2.1 ACTION PLANS and IDENTIFICATION CARDS

There are several different Action Plan Cards used during the STICS studies. There are different action plans for the Run-In period and the Treatment Phase of the study.

These cards provide a quick reference for the parent/guardian to use in monitoring the participant's asthma. They provide instructions for daily activities, when to start Yellow Zone medications, when the study team should be contacted and when to seek immediate medical help. The tri-fold ID card includes similar instructions, but is smaller and can be carried in a wallet or purse. In addition, it contains instructions for treatment of asthma attacks by physicians and ER personnel who may not be familiar with the STICS study. The parent/guardian should be encouraged to keep the tri-fold ID Card with them at all times. The Action Plan should be reviewed at all study visits.

Visit 1

Dispense STICS Run-in Action Plan Card

The STICS Run-In Action Plan Card should be dispensed at Visit 1 and used during the Run-in only.

Complete the participant's ID number and the phone numbers of study contacts and emergency contacts.

Review the contents of the card with the parent/guardian and explain the use of the card. For example, you could say:

> "It contains information regarding what to do if your child's asthma gets worse and he/she needs emergency care. If you are unable to control his/her asthma with the rescue inhaler, please try to contact one of the phone numbers listed on this card. If you are unable to contact the study team, try to contact your primary care physician for assistance. Otherwise, go to the emergency department for treatment. Be sure to let any physician who attends to your child know that he/she is in this study and show them this card. It lists the recommended procedures for care. It is important that all participants in this study be cared for as similarly as possible. If the physician feels that alternative treatment is better for your participant, then your treatment will be changed accordingly."

Review when and where emergency care should be sought. Remind the parent/guardian that care should be sought for the participant from study personnel, if possible. However, parents/guardians should never delay seeking care if study personnel cannot be reached.

Treatment procedures have been developed with the utmost regard for participant safety. The parent/guardian should document the circumstances surrounding an emergency care event or illness, including a record of any non-study medications taken.

The back of the STICS Run-In Action Plan contains a 'Daily Activities Guide'. The guide contains a simple summary of the study activities that must be carried out each day, including instructions for study medications and the spirotel® device. It also provides instructions what to bring to the next study visit.

Visit 2

Dispense STICS Action Plan Card and STICS tri-fold ID Card

Collect the STICS Run-In Action Plan Card.

On the STICS Action Plan and tri-fold ID Card, write the participant's study ID number and the phone numbers of study contacts. Explain to the parent/guardian the purpose of the After Hours Phone Numbers.

Review the contents of the card with the parent/guardian. Review with the parent/guardian how/when to use albuterol, when to start the Yellow Zone, and 'Get Medical Help!'

The 'STICS Action Plan Card' and the 'STICS tri-fold ID card' should be dispensed at Visit 2 and used for the remainder of the STICS study.

The back of the STICS Action Plan contains a 'Daily Activities Guide'. The guide contains a simple summary of the study activities that must be carried out each day, including instructions for study medications and the spirotel® device. It also provides instructions for what to bring to the next study visit.

Evening Routine

It is important to get the parent/guardian into an evening routine with the nightly tasks.

The following order of events should be encouraged:

- Complete the spirotel® session (parent completes Q1-Q15, participant performs peak flows)
- Give the participant required puffs from Green or Yellow Inhaler
- Put participant to bed

Visit 3-7

Review the Action Plan Cards

Review when and where emergency care should be sought. Remind the parent/guardian that care should be sought for the participant from study personnel, if

possible. However, parents/guardians should never delay seeking care if study personnel cannot be reached.

Review the instructions on how/when to use albuterol, when to start the Yellow Zone, and ‘Get Medical Help!’

Treatment procedures have been developed with the utmost regard for participant safety. The parent/guardian should document the circumstances surrounding an emergency care event, including a record of any non-study medications taken.

2.2 ADHERENCE

Participants enrolled in the STICS protocol are involved in daily study activities throughout the trial. A great deal is asked of the parent/guardian, and the quality of the study results is a function of their level of protocol adherence. Everyone must be given every opportunity to be compliant and successful.

Factors That Affect Adherence

It is important to be aware of factors that may affect adherence.

Parent/guardian Characteristics

- ability to comprehend and recall instructions
- support of family members for study participation
- satisfaction with care and caregivers
- degree of concern about participant's health
- perception of disease severity
- perceived costs and benefits of treatment

Site Personnel Characteristics

- consistency of AsthmaNet personnel with whom participants have contact during the study
- demonstration of interest and genuine concern for the participant's health
- warm and caring demeanor; approachable
- engagement in social conversation and active interchange
- presentation of clear instructions
- proficiency in clinical activities
- accessibility when the parent/guardian has questions, concerns or emergency needs

Clinic Characteristics

- positive and warm environment (unhurried and comfortable)
- timely appointments
- organized and efficient

Characteristics of Regimen (determined by the protocol)

- most important determinant of adherence
- should not be too complex
- side effects of study drug should not be a big problem/concern

- regimen should be adaptable to parent/guardian's life and work, not the other way around

Improving Adherence

A number of approaches can be used to improve adherence in the STICS trial:

- Educate the parent/guardian
  - Make sure the study activities are understood
  - Demonstrate the activities and have the parent/guardian do the same
  - Present instructions as clearly as possible
  - Have the parent/guardian repeat instructions
  - 'Quiz' the parent/guardian on the instructions
  - Teach the regimen in a stepwise fashion (i.e., step 1, step 2, step 3 for AM and PM activities)
  - Review the handouts at each visit
  - Use phone contacts to reinforce instructions and to ensure that the parent/guardian is performing activities correctly
- Provide positive reinforcement for excellent participant adherence
- Encourage support of family and friends during study participation
- Prepare parent/guardian for what will happen at upcoming visits
- Run the clinic on schedule and make good use of the parent/guardian's time
- Make sure the clinic is accessible with flexible hours and ample, convenient parking
- Avoid no-shows with a reminder phone call in advance of the visit date. Call the parent/guardian's residence and cell phone immediately if there is a no-show
- Ensure that clinic personnel are easily accessible by phone, pager, and e-mail

- Develop a friendly and caring relationship with the parent/guardian and participant

  An integral part of the visit is interacting with the study personnel. A feeling of attachment or obligation to an individual improves adherence and reduces withdrawals.

Counseling for Non-Adherence

At each visit the parent/guardian's level of adherence with study procedures must be assessed. Individuals who have maintained high levels of adherence should be applauded. If adherence levels are low, this should be addressed with the parent/guardian.

During each visit, review the necessity of correct study medication use and the importance of avoiding medications that are not allowed during the study. Remind the parent/guardian that correctly following study procedures is crucial to the study; it is a part of the commitment he or she made when agreeing to participate.

When dealing with problems it is best to re-explain procedures slowly and thoroughly and to rationalize and persuade logically. Attribute lack of adherence to a misunderstanding between clinic staff and the parent/guardian. Ensure that the parent/guardian is aware of the resources available to help him or her understand the study procedures, such as study handouts and the availability and willingness of clinic personnel to answer questions whenever they arise.

Visit 2

It is very important at this visit to get a good sense of the ability of the parent/guardian to comply with study procedures, before allowing the participant to proceed and be randomized. The parent/guardian is required to have at least 75% adherence during the Run-In period with regards to the spirotel® completion in order to be eligible for STICS. In addition, the parent/guardian is required to have at least 75% adherence during the Run-In period with taking the study medications. If the coordinator feels that the participant will not be able to comply with the study procedures, the participant should not be randomized into STICS.

Adherence with the spirotel® completion and study medications is assessed on Eligibility Checklist 3. See the Spirotel® Section for further details.

See *"Forgotten Study Materials"* for instructions on what to do if items for determining adherence are forgotten at a study visit.

Visit 3-8

Adherence with the spirotel® completion is assessed via reports once the spirotel® data is downloaded. The study medication adherence gets calculated on the P7_COMPLY form based on the yellow and green inhaler counters. See the Spirotel® Section for further details.

In addition, for the STICS studies, the coordinator should record any use of antibiotics and nasal steroids on the CMED form. Information on antibiotic and nasal steroids needs to be collected for the BIOME mechanistic study.

2.3 ADVERSE EVENTS

Adverse events include the following:

- Clinical Adverse Events: unintended worsening in structure or function of the body; any illness that occurs during the trial.

- Significant Asthma Exacerbation: increase in asthma symptoms (e.g., cough, wheezing, and chest tightness) which results in the need for an increase in asthma controller medications, typically inhaled corticosteroids and/or oral/systemic corticosteroids.

- Serious Adverse Events: any experience that poses a significant hazard to a patient or participant. With respect to human clinical experience, a serious adverse event includes any experience that is fatal or life threatening, results in significant or persistent disability, requires or prolongs an existing hospitalization, results in a congenital anomaly/birth defect, or represents other significant hazards or potential serious harm to research participants or others, in the opinion of the investigators. Note that any inpatient hospitalization, even for elective surgery, constitutes a serious adverse event and should be documented as such. This includes, but is not limited to, a hospitalization for an asthma exacerbation. Important medical events that may not result in death, be considered life-threatening, or require hospitalization may be classified as serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the listed outcomes. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an ER or at home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or abuse. Serious adverse events are reported on the Serious Adverse Events Reporting (SERIOUS) form.

For detailed information on adverse events, see Section 4 in the AsthmaNet General Manual of Operations. In general, ICD-9 codes describing an adverse event of any type should be obtained by searching the AsthmaNet Adverse Events ICD-9 Code Spreadsheet that is located on the secure AsthmaNet website. This spreadsheet can be accessed on the secure website in the Applications folder or through a link provided in concurrent forms entry. The spreadsheet includes the ICD-9 code for a particular diagnosis, along with long and short text descriptions of the related diagnosis. Clinical personnel can search the spreadsheet for a specific condition to find an appropriate code. Codes and their associated descriptions were downloaded from the Department of Health & Human Services, Centers for Medicare & Medicaid Services (CMS) website. They are from version 27 of the full and abbreviated code titles of the ICD-9-CM codes effective October 1, 2009. This code library will be used for the duration of AsthmaNet to ensure standardization across trials. Note that no other ICD-9 code references are acceptable.

