablets remaining in the bottle
- Complete Patient Bottle Accountability Log (PD)
 - Record the Visit ID and date dispensed for the appropriate bottle
- Complete a Tablet Dispensing and Counting (DD) Form
 - Remove tear-off label attached to bottle and affix to DD form
 - Record the bottle sequence numbers of all bottles dispensed to the participant that day

3.10.2. Dispensing and compliance monitoring

- Instruct participant to:
 - Take one tablet twice daily
 - Contact study personnel if side effects occur
 - Bring in all study tablet bottles (empty and partially used) to each clinic visit

Compliance Monitoring (V3-V9)

- **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 bottles (including empties) to each clinic visit
 - Count remaining tablets in bottles
 - When bottles are retained by the clinic, record information on bottle return and tablet counting on the Tablet Dispensing and Counting (DD) Form and on the Patient Bottle Accountability Log (PD)
- **Returned study tablets should be stored until the end of the study**
 - The DCC will notify clinics when it is okay to destroy returned study tablets
 - Study tablets should be destroyed per local institutional guidelines
 - Destruction of study tablet kits must be recorded on the Study Kit Accountability (DA) Log and Patient Bottle Accountability (PD) Log
 - Never put study tablets returned by a participant back into study tablet stock

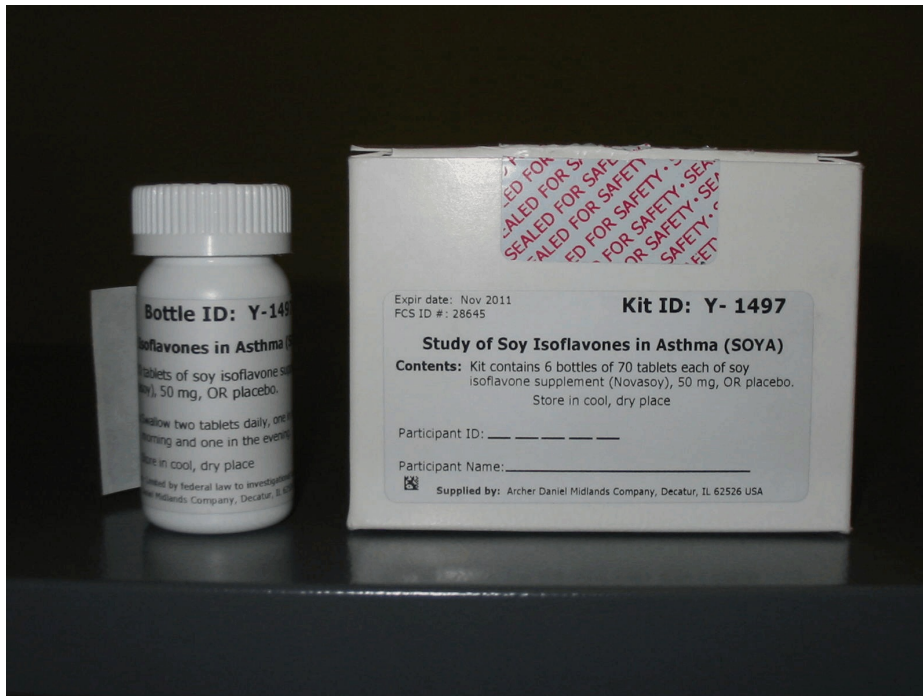
Forms (abbreviation)

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

Log/Administrative form (abbreviation)

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

3.10.3 Study supplement labels



Supplement bottle label

Expir date: Nov 2011 FCS ID #: 28645	Bottle ID: Y-XXXX-X Study of Soy Isoflavones in Asthma (SOYA)	SOYA Study Tablet Bottle ID: Y-XXXX-X Expir date: Nov 2011 FCS ID #: 28645
Participant ID: _____ Participant Name: _____ Issue Date (dd - mm - yy): _____ Physician: _____ Emergency Call: _____	Bottle contains 70 tablets of soy isoflavone supplement (Novasoy), 50 mg, OR placebo. Directions: Swallow two tablets daily, one in the morning and one in the evening. Store in cool, dry place <small>Caution: New Drug - Limited by federal law to investigational use. Supplied by: Archer Daniel Midlands Company, Decatur, IL 62526 USA</small>	Detach and affix this portion to DD form

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 SOYA 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 SOYA Supplement 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 SOYA Supplement 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: _____