If an acceptable code cannot be located, the Primary Data Manager for the study protocol should be contacted for assistance. No other ICD-9 code references are acceptable.

Note that ICD-9 codes should describe the underlying condition or disease that resulted in the adverse event. For example, if a participant is hospitalized for a tonsillectomy that was necessitated by obstructive sleep apnea, the ICD-9 code for obstructive sleep apnea should be recorded on the Clinical and Laboratory Adverse Events (AECLIN) form. The procedure code for tonsillectomy should not be recorded.

Visit 1

Record Clinical Adverse Events

Clinical adverse events that occur since the signing of the informed consent are recorded on the Clinical Adverse Events form (AECLIN). All adverse events should be followed to completion during the study.

At Visit 1 a complete medical history is taken. As part of this history, it is important to probe for pre-existing conditions. This baseline knowledge is necessary to determine if conditions experienced during the study should be considered clinical adverse events (i.e., worsening of a chronic condition or a condition that appears for the first time during the study). Pre-existing conditions should not be recorded on the data collection forms, except as noted above, but they should be noted in the participant's clinic notes for future reference.

The only adverse events that should be recorded at Visit 1 are those that began since the signing of the informed consent. For most participants, no entries will be made on the AECLIN form until the second visit.

Relating AECLIN entries to CMED entries

If an asthma- or allergy-related medication is given as a result of an adverse event, the medication should be recorded on the CMED form. There is a column on the CMED form (Related Event) which links the medication back to the Adverse Event for which it was given. See the Standard Forms section of the AsthmaNet General MOP for more information.

Visits 2-8

Follow up Clinical Adverse Events from previous Visits and Record any new Clinical Adverse Events (AECLIN)

Review the participant's file to determine if there were any ongoing adverse events at the previous visit or if any new events were reported to clinic personnel between visits. If an ending date for an ongoing adverse event is now known, update the Clinical Adverse Events form (AECLIN) with the new information. Probe the parent/guardian for the occurrence of any adverse events that were not previously reported and record these on the AECLIN form.

The parent/guardian should be instructed to keep track of illnesses, injuries and medications between visits. This may be useful in completing the AECLIN form. See Section 5 of the General MOP for more information on completing the AECLIN form.

Serious Adverse Events

If an adverse event is deemed serious by the above definition, a Serious Adverse Event Reporting Form (SERIOUS) MUST be completed and faxed to the DCC as soon as possible, preferably within 72 hours of clinic notification. Promptly faxing this form to the DCC expedites communicating the details documenting the adverse event to the Steering Committee and the Data Safety and Monitoring Board (if necessary). A copy of the MedWatch report will also be faxed to the FDA if the event requires reporting to the FDA.

Serious adverse events (SAEs) that occur after the signing of the STICS informed consent but before Visit 1 will be reported by the DCC as SAEs P1, P2, P3, etc. Those that occur during the Run-In will be designated R1, R2, R3, etc. Those that occur during the Treatment Phase will simply be numbered 1, 2, 3, etc.

2.4 APPOINTMENTS: CONFIRMING AND SCHEDULING

Explain the importance of completing the visits within the visit windows and verify that the participant will be able to make all of the scheduled visits. The parent/guardian should consider school, sports, and work schedules, along with upcoming vacations when finalizing a schedule. If a parent/guardian knows that the participant will not be able to keep some of the scheduled visits, then the initial visit should be rescheduled for a date that results in a study visit schedule that is more agreeable to the family, as much as possible.

Include a copy of the STICS Participant Visit Schedule(s) in the participant's study handout folder so that the family can adjust their schedules for the best adherence. Also include a copy of this schedule in the participant's study folder at the site.

If a study participant routinely fails to keep scheduled visits, the parent/guardian and study participant should be counseled by the study coordinator and, possibly, by the Principal Investigator at the site. If such counseling does not improve the participant's adherence, contact the DCC for guidance.

Visits for a given participant should be scheduled for the same time of day (+/-3 hours) to avoid the introduction of circadian variability into the assessment of lung function. Once the participant is randomized, the time spirometry occurred at Visit 2 should be used as the reference. If a participant needs to be scheduled outside the 3-hour window, the STICS scientific coordinator at the DCC should be contacted to obtain an exception.

See the Visit Schedule and Visit Windows discussions in section 2.54 for further details.

Splitting Visit 1 into 2 visits

If it is preferable to the parent, Visit 1 can be split over 2 days. The two partial visits should be completed within 7 days.

On the Visit 1 Procedure Checklist, the following items should be completed on the **first day** of Visit 1: #1-#6, #9, and #16-#17. #7 and #8 can be completed as long as the participant isn't on Step 3 Controller Therapy. If the participant is on Step 3 Controller Therapy, please complete the P7_ELIG1 form up to Q33 then stop. Q33 through Q36 should be completed during the second day of Visit 1 (since it is important that the CACT score be captured on the second day), and the date on the P7_ELIG1 form should be the date of the second day.

On the Visit 1 Procedure Checklist, the following items should be completed on the **second day** of Visit 1: #10-#15 and #18-#43.

2.5 BLOOD SAMPLING PROCEDURES

Visit 2

Materials required:

- **1 gold-top serum separation tube (5 mL draw capacity)**
  - BD Vacutainer #367986, Fisher catalog #02-683-97
- **1 small purple-top EDTA tubes (2 mL draw capacity)**
  - BD Vacutainer #367841, Fisher catalog #02-683-99A
- **1 plastic purple-top EDTA tube (10 mL draw capacity)**
  - BD Vacutainer #366643, Fisher catalog #02-657-32
- **Sample tubes/vials (need two sizes)**
  - Fisherbrand 5.0 mL cryogenic vials, Fisher catalog #10-500-27
- **Cryovial storage boxes for freezing of sample vials**
- **Venipuncture supplies**
  - Butterfly needles, tourniquet, alcohol wipes, gauze, Band-Aids

Tests to be performed:

The following blood tests will be performed in STICS at Visit 2. If you have difficulty drawing blood on the participant at Visit 2, the blood draw should be reattempted at a later date.

- ImmunoCap Testing for food/aero-allergen sensitization and total IgE
- CBC with differential (total WBC and Eosinophils)
- Genetic Analysis (optional)

General Blood Draw Procedures:

The volume of blood to be drawn should conform to local IRB regulations (which are typically based on the child's body weight). A **total of no more than 15-20 mL** of blood will be drawn into **3 different tubes**. In the event that you are unable to collect all of the required blood to fill each of the tubes, proceed in the order listed below. Additional blood may be collected at a later date.

Draw the following tubes of blood ***in the order listed below***:

- **Tube #1:**
  - 5 mL in one gold-top tube for Immunocap
- **Tube #2:**

  - 1 mL in one small purple-top EDTA tube for CBC with differential
- **Tube #3:**
  - 10 mL in one plastic purple-top EDTA tube for genetics

The processing and storage of each of these blood samples is discussed below. **Note: Samples should be immediately transported to the laboratory for processing**. The centrifuge instructions below are expressed as RCF (g). If your centrifuge only has RPMs, calculate the necessary RPMs with the following equation:

$$RPM = \sqrt{[(RCF \times 10^5)/(1.12 \times r)},$$

where "r", expressed in cm, is the radial distance from the centrifuge head to the bottom of the tube.

If using a refrigerated centrifuge, the centrifuge temperature should be set to room temperature (approximately 20 to 25 degrees Celcius) before spinning samples. Cold temperatures can lead to ice crystal formation within the red blood cells, causing them to burst and disrupt the assays.

ImmunoCap and Total IgE Procedures

***These instructions refer to the 5 mL gold-top tube.**

1. Immediately after collection, invert the tube 5 times and store upright at room temperature until transport to the laboratory. Do not place on ice.
2. Allow the tube to clot for a minimum of 60 minutes, and no longer than 120 minutes.
3. Centrifuge the tube at 1000-1300 RCF (*g*) for 10 minutes to separate the serum.
4. Add **serum to one large microcentrifuge tube (5 mL capacity, cat #10-500-27)** for ImmunoCap and IgE testing.
5. Discard the gold top blood collection tube.
6. Store the ImmunoCap/IgE vial in a box and freeze immediately at -20° to -80° C.
7. Samples will be shipped monthly **on dry ice** on the first Monday of each month (if Monday is a holiday, then ship on Tuesday) (see shipping section below).

CBC with Differential (Total WBC, Eosinophils) Procedures

***These instructions refer to the small 2 mL purple-top EDTA tube that is collected.**

1. Draw 1 ml of whole blood into the tube.
2. Immediately after collection, invert the tube 8-10 times and store upright at room temperature until transport to the laboratory. Do not place on ice.

3. Send the tube to the site's local laboratory for processing. Note: A manual count is NOT required; an automatic count is sufficient.
4. The results of the CBC (WBC and eosinophils) are recorded on the Laboratory Tests (P7_LAB) form. See Section 4 for more detail on completing this form.

Genetic Analysis Procedures

***These instructions refer to the medium, 10 mL purple-top EDTA tube.**

1. Immediately after collection, invert the tube 8-10 times and store upright at room temperature until transport to the laboratory. Do not place on ice.
2. Store tube in the refrigerator (2-8° C).
3. Samples should be shipped weekly to Fernando Martinez, Tucson Genetics of Asthma Laboratory, Tucson, AZ (see shipping section below). **Do not place samples on dry ice when shipping.**

Specimen Tracking – Collection Day

Enter the participant's ImmunoCap blood draw information into the Biological Sample Tracking module. Label each tube with a barcode label generated through the AsthmaNet Biological Sample Tracking module.

Label specifications: Diversified Biotech (www.divbio.com).
Labels: Diversified biotech White Laser Cryo-Tags 1.50" x.75"
http://divbio.com/lasercryo-tags169x0751040pk.aspx

When printing labels, be sure to save the label sheet as a PDF to your Desktop in case the labels do not print successfully.

Size Option:
• "Fit" or "Shrink oversized pages" in Adobe X
• "Fit to Printable Area" or "Shrink to Printable Area" in Adobe 9
• Do NOT select "Actual Size" or "None" as labels will not position correctly on the page.

Scan the samples into the Biological Sample Tracking (BST) module using the procedures outlined in section 7 of the AsthmaNet General Manual of Operations. The samples should be frozen at (-20 to -80° C) until shipping.

Specimen Tracking – Shipping Day

The samples should be scanned a second time on the day they are being shipped. Each shipment will receive a unique shipment ID number when a given shipment is

confirmed by a performance site. A shipment inventory will be generated that contains: date of shipment, shipper tracking number, site of origination, shipment ID, and an inventory detailing all the tubes in the shipment with their barcode numbers and participant information (study ID number, initials, visit number and blood draw date). Print the shipment inventories for inclusion in the shipment. Samples must be shipped via FedEx priority overnight. See complete packaging and shipping instructions below.

Once the shipment is confirmed in the BST module, an e-mail will automatically be sent to the lab that will be receiving samples the next morning. The e-mail will include an export file from the database that shows the information from the shipment inventory. A summary of the shipment will be included in the body of the e-mail message.

Packaging Instructions for Samples that Require Shipping on Dry Ice (This refers to all samples except blood for genetics)

Note: The instructions below meet the minimum federal standards. Each site's institution may have additional guidelines. Sites should follow their institutional guidelines as long as they are in compliance with these minimum federal standards.

1. Place tubes and absorbent material (see below for absorbent material information) into the recommended plastic transport bags (VWR Scientific Co, 1-800-932-5000) and seal.
    - These are 9 x12 liquid tight clear plastic bags, suitable for most shipments (this size will hold approximately 10-15 tubes). Other sizes are available also.
        - Infecon Transport Bags 11217-194 250/case $204.59, or
        - Bitran Specimen Bags 11217-126 250/case $224.69

2. Tubes should be packed in the bags so that they lie flat and will have as much contact with the dry ice as possible

3. Include the absorbent material (absorbs up to 250ml) in the plastic transport bag.
    - Recommended material is from FisherScientific (1-800-926-1166)
    - sheets 19-075-383C 100/case $20.36

4. If shipping more than 25 tubes use additional sheets. If shipping fewer than 12 tubes half sheets may be used.

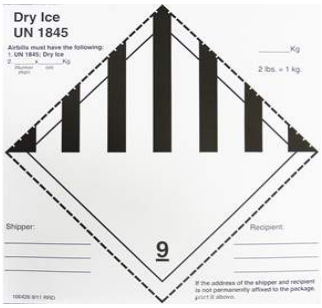
5. Use bubble wrap or cardboard to keep the tubes stable should the dry ice dissipate.

6. Fill bottom of shipping box with dry ice. **NOTE: There should be sufficient dry ice to keep the samples frozen until they reach the laboratories.**
   Suggestions:
   - Plastic bubble wrap can be used at the bottom and top of the shipping container.
   - Plastic bubble wrap can be reused if there is no leakage
   - Cardboard can also be used to stabilize tubes.

7. The Styrofoam boxes should be sufficient in size and must be shipped in a cardboard carton.

8. Boxes must have the label “Exempt Human Specimen” attached. (Fisher Scientific, Catalog #22-130-070: Therapak “Exempt Human Specimen” label). Cardboard cartons can be obtained from Fisher Scientific (Catalog #03-525-36: Tefrant Thermosafe Insulated Shipper Multi-purpose Containers, Case of 12 for #159.31)

9. Affix the dry ice label “DRY ICE – UN 1845” to the carton. Mark the approximate weight of dry ice in kg for each shipment. (Air Sea Containers, http://www.airseacontainers.com, Product name: Dry Ice UN 1845 Label, Roll of 500 (No product number),1-866-272-9880)



10. The name, address, and telephone number of a person responsible for the shipment is required on the box.

11. Boxes of various sizes have been subjected to the required drop test.

Shipping Specimens that Require Dry Ice (This refers to all samples except blood for genetics)

The samples should be placed into a shipping box containing a sufficient amount of **cubed/chipped dry ice**. Put 1 inch of crushed dry ice in the bottom of the shipping box. Add a plastic transport bag containing blood in the screw top tubes. Lay flat on top of the first ice layer. Layer more crushed dry ice so that the bag of tubes cannot be seen – at least one inch. If there is additional space in the box, add another plastic transport bag containing blood in the screw top transfer tubes. Make sure there is room for 2 inches of dry ice at the top. There is no limit to the number of tubes that can be put in the box. Just be sure that the box is large enough to include enough dry ice. (Close the box in such a way that the lab address is showing.) The box is then sealed with tape. Please do not completely seal the stryrofoam box so that it is airtight because the carbon dioxide from the dry ice must be allowed to escape. The dry ice poundage should be marked on the dry ice label on the box.

All blood specimens should be sent FedEx Priority Overnight. No other form of shipping is acceptable. Blood samples should be shipped on the first Monday of each month (if Monday is a holiday, then ship on Tuesday). If you are unable to ship the samples on the designated shipping day, you **MUST** contact the lab to make sure the lab person is available to receive the shipment on the alternate day.

CBC with differential samples

Record the participant's total WBC and relative eosinophil count on the Laboratory Tests form (P7_LAB). It is important that both the total white blood cell count and the relative eosinophil count are recorded so that the total eosinophil count can be

calculated. See Section 4 in this manual for further details regarding this form. Store the original lab report in the participant's study folder at the site; forward a copy to the DCC for verification after blackening out any participant identifiers.

Genetic samples

- Complete Genetic Analysis Blood Draw (GABLOOD) form
- Enter participant's genetics blood draw information into Genetics Sample Tracking module.
- Samples must be shipped **weekly** via FedEx priority overnight. The STICS genetic samples can be shipped with the APRIL genetic samples as long as APRIL is still recruiting. The DCC FedEx number can be used to ship the joint shipments. Once APRIL is finished recruiting and genetic samples are no longer being collected, each site is responsible for the cost of the genetic shipping. **Please refer to the AsthmaNet General MOP for shipping instructions. Do not place genetic samples on dry ice.** Samples should be shipped to the following address:

  Arizona Genetics Lab
  Keating Building
  1657 East Helen Street
  Tucson, AZ 85721-0240
  Tel: (520) 626-7670
  ATTN: Penelope Graves
  Email: pgraves@email.arizona.edu

Immunocap samples

- Enter participant's blood draw information into the Biological Sample Tracking module.
- Samples must be shipped **monthly** via FedEx priority overnight.
- Samples should be shipped to the following address:

  ADx at National Jewish Health
  Attn: Client Services
  1400 Jackson Street
  Room M013
  Denver, CO 80206
  ATTN: Brock Harper
  Tel: (303) 270-2663
  Email: harperb@njhealth.org

2.6 CACT: Childhood Asthma Control Test

Visits 1-8 and Phone Contacts

Administer Childhood Asthma Control Test

Childhood Asthma Control Test (CACT)

The CACT is a trade-marked 7-item questionnaire that was developed through research by GlaxoSmithKline. AsthmaNet has received permission from GSK to use the CACT in the STICS trial. AsthmaNet was refused permission to implement any formatting changes to make it more compatible with our database. See the data management guidelines for this form in section 10 of the AsthmaNet General Manual of Operations for more information.

The CACT gathers information from the perspective of the young participant and from the perspective of his/her parent/guardian. The child answers the first four questions and may receive help reading and understanding the questions. The parent/guardian answers the last three questions and is asked not to let the child's answers influence his/her response. The last three questions use a 4-week recall window similar to the adult version of the ACT. The CACT should be administered and completed by the parent/guardian during the visit.

No source documentation can be provided on this questionnaire due to the constraints imposed by GSK.

Administration

The Childhood Asthma Control Test (CACT) is administered at all visits and phone contacts. The CACT has been validated for use in adolescents ages 4 - 11.

The administration of the CACT is one of the first procedures performed at a visit. This timing in the visit structure is intentional so that a participant's responses are not affected by other study procedures, such as spirometry and e-diary review. Study coordinators should observe the order of procedures as they are laid out on the visit procedure checklists to ensure that CACT results are not biased by other study activities.

When administering the CACT questionnaire, request that the participant or his/her parent/guardian complete the entire form and provide answers as completely and as accurately as possible. No stated or implied time limit should be set. If the participant or guardian requests help with or clarification of any question, the study coordinator should instruct him/her to reread the instructions and to give the best answer possible to each question. The study coordinator should not provide an answer to any question. Providing guidance may bias the responses.

Following are guidelines for CACT administration to ensure the best quality data:

- Provide the participant and his/her parent/guardian in the case of a child a quiet place to complete the questionnaire.
- Before the participant or guardian completes the CACT, the study coordinator should do the following:
    - Complete the information in the form header.
    - Tell the participant and guardian that all questions should be answered.
    - Tell the participant and guardian that only one response may be given for each question.
    - Remind the participant or guardian that he/she is scoring problems experienced due to asthma and not because of any other conditions.
    - Remind the parent/guardian or guardian that the CACT is collecting data about their/their child's asthma over the past 4 weeks.

Participants or guardians should use a black or blue pen to complete the questionnaire. If the respondent wishes to change a response, the original response should be crossed out with a single line and then dated and initialed. The final response should be circled for clarification. No changes to the participant-completed or guardian-completed form may be made by study personnel; changes may only be made by the respondent.