_____ J H U _____

Satellite name (if appropriate): _____

Entry	Kit ID	Exp Date	Received		Date Rec'd	Assigned/Sent/Destroyed					
			Supp Distr Center	Center/Satellite Name		Specify Recipient			Destroyed	Date	
1	Y-1234	Nov 2011	✓		14 June 10	YE101	ELBR0				16 Jun 10
2	Y-1258	Nov 2011	✓		14 June 10	YE102	RAZH0				17 Jun 10
3	Y-1569	Nov 2011	✓		8 Jul 10	YE103	AXLDP				12 Jul 10
4	Y-1693	Nov 2011	✓		20 Jul 10			SPH			23 Jul 10
5	Y-2311	Nov 2011	✓		18 Aug 10	YE104	JPNKT				19 Aug 10
6	Y-2481	Nov 2011	✓		18 Aug 10	YE101	ELBR0				27 Aug 10
7	Y-2544	Nov 2011	✓		25 Aug 10	YE102	RAZH0				30 Aug 10
8	Y-3678	Nov 2011	✓		31 Aug 10			SPH			3 Sep 10
9	Y-3814	Nov 2011	✓		7 Sep 10	YE103	AXLDP				10 Sep 10

Study Kit Accountability Log
Continuation Page

Instructions: Proceed with filling in transactions as described in the instructions on page 1. Use as many continuation pages as necessary. Number continuation pages at the upper right corner.

a. Kit ID	Exp Date	b. Received		Date Rec'd	c. Assigned/Sent/Destroyed					
		Supp Distr Center	Center/ Satellite Name		Participant ID	Name Code	Center/ Satellite Name	Other (explain)	Destroyed	Date
10	Y-4012 Nov 2011	✓		7 Sep 10	YZ105	CLHVE				13 Sep 10
11	Y-4259 Nov 2011	✓		7 Sep 10	YZ104	JPNKT				22 Sep 10
12	Y-4814 Nov 2011	✓		15 Sep 10			SPH			9 Nov 10

Patient Bottle Accountability Worksheet

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, dispensed, or returned.
Instructions: Maintain one log for each SOYA participant. Record the date and visit dispensed, returned, and/or destroyed for each bottle.

Clinical center ID: _____

_____ J H U

Participant ID: _____

Y 7 1 0 1

Satellite name (if appropriate): _____

SOYA Kit ID: _____

Y - 1 2 3 4

Expiration date: November 2011

a. Bottle	b. Dispensed/Returned/Destroyed				Comments
	Dispensed		Returned		
	Visit ID	Date Dispensed	Visit ID	Date Used Bottle Received	Date Destroyed
A	V2	16 June 10	V4	27 Aug 10	
B	V4	27 Aug 10	V5	29 Sep 10	
C	V5	29 Sep 10	V6	25 Oct 10	
D	V6	25 Oct 10	V7	30 Nov 10	
E	V7	30 Nov 10			
F					

3.10.5 Temporary withdrawal or termination of study supplement

Purpose

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

When

- Anytime after completion of Randomization Visit (V2) when study supplement is temporarily or permanently stopped due to adverse event, participant request, lost to followup, pregnancy, or other reason
- At end of study (completion of V9)

Tasks

- **Unscheduled temporary supplement termination**
 - Record information relating to the hiatus in study supplement treatment on the Clinic Visit form (CV)
 - Complete an Unusual Event (UE) form or Serious Adverse Event Report (SR) form as appropriate
- **Unscheduled permanent supplement 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 supplement
 - Study physician will determine if study supplement 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 3.11)
 - Regardless of severity, all potential side effects should be recorded on Clinic Visit form (CV), items 28, 36 - 37
 - Complete Treatment Termination (TT) form
 - Collect all study supplement bottles and kits (including all unused tablets) from participant
 - Complete Tablet Dispensing and Counting (DD) form
 - Continue to follow participant for all study visits (i.e., continue all relevant study procedures) through Visit 9
 - If early unmasking is necessary refer to MOP Section 3.10.6
- **Supplement termination at end of study**
 - Complete Treatment Termination (TT) form
 - Collect all study supplement kits and bottles (including all unused tablets) from participant
 - Complete Tablet Dispensing and Counting (DD) form
 - Conduct exit procedures as detailed in MOP Section 3.12

Forms (abbreviation)

- Clinic Visit Form (CV)
 - Serious Adverse Event Reporting Form (SR)
 - Tablet Dispensing and Counting Form (DD)
 - Treatment Termination Form (TT)
 - Unusual Event Form (UE)
-

3.10.6 Unmasking

Purpose

- Reveal treatment assignment to participant after the participant completes the study (i.e., after Exit Interview at V9)
- 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, V9
- Early unmasking
 - An acute, severe reaction suspected to be related to the study supplement where knowledge of treatment assignment will help to determine treatment
 - An overdose of study supplement by participant or someone else
 - Request by physician or participant

Supplies

- Participant exit letter (see MOP Section 3.12.2)
- 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 3.12 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/SOYA/SOYAHome.asp>
 - ▲ ! Click on Data System link
 - ▲ ! Click on SOYA 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
- Complete Treatment Termination (TT) and Unmasking (UM) forms

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

3.10.6. Unmasking

- Requests will be considered by the Director of the DCC and the ALA-ACRC Chair, 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
- Complete Treatment Termination (TT) and Unmasking (UM) forms, if applicable

Forms (abbreviation)

- Treatment Termination (TT)
 - Unmasking (UM)
-

3.11 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 treatment related is the responsibility of the study physician

When

- As needed whenever a serious unexpected adverse experience associated with study treatment or placebo is first reported or whenever follow-up information is received.