When the participant or guardian is finished with the questionnaire, collect it and review it for completeness before proceeding with the visit. If a question has been left blank, ask the participant or guardian to do his/her best to answer it. The answers to all of the questions are necessary to score the instrument. Check that the responses are clearly marked.

Phone Contacts

During all regular Phone Contacts (2A-7A), the parent/guardian should be instructed to complete the CACT form that was given to them at the last regularly scheduled visit. They should have also received a pre-addressed, postage-paid envelope. After completing the form with the participant, they should mail the form back to the site.

2.7 CERTIFICATION

Study Coordinators and Technicians

Coordinators who carry out STICS study visits must be certified to do so. That is, personnel who complete pregnancy tests (PREG_TEST form) or any of the protocol-specific STICS forms (designated by a P7 prefix in the form name) must possess STICS protocol certification, as well as certification in Human Subjects Protection Training, HIPAA and Good Clinical Practice. Note that protocol-specific forms include completion of the STICS Pulmonary Procedure Checklist (P7_PULMONARYCHK).

To obtain STICS coordinator certification, clinic personnel must complete the following steps:

- Thoroughly read the STICS protocol and this Manual of Operations.
- Pass the STICS coordinator certification exam. This exam can be found on the AsthmaNet secure website in the Certification: STICS folder. Exams should be completed, scanned into a pdf file, and e-mailed to the AsthmaNet-Certification alias. Include 'STICS Exam' and your performance site number on the subject line of the e-mail message to ensure efficient processing and routing at the DCC.

Any individual who performs spirotel® procedures, spirometry, methacholine challenge, IOS (if applicable) or FeNO testing as part of a STICS visit must be AsthmaNet certified in these procedures or be supervised by a certified technician, as applicable. Certification for these procedures is tracked independently of STICS study certification. It is acceptable for these procedures to be performed during the STICS study by technicians who possess only individual procedure certification and not STICS protocol certification, but it is preferred that technicians review the protocol and take the certification exam, as well. If a technician is only certified in spirometry and not in the STICS protocol, a STICS-certified coordinator must complete the STICS Pulmonary Procedure Checklist (P7_PULMONARYCHK) to qualify participants for spirometry and methacholine challenge testing.

Protocol deviations will be assigned when an uncertified individual performs protocol-related tasks or carries out procedures for which he/she is uncertified. Protocol violations will be assigned if this persists at a given site over a period of time. The AsthmaNet Quality Control Committee (QCC) will be informed of continued neglect of appropriate certification procedures.

The quality of AsthmaNet data is tracked and reported on a regular basis to the individual performance sites, clinical center partnerships, the AsthmaNet Quality Control Committee (QCC), and to the Data and Safety Monitoring Board (DSMB). It is possible to become decertified in some of the procedures (e.g., spirometry) if lack of quality

becomes an issue and the study data begins to be affected adversely. The DCC will contact individuals who are in danger of becoming decertified to discuss the situation before they are decertified formally in the certification tracking system. It is also possible to become decertified if a coordinator or technician leaves the Network and returns later, not having performed spirometry or other procedures for an extended period of time. See the individual procedure MOPs in the AsthmaNet General MOP for details.

Licensed Medical Practitioners (LMPs)

Physicians who are listed on the local IRB application as 'key personnel' must take and pass the STICS physician certification exam before interacting with study participants. The physician exam is located on the secure website in folder Certification: STICS.

Non-physician LMPs, such as nurse practitioners and physician's assistants, may perform physical exams for the STICS study (see the Physical Exams discussion in this section for details). If these individuals will be performing exams for STICS participants on a regular basis, then they should take either the coordinator or the physician exam and become certified. If they fill in for study physicians only occasionally, then certification is not required. Note that certification requirements for non-physician LMPs will vary from study to study.

Data Entry Personnel

Individuals who are only providing data entry support for the STICS study and are not collecting data or performing study procedures do not have to meet any specific AsthmaNet certification requirements. However, it should be ensured that local institutional requirements for these individuals (e.g., HIPAA, GCP, and Human Subjects' Protection) have been met and are clearly documented on-site. This documentation may be subject to audit during an AsthmaNet site visit.

2.8 CONCOMITANT MEDICATIONS

Visits 1-8

Record Concomitant Medications

Medications used to treat asthma and allergies that are taken since the signing of the informed consent should be recorded on the Concomitant Medication form (CMED). If the concomitant medication was used for an adverse event, record the corresponding AECLIN event number. If the concomitant medication was taken to treat asthma/allergies and was unrelated to an adverse event, please check the N/A box. Refer to Section 4 of the AsthmaNet General MOP for applicable drug codes (Q1010).

Participants in AsthmaNet protocols are likely to be taking medications for asthma and allergy-related symptoms, both over-the-counter and prescription. It is important to document the medications a participant is taking, or begins to take, throughout the study to ensure that participants are not taking medications that are excluded during the trial because they may confound the study results. Further, it is important to document any non-study asthma medications the participant begins using during the trial, as such use may indicate that the participant has experienced, or is experiencing, a significant asthma exacerbation.

The STICS study will employ the two standard concomitant medications forms: Concomitant Medications for Asthma/Allergy and Adverse Events (CMED) and Concomitant Medications for Non-Asthma Drugs (CMED_NON)**.**

Medications taken for treatment of adverse events, both asthma-related and those unrelated to asthma, should be recorded on the CMED form. Medications taken for treatment of asthma/allergy symptoms, other than dispensed study medications, should also be recorded on this form.

Medications not taken for asthma, allergies or adverse events should be recorded on the CMED_NON form. Examples include multivitamins and herbs the participant is taking for health maintenance and maintenance drugs taken for a pre-existing condition (e.g., Paxil for depression) at the time of Visit 1. Other non-asthma, non-allergy drugs the participant takes chronically, such as oral contraceptives, should also be recorded on this form. After Visit 1, if a participant begins to take a new medication to treat a pre-existing condition, the new medication should be recorded on the CMED form. Need for a new medication for an existing disease or condition is loosely viewed as an adverse event, even though no related adverse event may be recorded on the Clinical and Laboratory Adverse Events (AECLIN) form.

Study medications generally are not considered concomitant medications and, therefore, should not be recorded on the CMED or CMED_NON form. Run-in study

medications include rescue inhalers dispensed as part of protocol dispensation procedures. Additional steroids prescribed for treatment of a significant asthma exacerbation are considered concomitant medications and should be recorded on the CMED form and linked to the corresponding adverse event on the Clinical and Laboratory Adverse Events (AECLIN) form. To clarify, the STICS meds dispensed at a regular visit as part of study dispensation procedures are considered study medications and should not be recorded on the CMED form. If a participant experiences a significant asthma exacerbation and is given an extra QVAR inhaler, the 'extra' inhaler is considered a concomitant medication and should be recorded on the CMED form as such. Note that participants who experience a significant asthma exacerbation during the common run-in period are ineligible for continued study participation.

The following classes of drugs/solutions do not need to be recorded on a participant's CMED or CMED_NON form:

- Anesthesia medications administered during surgery and outpatient procedures
- Sedatives used prior to and during procedures
- Novocain and other dental anesthetics
- Solutions/drugs taken prior to specialized procedures (e.g., Golytely (Colye, Nulytely), phospho-soda, and sodium phosphate tablets (Osmo-Prep, Visicol) taken prior to colonoscopy, Glucola taken during an oral glucose tolerance test)
- Iodine dye and other contrast materials used for MRIs and other procedures

Visit 1

Record concomitant medications the participant has taken since signing the informed consent on the appropriate concomitant medications (CMED, CMED_NON) form

During the first visit, prompt parents/guardians with the following questions:

- What over-the-counter medications does the participant typically take during a given month, including continuous use and as-needed medications, such as laxatives, antacids, stool softeners, ibuprofen, etc.? Inquire about the participant's use of vitamins and herbal remedies. Use of certain herbs, such as St. John's wort or valerian, during study participation should be discouraged.

- What prescription medications does the participant typically take during a given month, including continuous use and as-needed medications?

- What over-the-counter medications does the participant typically pack when you go on vacation or away for business? What prescription medications?

If the participant has taken any medications for asthma or allergies or adverse events that occurred since the informed consent was signed (original signature date), record them on the Concomitant Medications for Asthma/Allergy and Adverse Events (CMED)

form. Record medications taken on the day of Visit 1, even if the parent/guardian has agreed to stop giving them to the participant after completing the visit. List the actual date, or approximate date, the participant started taking each medication. If no drugs are recorded for the participant, check the 'None' box.

Any medications not taken for asthma, allergies or adverse events since the parent/guardian signed the informed consent should be recorded on the Concomitant Medications for Non-Asthma Drugs (CMED_NON) form.

Probing for medication use during Visit 1 affords an opportunity to recognize clinically significant medical problems early in the study. For example, a participant may take several medications to treat gastroesophageal reflux disease. The participant's condition may be deemed unstable and, therefore, ineligible on the basis of the information collected for the concomitant medications form. If a participant is taking medications for a condition that may exclude him or her from study participation, first check the Exclusionary Medical Conditions (P7_EXCLMED) reference card. If the applicable condition is not listed specifically, contact the DCC for guidance.

When scheduling Visit 1, the parent/guardian should be asked to bring all over-the-counter and prescribed medications the participant is currently taking to the visit. Alternatively, the parent/guardian may write down the names of the medications and the date the participant started taking each medication and bring this list to the visit.

Visits 2-8

Follow up medication use from the previous visit and record any new concomitant medications (CMED, CMED_NON)

Each time the clinic has contact with a participant, whether for a scheduled visit or by phone, information on concomitant medications should be collected. During these contacts, the concomitant medication information obtained during previous contacts should be updated. If the participant discontinued a medication that he or she was taking, update the stop date on the CMED or CMED_NON form, as appropriate. Probe the parent/guardian for any new medications that may have been taken and record these on the appropriate form. If the participant began taking a new medication for a condition or disease that existed prior to study enrollment at Visit 1, record this information on the CMED form and link it to the related adverse event recorded on the Clinical and Laboratory Adverse Events (AECLIN) form, if applicable. If the participant has not taken any new medications for asthma, allergy or an adverse event, mark the 'None' box on the CMED form for the applicable visit.

Medications that are ongoing at the time of the visit should be left open for stop dates (i.e., coded as 'ongoing at current visit') until a stop date is known. When a stop date becomes available, the database should be accessed to update the participant's data. If a medication that has been recorded is still ongoing when the participant completes

the study or terminates participation in the STICS studies, the record should be marked 'ongoing at final visit.'

Collecting Non-Study Use of Antibiotics and Nasal Steroids

The coordinator should record any use of antibiotics and nasal steroids on the CMED form. This information will be used for the BIOME mechanistic study.

Visits 8 – Follow-up Medication Prescription

The Principal Investigator or Study Physician (or the Physician Assistant with the approval of the Study Physician) should review the participant's medical course and provide a recommendation for further treatment. This can take the form of a prescription, provision of sample medication, or a stock supply of medication.

Follow-up care should also be recommended. The study site, with the approval of the participant or parent/guardian, can then communicate the recommendation to the clinician who will assume future asthma care.

Any medications that are prescribed to the participant at the last visit should be recorded on the CMED form with a start date the same as the Visit 8, and the 'ongoing at final visit' box should be checked.

2.9 CONTACT INFORMATION

Visit 1

Administer Pediatric Participant Contact Information (CONTACT_PEDS) form

The Pediatric Participant Contact Information (CONTACT_PEDS) form is completed by the parent/guardian. Its purpose is to collect pertinent participant identification information such as full name, address, and telephone number, as well as alternative ways to contact the parent/guardian through work, family, or friends.

- This form serves as source documentation proving the existence of the participant. It **must** be completed.

- It is important to obtain complete and accurate phone number information for the parent/guardian during Visit 1. Parents/guardians will need to be contacted if they miss a visit or for regular phone contacts as part of the STICS studies.

- A space for the participant's social security number (and parent/guardian social security numbers for pediatric participants) has been included on the form for the convenience of the performance site in paying participant stipends. This field may be left blank if institutional policies prohibit recording and storing this information with the clinical records, or if social security number is not needed.

- Store the CONTACT form in the participant's study folder; do not forward it to the DCC. This form contains the participant's name, address, and other identifying information. A protocol violation may be assigned if this form is misdirected to the DCC or another off-site group affiliated with AsthmaNet (e.g., Madison Lab, ADx Lab, etc.).

2.10 ELIGIBILITY CRITERIA

Visit 1

Inclusion/Exclusion Criteria (P7_ELIG1)

Inclusion Criteria

The following inclusion criteria pertain to STICS. Participants may be reassessed if not initially eligible.

1. Willingness to provide informed consent by the participant's parent/guardian or guardian for the STICS study.

2. Willingness to provide informed assent by the participant (age determined by local IRBs) for the STICS study.

3. 5-11 years of age. Note: Participants who are 12 years old or older at the time of *enrollment* are not eligible for STICS. A participant is eligible as long as he/she is enrolled before his/her 12th birthday.

4. Up to date with immunizations, including varicella (unless the participant has already had clinical varicella). The parent/guardian's word is sufficient. If the participant needs varicella vaccine, this will be arranged with the primary care physician and must be received prior to randomization.

5. At least 1 exacerbation treated with systemic (oral or injectable) corticosteroids in the past 12 months.

6. Able to perform reproducible spirometry.

7. Prebronchodilator $FEV_1 \geq 60\%$ predicted at Visit 1.

Exclusion Criteria

Participants who meet any of the following criteria are NOT eligible for enrollment, but may be re-enrolled if these exclusion criteria are resolved:

1. If receiving allergy shots, change in dose within the past 3 months. Participants should NOT change their maintenance regimen during the course of the STICS study.

2. More than 5 prednisone treated exacerbations in the past 12 months.

3. More than 1 hospitalization for asthma lasting >24 hours in the past 12 months.

4. Participation presently or in the past month in another investigational drug trial.
   Note: This criterion does not apply to participants in other AsthmaNet studies that are not randomized. Therefore, BARD run-in failures that meet all of the STICS eligibility criteria at Visit 1 do not have to wait a month to be enrolled into STICS.

5. Evidence that the family may be unreliable or nonadherent, or may move from the site area before trial completion.

6. Parent/guardian is unable to perform study procedures (i.e. use the spirotel® e-diary correctly).

7. Use of any systemic corticosteroids in the 2 weeks prior to enrollment.

8. Current or prior use of medications known to significantly interact with corticosteroid disposition (within a 2 week period of Visit 1) including but not limited to carbamazepine, erythromycin, phenobarbital, phenytoin, rifampin, and ketoconazole.
   .
   Note: For medication exclusion criteria, if the medication was prescribed, but was not taken by the child, it should not count towards the exclusion criterion.

Participants who meet any of the following criteria are NOT eligible for enrollment:

1. Concurrent medical conditions other than asthma that are likely to require oral or injectable corticosteroids during the study (i.e. thyroid disease, diabetes mellitus, Cushing's disease, Addison's disease, hepatic disease)

2. A history of cataracts, glaucoma, or any other medical disorder associated with an adverse effect to corticosteroids.

3. History of significant adverse reaction to any study medication ingredient (fluticasone, oral corticosteroids and albuterol).

4. Gestation less than late preterm as defined as birth before 35 weeks gestational age.

5. Pregnancy or lactation.

6. If of child bearing potential, failure to practice abstinence or use of an acceptable birth control method

7. Chronic or active lung disease other than asthma.

8. Presence of other significant medical illnesses (cardiac, liver, gastrointestinal, endocrine) that would place the study participant at increased risk of participating in the study (See P7_EXCLMED).

9. History of life-threatening asthma exacerbation requiring intubation, mechanical ventilation or resulting in a hypoxic seizure.

10. The participant has significant developmental delay/failure to thrive. Significant developmental delay/failure to thrive is defined as the following: If a participant's height or weight is < 2nd percentile for age and gender

NOTE: Siblings **can** be enrolled in STICS at the same time. Coordinators should clearly label the inhalers with the participants' names to avoid mixing them up.

Inclusion Criteria – Medications

Participants who are ICS- and LTRA-naïve, as well as children on current step 2 therapy or current step 3 therapy may be eligible.

Identify the medication that the participant is taking in the table below. This table is also included on the Eligibility Checklist 1 (P7_ELIG1) form. Based on the current dose, determine if the participant is on Low Dose ICS or Medium Dose ICS. Participants are required to be taking the controller medication for the past 4 weeks. If the participant has been taking the medication for less than 4 weeks, he/she must meet the symptom requirements for participants who are naïve to controller therapy. For participants who have been taking controller therapy less than 4 weeks, Q1310 should be answered 'No'.

Medication		Number of puffs/nebs/ inhalations per day	Low Dose (Step 2 Controller Therapy)	Medium Dose (Step 3 Controller Therapy)
Advair (fluticasone-salmeterol)	DPI: 100/50 mcg/inh DPI: 250/50 mcg/inh DPI: 500/50 mcg/inh	_ _ inhs/day	None	1-2 inh 1 inh None
Advair (fluticasone-salmeterol)	HFA: 45/21 mcg/inh HFA: 115/21 mcg/inh HFA: 230/21 mcg/inh	_ _ inhs/day	None	1-4 inh 1-2 inh 1 inh
Symbicort (budesonide-fomoterol)	80/4.5 mcg/inh 160/4.5 mcg/inh	_ _ inhs/day	None	1-3 inh 1-2 inh

Medication		Number of puffs/nebs/ inhalations per day	Low Dose (Step 2 Controller Therapy)	Medium Dose (Step 3 Controller Therapy)
Dulera (mometasone - formoterol)	100/5 mcg/inh 200/5 mcg/inh	_ _ inhs/day	None	1-2 inh 1 inh
Beclomethasone	HFA: 40 mcg/puff	_ _ puffs/day	1-4 puffs	5-8 puffs
Beclomethasone	HFA: 80 mcg/puff	_ _ puffs/day	1-2 puffs	3-4 puffs
Budesonide	Nebulizer 0.25mg suspension	_ _ nebs/day	1-2 nebs	3-4 nebs
Budesonide	Nebulizer 0.5mg suspension	_ _ nebs/day	1 neb	2 nebs
Budesonide	Nebulizer 1mg suspension	_ _ nebs/day	None	1 neb
Budesonide	Flexhaler: 90 mcg/inh	_ _ inhs/day	1-4 inh	5-8 inh
Budesonide	Flexhaler: 180 mcg/inh	_ _ inhs/day	1-2 inh	3-4 inh
Ciclesonide	HFA: 80 mcg/puff	_ _ puffs/day	1-2 puffs	3-4 puffs
Ciclesonide	HFA: 160 mcg/puff	_ _ puffs/day	1 puff	2 puffs
Flunisolide	HFA: 80 mcg/puff	_ _ puffs/day	1-3 puffs	4-6 puffs
Fluticasone	HFA: 44 mcg/puff	_ _ puffs/day	1-4 puffs	5-8 puffs
Fluticasone	HFA: 110 mcg/puff	_ _ puffs/day	1 puff	2-3 puffs

Medication		Number of puffs/nebs/ inhalations per day	Low Dose (Step 2 Controller Therapy)	Medium Dose (Step 3 Controller Therapy)
Fluticasone	HFA: 220 mcg/puff	_ _ puffs/day	None	1 puff
Fluticasone	DPI: 50 mcg/inh	_ _ inhs/day	1-4 inh	5-8 inh
Fluticasone	DPI: 100 mcg/inh	_ _ inhs/day	1-2 inh	3-4 inh
Fluticasone	DPI: 250 mcg/inh	_ _ inhs/day	None	1 inh
Mometasone	DPI: 110 mcg/inh	_ _ inhs/day	1 inh	2-4 inh
Mometasone	DPI: 220 mcg/inh	_ _ inhs/day	None	1-2 inh
Singulair	4 or 5 mg/tablet	_ _ tablets/ day	1-2 tablets	1 tablet + Step 2 ICS therapy
Singulair	4 mg/packet	_ _ packet/ day	1-2 packets	1 packet + Step 2 ICS therapy
Triamcinolone	MDI: 75 mcg/puff	_ _ puffs/day	1-8 puffs	9-12 puffs

Inclusion Criteria – Symptoms

1. Participants who are currently naive asthma controller therapy must have **at least one** of the following criteria:

    - Daytime asthma symptoms more than 2 days per week (average over the past 4 weeks)
    - More than 2 nighttime awakening from asthma (over the past 4 weeks)

2. Participants who are currently taking Low Dose (Step 2 Controller Therapy) based on the table above, are eligible and do not have to meet any symptom criteria.