Tasks

- Report a serious adverse event to the DCC by telephone (443-287-3170) within 3 working days
- Fax a completed Serious Adverse Event Report (SR) form to the DCC at 775-871-4030 within 3 working days. 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 follow-up 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 supplement, other asthma treatment) should be determined per best medical judgment of the study physician
- Record event on CV form, item #38

Forms (abbreviation)

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

3.12 Exit procedures

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3.12.1 Exit tasks

Purpose

- Notify participant of study treatment via sealed Treatment Assignment Envelope after participant completes Visit 9

Note: Study staff should remain masked throughout trial.

Time frame

- Conducted at Visit 9
- If participant does not return to clinic for Visit 9, 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. (Treatment assignment was included with participant's randomization kit.)

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 3.12.2)
 - 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 (see MOP section 3.4.3)
- Key forms into SOYA data system within 10 working days

Forms (abbreviation)

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

3.12.2 Prototype participant exit letter

Dear _____,

Thank you for participating in the clinical trial Study of Soy Isoflavones in Asthma or SOYA. The purpose of the trial is to determine if taking a dietary soy supplement will improve lung function. 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 (breathing 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. Be sure to follow the guidelines on your Asthma Action Plan card. If you have problems with your asthma medication before you see your asthma care provider, you can call our clinic at: XXX-XXX-XXX.

There are other participants in the study, enrolled after you, who are still being treated and followed 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 these people. We make it a point not to know what treatment participants are assigned, during the study so that knowledge of the treatment assignment does not influence the data we are collecting.

Again, thank you for your participation in SOYA.

Sincerely,

Principal Investigator
Institution Name

Enclosures: Treatment assignment envelope
Results of final pulmonary function tests

SOYA MOP

4. Data collection and forms completion

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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	✓
SOYA Diary Card	DC	✓
Study Kit Dispensing and Counting Form	DD	✓
Exit Interview	EI	✓
Methacholine Challenge Testing	MC	✓
Missed Data	MD	✓
Nitric Oxide Form	NO	✓
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	✓
Treatment Termination	TT	✓
Unusual Event	UE	✓
Unmasking	UM	✓
Questionnaires		
Asthma Symptom Utility Index	AS	✓
Block 2005 Food Frequency	BF	No
Block Kids 2004 Food Frequency	BK	No
Block Soy Questionnaire	BS	No
Child Health Questionnaire (CHQ-PF50)	CH	✓
Asthma in Females Questionnaire	FQ	✓
Medical Outcomes Study SF-36	MO	✓
Marks Asthma Quality of Life Questionnaire	MQ	✓
Children's Health Survey for Asthma	PQ	✓
Sino-Nasal Questionnaire	SI	✓
Home Smoking Activity and Child Exposure to Tobacco Smoke	SQ	✓
Asthma Control Test	TA	✓

SOYA MOP

4. Data collection and forms completion**4.1. List of forms and logs**

Form/Log name	Abbreviation	Data entered
Logs/Administrative forms		
Study Kit Accountability Log	DA	No
DNA Specimen Transmittal Sheet	DT	No
ACRC Supply General Order Form	GO	No
Methapharm SOYA Order Form	MP	No
Methacholine Worksheet	MW	No
Patient Bottle Accountability Log	PD	No
Peak Flow Meter Order Form	PO	No
Patient Screening Log	PS	Yes
Questionnaire Transmittal Sheet	QT	No
Specimen Transmittal Sheet	ST	No
SOYA Supply Order Form	YO	No
Information sheets		
Asthma Action Plan card	AAP	No
Instructions for SOYA Diary Cards	IDC	No
Instructions for Preparation of Methacholine Challenge Test	IMC	No
Instructions for Measuring Peak Flow	IPF	No
General Asthma Educational Materials		No
SOYA Schedule of Visits	SOV	No
SOYA Wallet Card	-	No
Temporary Asthma Action Plan Sheet - Visit 1	TAP	No
Certification forms		
Clinical Center Certification	CC	No
SOYA Methacholine Challenge Test Assurance Statement	MA	No
SOYA Personnel Assurance Statement	PA	No
Spirometry Assurance Statement	SA	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 clinic label sheet - example)
- 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