3. Participants who are currently taking Medium Dose (Step 3 Controller Therapy) based on the table above, must meet all of the following symptom criteria:

    - Visit 1 CACT Score must be > 19

- 2 or fewer asthma exacerbations requiring oral or systemic corticosteroids in the past 6 months
- Visit 1 pre-bronchodilator FEV_1 % predicted ≥ 80%

→ The participant is eligible if **all of the above are true**, but the Step 3 Controller Therapy must be stepped down to Step 2 Controller Therapy at enrollment. This is accomplished by starting the Run-In medications. There is no formal 'step-down' procedure prior to enrollment.

Visit 2

The Inclusion/Exclusion criteria are assessed at Visit 2 on the Eligibility Checklist 3 (P7_ELIG3) Form.

Q1000: If the participant had any exacerbations requiring systemic steroids while in the Run-In, he/she is not eligible. In addition, if the participant is going to be re-enrolled, it is necessary to wait 4 weeks before re-enrolling the participant.

Q1020: If the participant took any asthma medications other than the study medications during the Run-In, he/she is not eligible.

Q1030: The participant must have at least 75% compliance with the required sessions based on the spirotel® Participant Compliance Report (P7_COMPLY).

Q1040: The participant must have at least 75% compliance with the required doses from the green inhaler based on the spirotel® Participant Compliance Report (P7_COMPLY).

Note that if the participant does not meet the compliance criteria with the study medications and/or spirotel sessions, the procedures that are listed on the Visit 2 checklist prior to completion of the P7_ELIG3 form should not be performed (i.e. spirometry, methacholine challenge, etc.). The visit should be stopped after compliance is assessed.

If compliance is close to 75% (i.e. 65%-75%), then the Run-In can be extended for another 2 weeks. If compliance is <65% and the site feels that the compliance problems can be corrected, the participant can be re-enrolled.

Q1050: The participant's CACT score at Visit 2 must be ≥ 20 for the participant to be eligible.

Q1060: The participant's pre-bronchodilator FEV_1 at Visit 2 must be ≥ 80% predicted for the participant to be eligible.

Exclusionary Medical Conditions during STICS

Addison's disease
AIDS
Cardiac arrhythmias (clinically significant)
Cardiac disorder (except hemodynamically insignificant ASD, VSD or heart murmur)
Cataracts
Chest surgery (call for exception, if warranted)
Clotting disorders
Congenital anomalies of lung and chest, including growth abnormalities that affect predictability of expected lung function parameters
Congestive heart failure
Coronary artery disease (unstable or severe)
Cushing's disease
Diabetes mellitus (poorly controlled)
Dyspnea by any cause other than asthma
Eating disorder (e.g. anorexia or bulimia (active disease))
Eczema, severe (if likely to require oral/systemic corticosteroid treatment)
Factor deficiency
Failure to thrive
Gastroesophageal reflux (GERD) (if not controlled by standard medical therapy)
G6PD deficiency
Glaucoma
Hematologic disease (unstable, e.g. severe anemia)
Hepatic disease
Hypertension (poorly controlled)
Hyperthyroidism
Immunologic compromise
Inflammatory bowel disease (IBD, including Crohn's disease and ulcerative colitis) (if likely to require oral/systemic corticosteroid treatment)
Lactation
Lung disease other than asthma (COPD, emphysema, chronic bronchitis, pulmonary embolism, malignancy, cystic fibrosis, bronchiectasis, bronchopulmonary dysplasia, among others)
Lupus (active disease requiring immunosuppressant)
Any malignancy other than basal cell skin cancers
Mental illness (uncontrolled)
Mental retardation
Myasthenia gravis
Neurologic disease (including epilepsy requiring treatment and febrile seizure in infancy)
Osteogenesis imperfect
Peptic ulcer disease (active)

Phenylketonuria
Pregnancy
Premature birth (before 35 weeks gestation)
Renal disease (active disease requiring treatment with medications that affect study drugs)
Rheumatoid arthritis (if likely to require oral/systemic corticosteroid treatment)
Schizophrenia
Skeletal disorders, including osteoporosis
Sleep apnea (untreated)
Thyrotoxicosis
Tracheomalacia
Tuberculosis (active disease; history of positive skin test with negative chest x-ray allowed)
Urinary retention (active symptoms within last 6 months)
Vocal cord dysfunction (diagnosis of)

Allowed medications during STICS

acetaminophen
analgesics for acute/chronic pain management (with MD discretion)
antianxiety agents/anxiolytics (e.g., diazepam, chlordiazepoxide, alprazolam, lorazepam, gabapentin, buspirone) at a stable dose
antibiotics (e.g., tetracycline, penicillin, cephalosporin, quinolones, monobactam, sulfonamides, minocycline, nitroimidazoles (Flagyl), macrolides (for intermittent use to treat acute adverse events only))
antibiotics for acne (topical/oral) (macrolides allowed for intermittent use only)
anticholesterol medications (e.g., Lopid, statin medications)
specific antidepressants at a stable dose
Selective Serotonin Reuptake Inhibitors (SSRI) (e.g., alaproclate, etoperidone, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, zimelidine)
Selective Serotonin Norepinephrine Reuptake Inhibitors (SSNRI) (e.g., desvenlafaxine, duloxetine, venlafaxine)
Non-SSRI/SSNRI antidepressants (except MAOI class drugs) (e.g., amitriptyline, amoxapine, bupropion, mirtazapine, nefazodone, trazodone and others)
antifungal medications (topical preparations only) (e.g., clotrimazole, ketoconazole, miconazole, and others)
antihistamines (e.g., chlorpheniramine (Chlor-Trimeton), desloratadine (Clarinex), diphenhydramine (Benadryl), fexofenadine (Allegra, Allegra-D), loratadine (Claritin), and others)
specific antihypertensive medications
alpha blockers (e.g., doxazosin, prazosin, terazosin)
angiotensin converting enzyme (ACE) inhibitors (e.g., benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril, ramipril)
angiotensin receptor blockers (Sartans) (e.g., candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan)

calcium channel blockers (e.g., amlodipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine, verapamil)
diuretics (e.g., amiloride, bumetanide, chlorothiazide, chlorthalidone, furosemide, hydrochlorothiazide, indapamide, methyclothiazide, metolazone, spironolactone, triameterene)
mineralocorticoid receptor antagonists (e.g., eplerenone)
sympathetic nerve inhibitors (e.g., clonidine, guanabenz, guanfacine, methyldopa)
antitussives (over-the-counter) (e.g., dextromethorphan)
bisphosphonates (e.g. alendronate (Fosamax), ibandronate (Boniva), zoledronic acid (Zometa))
calcium-based antacids (e.g., TUMS®)
calcium supplements
CNS stimulants/appetite suppressants/ADHD medications (e.g. lisdexamfetamine, methylphenidate hydrochloride (Ritalin), amphetamine preps, dextroamphetamine/amphetamine (Adderall) sibutramine)
Cox-2 drugs (e.g., celecoxib (Celebrex), rofecoxib (Vioxx) and valdecoxib (Bextra))
decongestants (e.g., pseudoephedrine (Sudafed), oxymetazoline (Afrin), and others)
oral diabetes medications (for treatment of stable, controlled diabetes)
expectorants (over-the-counter) (e.g., guaifenesin)
eye preparations for allergic eye symptoms (topical) (e.g., antihistamines, NSAIDS, antiallergic compounds)
H_2 blockers (e.g., ranitidine, cimetidine, famotidine, nizatidine) for GERD
hemorrhoid treatments
herpes medications (e.g., acyclovir (Zovirax), valacyclovir (Valtrex))
insulin (for treatment of stable, controlled diabetes)
intranasal steroids (any drug)
laxatives
Librax
lipase inhibitors (e.g., Alli®, Xenical®)
lithium
migraine analgesics/preventatives (e.g., butalbital, Midrin, sumatriptan, topiramate)
nasal antiallergic spray (Cromolyn/Atrovent)
nasal saline spray
non-steroidal anti-inflammatory medications (e.g., ibuprofen, naproxen, ketoprofen)
pimecrolimus for atopic dermatitis – avoid daily use
proton pump inhibitors (e.g., omeprazole (Prilosec), lansoprazole (Prevacid), esomeprazole (Nexium)) for GERD
psyllium
sleep aids (prescription or over-the-counter) used PRN
stool softeners
study medications
tacrolimus for atopic dermatitis – avoid daily use
thyroid replacement medication (e.g., Levothroid, Levoxyl, Synthroid)
tretinoin (Retin-A) for acne
vitamins, minerals

Low potency topical corticosteroids (BID)

- aciometasone dipropionate
- desonide
- dexamethasone
- dexamethasone sodium phosphate
- fluocinolone acetonide
- hydrocortisone
- hydrocortisone acetate