4.2. ID codes**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
Duke University Medical Center	DUKE
Illinois Consortium	IC
Indiana University, Asthma Clinical Research Center	IU
North Shore/Long Island Jewish Health System	LIJ
Louisiana State University Health Sciences Center, The Ernest N. Morial Asthma Allergy and Respiratory Disease Center	LSU
Nemours Children’s Clinic	NCC
National Jewish Health	NJC
Northern New England Consortium	NNEC
Columbia University - New York University Consortium	NYC
Maria Fareri Children’s Hospital at Westchester Medical Center and New York Medical College	NYMC
Ohio State University Medical Center/Columbus Children’s Hospital	OSU
Washington University/St. Louis University	STL
University of Missouri, Kansas City School of Medicine	UMKC
University of Miami/University of South Florida	UMSF
University of California, San Diego	UCSD
University of Arizona	UAZ
University of Virginia	UVA

4.2.1 Example of Clinic Label Sheet

Clinic Label Sheet	Clinical Center Z: TEST	To assign participant ID: Attach next sequential label to #2 on Screening Form (SC)
YZ100	YZ101	YZ102
YZ103	YZ104	YZ105
YZ106	YZ107	YZ108
YZ109	YZ110	YZ111
YZ112	YZ113	YZ114
YZ115	YZ116	YZ117
YZ118	YZ119	YZ120
YZ121	YZ122	YZ123
YZ124	YZ125	YZ126

4.3 Completing forms

4.3.1 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

4.3.2 Error correction

- Do not obliterate erroneous responses
- Never use White-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

4.3.3 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

4.3. Completing forms

- 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.

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4.4.1 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 Visit 1 to establish asthma history, asthma treatment, and smoking history
- **Clinic Visit Form (CV)** - completed at Visits 2, 4-9 to record information about diary cards, asthma symptoms, and interim medications
- **Tablet Dispensing and Counting (DD)** Used to record the issuing and counting of study tablets to and from participant
- **Exit Interview (EI)** - completed at Visit 9 to obtain the participant's impression of the treatment received
- **Methacholine Challenge Testing (MC)** form - used to record the results of testing at Visits 1 for participants who take the methacholine challenge test for eligibility
- **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 Visits 2, 4 - 9 to record eNO levels
- **Participant Information (PI)** - completed at 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 Visit 3 to assess compliance, side effects, and asthma control
- **Physical Exam (PE)** form - completed by study physician at Visit 1 and 9 to assess participant's general health and note any abnormalities
- **Pulmonary Function Testing (PF)** form - completed at Visits 1, 2, 4 - 9 to record the results of pulmonary function tests, including peak flow and spirometry
- **Randomization (RZ)** - completed and entered into the database at 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
- **SOYA 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 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 SOYA
- **Serious Adverse Event Report (SR)** - completed if an event deemed reportable according to Section 3.11 of the MOP occurs. The form must be faxed to the DCC and keyed to the database within 10 working days

4.4.1. Data forms

- **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
-

4.4.2 Questionnaires

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4.4.2.1 Overview

Purpose

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

Summary

- Asthma Control
 - Asthma Control Test (TA)
 - Asthma Symptom Utility Index (AS)
- Quality of Life
 - Marks Asthma Quality of Life Questionnaire (MQ)
 - Children's Health Survey for Asthma (PQ)
 - Your Health and Well-Being - MOS SF-36 v2 (MO)
 - Child Health Questionnaire PF-50 (CH)
- Dietary Intake
 - Block 2005 Food Frequency (BF)
 - Block 2004 Kids Food Frequency (BK)
 - Block Soy Questionnaire (BS)
- Menstruation and Asthma
 - Asthma in Females Questionnaire (FQ)
- Sinusitis Symptoms
 - Sino-Nasal Questionnaire (SI)

Timeframe

- **Asthma Control Test (ACT) (TA)** - administered at each clinic visit. The questionnaire asks about asthma symptoms during the past 4 weeks
- **Asthma in Females Questionnaire (FQ)** - administered at V2 to post - menarche female participants who have consented to participate in the menstruation ancillary study.
- **Asthma Symptom Utility Index (ASUI) (AS)** - administered at each clinic visit. The questionnaire asks about asthma symptoms within the past 2 weeks
- **Children's Health Survey for Asthma (CHSA) (PQ)** - measures functional impairments that are most troublesome to children as a result of their asthma over the past four weeks
- **Marks Asthma Quality of Life (MQ)** - administered at each clinic visit to measure asthma specific quality of life during past four weeks
- **Block Food Frequency Questionnaires (BF, BK)** - administered at V2 and V9. The questionnaire asks about the food that the participant usually eats
- **Block Soy Questionnaire (BS)** - administered at V1, V2 and V9. The questionnaire asks about the soy food consumption
- **Your Health and Well-Being (MOS SF-36 v2) (MO)** - administered at V1 and V9. The questionnaire asks about health concepts such as physical functioning, bodily pain, emotional health and social functioning
- **Child Health Questionnaire (CHQ-PF50) (CH)** - administered at V1 and V9. The questionnaire asks parents generic quality of life questions about their children between 5 - 18 years of age.
- **Home Smoking...Tobacco Smoke (SQ)** - administered at V2 to participants age 12-17 only. The questionnaire asks about home smoking activity and participant exposure to tobacco smoke
- **Sino-Nasal Questionnaire (SI)** - This questionnaire asks about sinusitis symptoms

4.4.2.1. Overview**Guidelines for administration and completion** (at the discretion of the coordinator)

- 12-17 years, by participant alone
- Questions should be read and answered as written
- Staff should remain neutral and never help participant choose an answer

Scoring

- Asthma Control Test (TA)
 - Add up the scores from each of the boxes.
- Sino-Nasal Questionnaire (S1)
 - Scored by averaging the responses from the 5 questions. The range of scores possible is 0-3.
 - Scoring: Never (0), 1-4 times per month (1), 2-6 times per month (2), Daily (3).
- If there are questions or issues with scoring of questionnaires, please contact DCC

Spanish

- All questionnaires are available in English and Spanish versions
 - Use the questionnaire version that is most comfortable for the participant
 - Download the appropriate language version of the questionnaire
 - A quantity of pre-printed Food Frequency and Soy Foods questionnaires will be supplied to each clinic at the beginning of the trial. Additional questionnaires can be ordered using the SOYA Supply Order Form (YO)
 - Data entry will be in English only
-

4.4.2.2 Food Frequency Questionnaire

Purpose

- To collect information about foods commonly eaten and the consumption of soy foods

When

- Visit 2 and Visit 9

Supplies

- Supplied by DCC
 - Food Frequency Questionnaire (BF)
 - Kids Food Frequency Questionnaire (BK)
 - Serving Size Choices reference sheet
 - Food Frequency Questionnaire labels with Participant ID visit number and Respondent ID Number
- Supplied by clinic
 - Soft-leaded (No. 2) pencil

Tasks

- Determine if participant should use adult or child versions of the questionnaire

<u>Questionnaire</u>	<u>Age range (yr)</u>
Block Food Frequency (BF)	18+
Block Kids Food Frequency (BK)	8-17

- Affix questionnaire label with proper participant ID and visit number on top of first page of questionnaire. There are two labels for each participant on the label sheet: one for Visit 2 and one for Visit 9
 - Copy the corresponding respondent ID number from the label to the rectangles in the Respondent ID table
 - Darken the appropriate numbered ovals under the rectangles to indicate the respondent ID number
- Participant completes the questionnaires. Refer to the Serving Size Choices reference sheet to answer “how much”
- For BK form, fill in Date, Age, Weight and Height information in box labeled “Office Use Only” on last page
- Make sure area for participant’s name is left blank or obscured with dark pen
- Questionnaires are not data entered. Clinics should save completed questionnaires and mail to DCC every 3 months

Shipping

- Ship batches of completed questionnaires at approximately 3 month intervals
- Shipping supplies
 - Questionnaire Transmittal Sheet (QT)
- Shipping tasks
 - Make photocopies of questionnaire for participants file
 - Complete Questionnaire Transmittal Sheet (QT) form and make copy to retain at clinic
 - Ship originals of questionnaires and completed Questionnaire Transmittal Sheet (QT) form

SOYA MOP**4. Data collection and forms completion****4.4.2.2. Food Frequency Questionnaire**

- Ship to:
ACRC Data Coordinating Center
Attn: Debbie Amend-Libercci
911 S. Ann Street
Baltimore, MD 21231
(443) 287-3170

Form (abbreviation)