Medium potency topical corticosteroids (BID)

- betamethasone benzoate
- betamethasone dipropionate
- betamethasone valerate
- clocortolone pivalate
- desoximetasone
- diflorasone .05%
- fluocinolone acetonide
- fluocinonide .05%
- flurandrenolide
- fluticasone propionate
- hydrocortisone butyrate
- hydrocortisone valerate
- mometasone furoate
- triamcinolone acetonide

Excluded Drugs for STICS

Excluded Drug	Generic Names (may not be inclusive)	Trade Names (may not be inclusive)	Washout Prior to Visit 1
Steroid Medications			
Oral or intravenous steroids for any reason, except prednisone as provided in study	prednisone, prednisolone, dexamethasone	Decadron, Medrol, Orapred, Prednisone, Prelone, Pediapred	2 weeks
Inhaled steroids, except as provided in study	beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone, triamcinolone acetonide	Aerobid, Alvesco, Asmanex, Azmacort, Flovent, Pulmicort, QVAR	None
Nonsteroidal Antiinflammatory Medications			
Leukotriene modifiers	montelukast, zafirlukast, zileuton	Accolate, Singulair, Zyflo	48 hours
Cromolyn/Nedocromil for asthma	cromolyn, nedocromil	Intal, Tilade	1 week

Daily NSAIDS			
Daily NSAIDS	acetaminophen, aspirin, ibuprofen, naproxen, ketoprophen	Tylenol, Advil, Motrin	48 hours
Bronchodilators			
Oral β-agonists	albuterol, metaproterenol, terbutaline	Alupent, Brethine, Bricanyl, Metaprel, Proventil, Repetabs, Ventolin, Volmax	1 week
Short-acting inhaled β-agonists	epinephrine	Bronkaid Mist, Duo-Medihaler, Medihaler-Epi, Primatene Mist	6 hours
Intermediate-acting inhaled β-agonists, except study RESCUE drug	albuterol, bitolterol, levalbuterol, metaproterenol, pirbuterol, terbutaline	Alupent, Brethaire, Brethine, Bronkometer, Maxair, Metaprel, Proventil, Tornalate, Ventolin, Xopenex	6 hours
Long-acting inhaled β-agonists, except as provided in study	formoterol, salmeterol	Advair, Dulera, Foradil, Serevent, Symbicort	24 hours
Short-acting inhaled anticholinergics	atropine, ipratropium bromide, pirenzepine, scopolamine	Atrohist, Atrovent, Bellatal, Combivent, Donnatal, Scopoderm, Transderm-Scop	8 hours
Long-acting inhaled anticholinergics	tiotropium	Spiriva	24 hours
Anticoagulant			
	Warfarin	Coumadin	2 weeks
Xanthine Derivatives			
Short-acting theophylline	theophylline	Aminophylline, Slo-Phyllin	12 hours
Long-acting theophylline	theophylline	Slo-bid, Theo-Dur	24 hours
Ultra long-acting theophylline	theophylline	Theo-24, Uniphyl	48 hours
Anti-IgE Therapy			
	omalizumab	Xolair	3 months
Drugs that Alter Steroid Metabolism			

Anticonvulsants	carbamazepine, phenobarbital, phenytoin	Carbatrol, Di-Phen, Dilantin, Epitol, Equetro, Luminal, Phenytek. Solfoton, Tegretol	2 weeks
Oral antifungal medications	clotrimazole, fluconazole, ketoconazole, miconazole, and others	Diflucan, Extina, Kuric, Nizoral, Xolegel, and others	2 weeks
Bactericidal Antibiotic	rifampin	Rifadin, Rifamate	2 weeks
Cardiac Drugs			
Alpha-beta blockers	labetalol	Normodyne	2 weeks
Beta blockers	acebutolol, atenolol, betaxolol, bisoprolol, carteolol, metoprolol, nadolol, penbutolol, pindolol, propranolol, timolol	Blocadren, Cartrol, Corgard, Inderal, Kerlone, Levatol, Lopressor, Sectral, Tenormin, Visken, Zebeta	48 hours
Psych or CNS-Related Drugs			
Monoamine oxidase (MAO) inhibitors	harmaline, iproclozide, iproniazid, isocarboxazid, nialamide, phenelzine, selegiline, toloxatone, tranylcypromine	Nardil, Parnate	4 weeks

Drugs/substances to be withheld prior to Visits *

Drug/Substance	Trade Names (may not be inclusive)	Washout Prior to Visits
Albuterol (study RESCUE inhaler)	Ventolin	6 hours
Methylxanthine-containing food or beverages (caffeinated colas, coffee, tea)	Coke, Barq's Rootbeer, Mello-Yellow, Mountain Dew, Pepsi, Red Bull	4 hours
Methylxanthine-containing medications	Anacin, Darvon, Esgic, Excedrin, No-Doz, Norgesic, Vivarin	4 hours

Drug/Substance	Trade Names (may not be inclusive)	Washout Prior to Visits
Alcohol-containing foods or beverages		4 hours

*These drugs/substances are allowed between visits, but not prior to pulmonary function testing.

2.11 EXHALED NITRIC OXIDE

Visits 2-8

Perform FeNO testing (ENO)

Levels of forced exhaled nitric oxide (FeNO) are known to be elevated in people with asthma. In addition, FeNO may be involved in airway inflammation. FeNO is an important secondary outcome variable in the STICS study.

Results are documented on the Exhaled Nitric Oxide (ENO) form. The FeNO collection procedures should precede any pulmonary function testing procedures at a given visit. Clinical personnel should follow the order of procedures outlined on the visit procedure checklists. Any deviation from this order of procedures will result in the assignment of a protocol violation.

The NIOX MINO will be used to measure FeNO. Any individual who participates in eNO collection must possess AsthmaNet eNO certification or be directly supervised by a certified coordinator. A biological control test must be performed on NIOX MINO every day before it is used with participants. This must be performed by a QC tester who has qualified for this procedure. See Appendix 8 of the AsthmaNet General Manual of Operations for details regarding certification and QC procedures.

Prior to proceeding with exhaled nitric oxide testing, participants must pass the eligibility checks on the STICS Pulmonary Procedure Checklist (P7_PULMONARYCHK). If any of the required washouts are not met, the participant should not proceed with collection of FeNO or pulmonary function testing at the visit. The FeNO levels may be affected by eating, drinking and strenuous activity/exercise, so participants should be encouraged to refrain from these activities for 1 hour prior to their visit. Testing will still be performed at the visit if a participant has eaten, drank, or taken part in strenuous activity/exercise in the past hour, but this will be documented on the ENO form. Mobile phones and cordless phones may interfere with the MINO, so they should be kept away from the MINO device.

The FeNO collection process may be attempted up to eight times in an effort to achieve an acceptable measurement. These eight attempts include all blows, even those when the NIOX MINO did not calculate and display a measurement because it did not find the maneuver technically acceptable.

The technician doing the collection should record the FeNO reading on the ENO form. If after eight attempts, no acceptable measurement was attained, the technician should record the time when the maneuver started and write “No acceptable maneuver” in Q6000.

Detailed instructions on using the NIOX MINO to collect exhaled nitric oxide measurements are documented in the Exhaled Nitric Oxide Manual of Operations located in Appendix 8 of the AsthmaNet General Manual of Operations.

2.12 FORGOTTEN STUDY MATERIALS

The table below details what to do regarding forgotten study materials at an STICS study visit. (Note that any forgotten item should be brought to the clinic at the next opportunity.)

Visit		2 (Randomization)	3, 4, 5, 6, 7	8 (Last Visit)
Forgotten Item	spirotel®	Visit must be rescheduled.	Visit must be rescheduled.	Visit must be rescheduled.
	Run-In MEDS	Visit must be rescheduled.	NA	NA
	STICS MEDS (yellow or green inhalers)	NA	Bring to next visit	Visit must be rescheduled.
	Albuterol/ Prednisone	Bring to next visit	Bring to next visit	Visit must be rescheduled.
	Nasal Samples	NA	Bring to next visit	Visit must be rescheduled.

2.13 GENETIC ANALYSIS PROCEDURES (See also AsthmaNet Genetics Manual)

Visit 2

Obtain blood sample for DNA extraction and genetic analysis (optional)
Complete Genetic Analysis Blood Draw (GABLOOD) form
Enter genetics sample information into Genetics Tracking module

Before drawing blood for genetic analysis, verify that the participant has given consent to participate in the genetic analysis component of the STICS study. The genetic analysis blood draw is optional; as stated in the consent, parents/guardians can refuse this blood draw and the participant can still participate in the STICS study. The genetic analysis participation rate for each clinical center partnership and performance site will be summarized on the STICS Accrual Report.

AsthmaNet genetics procedures are described in appendix 4 of the AsthmaNet General Manual of Operations. The standard blood sample for genetic analysis purposes is 10 ml (age 5-11 years). Make certain that all tubes are as full as possible to ensure sufficient DNA for future genetic analyses. If a participant cannot provide the full amount of blood, collect as much blood as possible and submit it to the Arizona Genetics Lab in Tucson for DNA extraction and storage.

Blood tubes collected for genetic analysis should be scanned into the AsthmaNet Genetics Tracking module immediately after they are drawn. The scan date is saved in the database and must be interpretable as the blood draw date. This information is forwarded to the Arizona Genetics Lab electronically and is needed for their tracking database and possible future sample submissions to the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC). Discrepancies between the scan date in the database and the blood draw date written on the blood tubes will be noted by the lab and reported to the DCC.

Complete the Genetic Analysis Blood Draw (GABLOOD) form for <u>all</u> participants, regardless of whether or not they consent to provide a genetics blood sample. For those who elect to provide a blood sample, this form records information about their level of consent for future genetic analyses, as well as the total volume of blood drawn. See section 10 and appendix 4 of the AsthmaNet General Manual of Operations for specific information on completing the GABLOOD form. Note that the parent/guardian must review the form and complete the source documentation information (initials and date), even if he/she did not provide a blood sample.