- Questionnaire Transmittal Sheet (QT)
-

**Food Frequency
Questionnaire (BF or BK) Labels**

Clinic: TEST

Place one label on BF or BK questionnaire
at V2 and V9

Participant ID: **YX100**
Visit 2
Respondent ID Number:
10 22 100 02

Participant ID: **YX101**
Visit 2
Respondent ID Number:
10 22 101 02

Participant ID: **YX102**
Visit 2
Respondent ID Number:
10 22 102 02

Participant ID: **YX100**
Visit 9
Respondent ID Number:
10 22 100 09

Participant ID: **YX101**
Visit 9
Respondent ID Number:
10 22 101 09

Participant ID: **YX102**
Visit 9
Respondent ID Number:
10 22 102 09

Participant ID: **YX103**
Visit 2
Respondent ID Number:
10 22 103 02

Participant ID: **YX104**
Visit 2
Respondent ID Number:
10 22 104 02

Participant ID: **YX105**
Visit 2
Respondent ID Number:
10 22 105 02

Participant ID: **YX103**
Visit 9
Respondent ID Number:
10 22 103 09

Participant ID: **YX104**
Visit 9
Respondent ID Number:
10 22 104 09

Participant ID: **YX105**
Visit 9
Respondent ID Number:
10 22 105 09

Participant ID: **YX106**
Visit 2
Respondent ID Number:
10 22 106 02

Participant ID: **YX107**
Visit 2
Respondent ID Number:
10 22 107 02

Participant ID: **YX108**
Visit 2
Respondent ID Number:
10 22 108 02

Participant ID: **YX106**
Visit 9
Respondent ID Number:
10 22 106 09

Participant ID: **YX107**
Visit 9
Respondent ID Number:
10 22 107 09

Participant ID: **YX108**
Visit 9
Respondent ID Number:
10 22 108 09

Participant ID: **YX109**
Visit 2
Respondent ID Number:
10 22 109 02

Participant ID: **YX110**
Visit 2
Respondent ID Number:
10 22 110 02

Participant ID: **YX111**
Visit 2
Respondent ID Number:
10 22 111 02

Participant ID: **YX109**
Visit 9
Respondent ID Number:
10 22 109 09

Participant ID: **YX110**
Visit 9
Respondent ID Number:
10 22 110 09

Participant ID: **YX111**
Visit 9
Respondent ID Number:
10 22 111 09

4.4.2.4 Soy Food Screener Questionnaire

Purpose

- To collect information about consumption of soy foods

When

- Visit 1, 2 and 9

Supplies

- Supplied by DCC
 - Soy Food Questionnaire (BS)
 - Serving Size Choices reference sheet
 - Soy Food Questionnaire labels with Participant ID, visit number and Respondent ID number
- Supplied by clinic
 - Soft-leaded (No. 2) pencil

Tasks

- Affix questionnaire label with proper participant ID and visit number to name box on questionnaires. There are three labels for each participant on the label sheet: one each for Visit 1, 2 and 9
 - Copy the corresponding respondent ID number from the label to the rectangles in the Respondent ID box
 - Darken the appropriate numbered ovals under the rectangles to indicate the respondent ID number
- Participant completes the questionnaires. Refer to the Serving Size Choices reference sheet to answer “how much”
- Make sure participant’s name is not visible on the form
- Questionnaires are not data entered. Clinics should save completed questionnaires and mail to DCC every 3 months

Shipping

- Ship batches of completed questionnaires at approximately 3 month intervals
- Shipping supplies
 - Questionnaire Transmittal Sheet (QT)
- Shipping tasks
 - Make photocopies of questionnaire for participants file
 - Complete Questionnaire Transmittal Sheet (QT) form and make copy to retain at clinic
 - Ship originals of questionnaires and completed Questionnaire Transmittal Sheet (QT) form

SOYA MOP**4. Data collection and forms completion****4.4.2.4. Soy Food Screener Questionnaire**

- Ship to:
ACRC Data Coordinating Center
Attn: Debbie Amend-Libercci
911 S. Ann Street
Baltimore, MD 21231
(443) 287-3170

Form (abbreviation)

- Questionnaire Transmittal Sheet (QT)
-

**Soy Foods (BS) Questionnaire
Labels**

Clinic: **TEST**

Place one label on BS questionnaire
at V1, V2 and V9

Participant ID: **YX100**
Visit 1
Respondent ID Number:
10 22 100 01

Participant ID: **YX101**
Visit 1
Respondent ID Number:
10 22 101 01

Participant ID: **YX102**
Visit 1
Respondent ID Number:
10 22 102 01

Participant ID: **YX100**
Visit 2
Respondent ID Number:
10 22 100 02

Participant ID: **YX101**
Visit 2
Respondent ID Number:
10 22 101 02

Participant ID: **YX102**
Visit 2
Respondent ID Number:
10 22 102 02

Participant ID: **YX100**
Visit 9
Respondent ID Number:
10 22 100 09

Participant ID: **YX101**
Visit 9
Respondent ID Number:
10 22 101 09

Participant ID: **YX102**
Visit 9
Respondent ID Number:
10 22 102 09

Participant ID: **YX103**
Visit 1
Respondent ID Number:
10 22 103 01

Participant ID: **YX104**
Visit 1
Respondent ID Number:
10 22 104 01

Participant ID: **YX105**
Visit 1
Respondent ID Number:
10 22 105 01

Participant ID: **YX103**
Visit 2
Respondent ID Number:
10 22 103 02

Participant ID: **YX104**
Visit 2
Respondent ID Number:
10 22 104 02

Participant ID: **YX105**
Visit 2
Respondent ID Number:
10 22 105 02

Participant ID: **YX103**
Visit 9
Respondent ID Number:
10 22 103 09

Participant ID: **YX104**
Visit 9
Respondent ID Number:
10 22 104 09

Participant ID: **YX105**
Visit 9
Respondent ID Number:
10 22 105 09

Participant ID: **YX106**
Visit 1
Respondent ID Number:
10 22 106 01

Participant ID: **YX107**
Visit 1
Respondent ID Number:
10 22 107 01

Participant ID: **YX108**
Visit 1
Respondent ID Number:
10 22 108 01

Participant ID: **YX106**
Visit 2
Respondent ID Number:
10 22 106 02

Participant ID: **YX107**
Visit 2
Respondent ID Number:
10 22 107 02

Participant ID: **YX108**
Visit 2
Respondent ID Number:
10 22 108 02

Participant ID: **YX106**
Visit 9
Respondent ID Number:
10 22 106 09

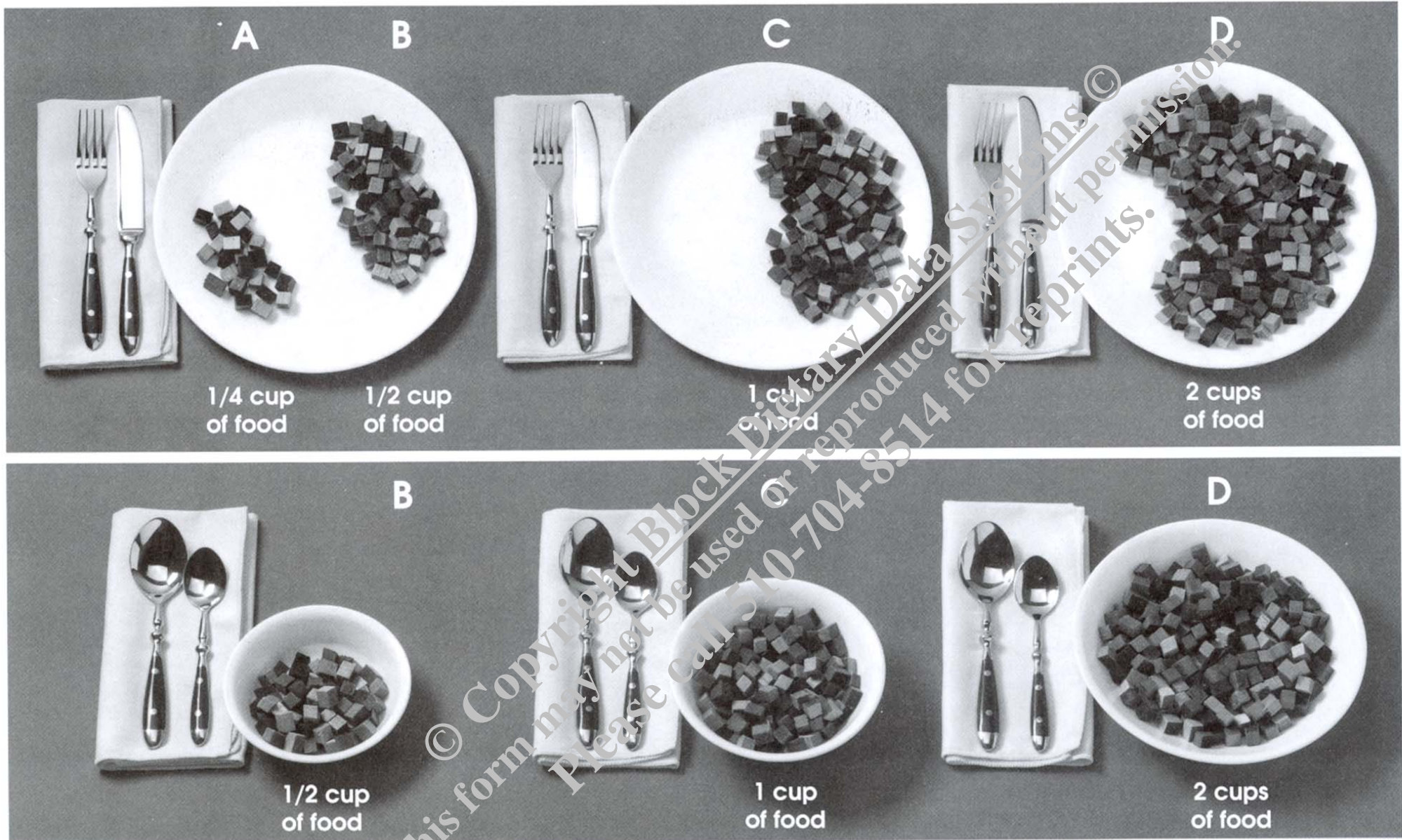
Participant ID: **YX107**
Visit 9
Respondent ID Number:
10 22 107 09

Participant ID: **YX108**
Visit 9
Respondent ID Number:
10 22 108 09

FOOD QUESTIONNAIRE
Serving Size Choices

Keep this in front of you while you are filling out The Food Questionnaire. You may use either the plates or the bowls to help you choose your serving size.

Choose A, B, C or D: **A** = 1/4 Cup of Food **B** = 1/2 Cup of Food **C** = 1 Cup of Food **D** = 2 Cups of Food



4.4.3 Logs/administrative forms

Purpose

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

Tasks/Time frame

- **Study Kit Accountability Log (DA)** - filled out whenever study supplement shipments are received, whenever supplement stock is destroyed, whenever study supplement kits are issued to a participant, and whenever study supplement is transferred to a satellite. A log should be maintained at each specific clinic that stocks supplement including satellite clinics (See Section 3.10.4 of MOP)
 - **DNA Specimen Transmittal Sheet (DT)** - to accompany transmittal of DNA specimens
 - **ACRC General Supply Order Form (GO)** - order form for general ACRC supplies
 - **Methapharm SOYA Order Form (MP)** - used each time methacholine is ordered from Methapharm, Inc (See section 3.7.9 of MOP)
 - **Methacholine Challenge Worksheet (MW)** - Worksheet for administering the MeCL Challenge Test
 - **Patient Bottle Accountability Log (PD)** - account for study supplement stock for each participant. An entry should be made whenever study supplement is assigned, dispensed and returned for the particular patient
 - **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
 - **Questionnaire Transmittal Sheet (QT)** - to accompany transmittal of Food Frequency and Soy Foods questionnaires
 - **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 (ST)** - to accompany transmittal of specimens in cryovials
 - **SOYA Supply Order Form (YO)** - order form for supplies specific to the SOYA trial
-

4.4.4 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 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 SOYA 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
 - **SOYA 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
 - **SOYA 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 out the blank items on the sheet and instruct the participant on the appropriate use of the sheet
-

4.4.5 Certification forms and consents

Certification forms

Purpose

- To assure that all necessary facilities, equipment, personnel, and approvals are in place before SOYA 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 SOYA are in place
- **SOYA Personnel Assurance Statement (PA)** - to be signed by all personnel requesting certification and a PIN to conduct SOYA. Signed statement sent to DCC and copy kept by clinic
- **SOYA Methacholine Challenge Test Assurance Statement (MA)** - to be signed by ACRC Clinical Center Director as assurance that methacholine challenge test is being conducted per SOYA protocol. Signed statement sent to DCC and copy kept by clinic
- **SOYA Spirometry Test Assurance Statement (SA)** - to be signed by ACRC Clinical Center Director as assurance that spirometry testing is being conducted per SOYA protocol. Signed statement sent to DCC and copy kept by clinic.

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.
-

4.4.6 Distributed data entry

Online data system background

- Distributed data entry for the ALA-ACRC SOYA trial will be conducted via the internet
- Clinic staff will be able to enter and edit data from any computer connected to the internet running Internet Explorer 5+ on Microsoft Windows
- Data will be double entered to ensure accuracy
- Error and consistency checks will be built-in to the data entry application
- The data entry application and clinical data will be secured with passwords and user names stored in the SOYA 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 SOYA web site at <http://www.jhcct.org/Secure/SOYA/SOYAHome.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 SOYA 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
-

SOYA MOP

5. Quality assurance

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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 treatment is distributed by the SOYA 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 Study Kit 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 kits from Methapharm, Inc.
-

5.2 Satellite clinics

- Satellite clinics are an adjunct to their 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 the lead coordinator at the primary clinical center
 - Other study personnel (e.g., data system operator) are optional and at the discretion of the satellite clinic and primary clinical center
 - Study treatments 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)
 - Study Kit Accountability Log (DA) and Patient Bottle Accountability Log (PD) separate from that of the primary clinical 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, and 7.0, 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 (SOYA Fed Ex number: 4895-2708-1)
 - 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 SOYA website, <http://www.jhcct.org/Secure/SOYA/SOYAHome.aspx> 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 4.3 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@jhspsh.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 SOYA study supplement 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 study Kit Accountability Log (DA) (one per clinic) and Patient Bottle Accountability Log (PD) (one per participant)
 - 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
-

SOYA MOP

6. Asthma medications

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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*)
 - Flunisolide (Aerobid)
 - Fluticasone (Flovent, Advair component*)
 - Mometasone (Asmanex)
 - Triamcinolone (Azmacort)
 - Ciclesonide (Alvesco, Omnaris)

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, Uniphyll, Theo-Dur, Slo-Bid, Theolair, Theo-24)

Oral antileukotrienes

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

Immunoglobulin E blockers (for subcutaneous injection)

- Omalizumab (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)
- Metaproterenol (Alupent, Metaprel)

Anti-cholinergic

- Ipratropium bromide (Atrovent, Combivent component*)

*Combination drug of which generic drug noted is a component