Note: If you have difficulty drawing blood on the participant, the blood draw may occur at a later visit. The GABLOOD form should be completed and data entered as a single form for the visit at which the blood draw takes place (e.g., Visit 3). If the blood draw is attempted at Visit 2 but is unsuccessful, and the participant is unwilling to have another

draw attempted at a future visit, then the GABLOOD form should be completed and data entered as part of the Visit 2 packet. In that case, Q1000 and Q1010 should be completed, indicating that a blood sample was not obtained, and the participant should provide source documentation. All individuals who make it past Visit 2 in the study must have a GABLOOD form present in the database.

2.14 GEOGRAPHIC INFORMATION SYSTEMS (GIS) ADD-ON STUDY

Dr. Fernando Holguin, an investigator from the University of Pittsburgh AsthmaNet site, is the Principal Investigator on an R01 grant that is studying the application of geographic information systems (GIS) methodology in clinical trials. He plans to analyze the effect that local neighborhood and environmental factors have on asthma and the response to asthma drugs used in clinical trials. He has received approval from the Protocol Review Committee and the Data and Safety Monitoring Board to add the GIS study to the BARD, SIENA and STICS protocols.

It is well known that environmental factors, like traffic emissions, outdoor air pollution and neighborhood characteristics are related to asthma. The add-on study will help determine whether participants living in more polluted environments are less responsive to treatment or, alternatively, whether a particular treatment protects from the effects of traffic or air pollution. The GIS analysis will link the location of each STICS participant's home to information about the local environment.

To carry out this project, Dr. Holguin must have access to a given participant's home address in order to map its geographic coordinates and link to databases that contain environmental, crime, and other statistics. A separate GIS consent has been developed to explain the project to each randomized participant (and his/her guardian, if applicable) and to ask for his/her consent for performance site personnel to download his/her address information to a secure site at the University of Pittsburgh where geographic coordinates will be determined and saved. Participation in the add-on study is optional. No participant stipend will be paid.

The full GIS add-on study protocol and Manual of Procedures will be posted on the secure website in the AsthmaNet: Protocols: GIS Add-On Study folder.

Visit 2 (for randomized participants only)

Administer GIS consent; document assent as appropriate.

After the participant is randomized at Visit 2, introduce the GIS add-on study. Explain that participation is optional and what it entails. Follow the GIS Add-On Study MOP for storage of consent documentation and general procedures related to this study. There are no data forms to complete for the STICS database related to this project.

2.15 GROWTH CHARTS

Height

Visits 1-8

Plot Height on Growth Chart

Note: An alternative to plotting is a website that can be used for calculating height percentiles. The current date, the participant's date of birth, gender and height will need to be entered. If you choose to use this calculator, please print a copy of the screen and file it in the participant's folder. The program can be found at:

http://spitfire.emmes.com/study/ped/resources/htwtcalc.htm

At Visit 1, plot the participant's height on the age-specific and gender-specific growth charts provided. The Growth Charts are located on the secure AsthmaNet website. If the participant's height is < 2nd percentile, he/she is ineligible.

See Physical Exam in the AsthmaNet General MOP for more information on measuring height.

The participant's height should be plotted at all visits to identify potential growth failures. See Growth Failure Protocol in this section for more information on growth failure.

Weight

Visits 1-8

Plot Weight on Growth Chart

Note: An alternative to plotting is a website that can be used for calculating weight percentiles. The current date, the participant's date of birth, gender and height will need to be entered. If you choose to use this calculator, please print a copy of the screen and file it in the participant's folder. The program can be found at:

http://spitfire.emmes.com/study/ped/resources/htwtcalc.htm

For Visit 1, plot the participant's weight on the age-specific and gender-specific growth charts provided. The Growth Charts are located on the secure AsthmaNet website. If the participant's weight is < 2nd percentile, he/she is ineligible.

See Physical Exam in the AsthmaNet General MOP for more information on measuring weight.

The participant's weight should be plotted at all visits to identify potential growth failures. See Growth Failure Protocol in this section for more information on growth failure.

2.16 GROWTH FAILURE PROTOCOL

Visit 1

Height and Weight

If the participant's height or weight plots less than the 2nd percentile for age and gender, the participant is ineligible.

Visits 2-8

Plot height/weight at each clinic visit throughout the 12 month study on a sensitive growth chart (HEIGHT_BOY, LENGTH_BOY or HEIGHT_GIRL, LENGTH_GIRL). The Growth Charts are located on the secure AsthmaNet website.

At Visits 2-8, the participant's height and weight should be monitored for growth failure. Possible Growth Failure evaluation should occur if any of the following are true:

1. If the participant's height/weight has crossed (downward) two major percentiles on the growth chart at any point during the study. Major percentile lines are: 5, 10, 25, 50, 75, 90 and 95.
2. If the participant's height/weight (previously above the third percentile) falls below the third percentile at any point during the study.
3. If the participant's growth has been less than 1 cm during a four month period (height only).

If you are using the website calculator rather than plotting the values on growth charts, you will need to compare the values from the previous visit for the 3 checks listed above.

The following procedure will be followed when potential growth failures are identified:

- Email notification should be sent to the head site PI and the DCC with the potential growth failure information. The email will also be forwarded to the lead PIs for the STICS study.
- The email will contain all information related to the participant's growth while in the STICS trial. The growth failure qualifier that has been met will also be noted.
- The DCC will request a response from the lead PI and CC within one week of the email notification. The response should indicate whether the event was deemed the result of measurement error or an actual growth failure and the rationale for reaching that conclusion. If measurement error is thought to be the cause, either the current or previous measurement should have been flagged as questionable. If an actual

growth failure is identified, the response should also include an action plan for the participant. The response should be sent to the DCC and the lead PIs for the STICS study.

If a participant is identified as a possible growth failure, a referral should be made to a pediatric endocrinologist for a growth evaluation. If the pediatric endocrinologist's assessment is that growth is impaired, a serious adverse event will be generated. The Serious Adverse Event Form (SERIOUS) must be completed and will be forwarded to the DSMB. The local PI in conjunction with the lead STICS PIs will decide if the participant will continue in STICS or be termed from the study.

2.17 HOME ENVIRONMENT QUESTIONNAIRE

Visit 1

Administer Home Environment Questionnaire (HEQ)

The Home Environment Questionnaire (HEQ) was developed by AsthmaNet. This questionnaire collects information about characteristics of the participant's home in general, his/her bedroom, his/her pets, and exposure to others' pets. Information regarding exposure to potential allergens that might affect the participant's asthma is collected in detail.

This questionnaire is completed by Parent/Guardian interview. The coordinator should provide assistance for any questions when requested. Question 27 should be answered 'yes' if the participant is attending pre-school.

When the parent/guardian returns the questionnaire, the coordinator should review it thoroughly to be sure all questions have been answered to the best of the parent/guardian's ability. If he/she would rather not answer certain questions, they may be left blank. The parent/guardian should initial and date the source documentation box on the last page of the form when he/she is finished.

2.18 HOSPITALIZATIONS

Participants who are hospitalized for an acute asthma exacerbation for >24 hours during STICS are assigned treatment failure status. A hospitalization lasting ≤ 24 hours is not a treatment failure, and the participant can continue in the study. Similarly, hospitalizations for reasons other than asthma are not treatment failures, and the participant can continue in the study. See the *Treatment Failure* discussion in this section for more details.

Hospitalization for any reason is a Serious Adverse Event and must be documented as such. See the *Adverse Events* discussion in this section of the STICS MOP and Section 4 of the General MOP for more information.

2.19 HOUSEHOLD SOCIO-ECONOMIC INFORMATION FORM

Visit 1

Administer Household Socio-Economic Information form (HOUSEHOLD_SEI)

Socio-economic status (SES) and health outcomes tend to be positively correlated (i.e., the higher the SES, the better the health outcome in terms of morbidity and mortality). Dr. Sheldon Cohen, affiliated with the Pittsburgh clinical center partnership, is an expert in this field and provided assistance for AsthmaNet to develop a very brief Household Socio-Economic Information (HOUSEHOLD_SEI) form. This form collects the highest level of education attained by members in a participant's household, the combined gross annual income of all members of the household, and the number of individuals supported by the income.

This form is completed by the parent/guardian. He/she can decline to answer any question he/she wishes.

2.20 IMMUNOCAP TESTING

Visit 2

An ImmunoCAP (Phadia) allergen-specific IgE will be assessed for the following allergens:

#	Allergen class	ImmunoCAP code	Allergen content
1	Cat	e1	Cat dander
2	Dog	E5	Dog dander
3	Mouse	E72	Mouse urine proteins
4	Mold mix	Mx1	Penicillium chrysogenum, Cladosporium herbarum, Aspergillus fumigates, Alternaria anternata
5	Cockroach (German)	i6	Blatella germanica
6	Grass mix	gx2	Bermuda, rye, Timothy, Kentucky bluegrass, Johnson, Bahia
7	Tree mix	Tx4	Oak, elm, maple, willow, cottonwood
8	Tree mix	Tx6	Box-elder, birch, beech, oak, walnut
9	Weed mix	Wx1	Common ragweed, mugwort, plantain, lamb's quarter, Russian thistle
10	Weed mix	W3	Giant ragweed
11	Mite	D2	D. farina
12	Mite	D1	D. pteronyssinus
13	Cow's milk	F2	Cow's milk
14	Egg white	F1	Egg white
15	Peanut	F13	Peanut
16	Rat	E74	Rat urine protein

Blood should be drawn and shipped to the Denver lab. See 'Blood Sampling Procedures' for more details.

The DCC will generate and send to all sites monthly reports with participant-specific information.

2.21 IMPULSE OSCILLOMETRY (IOS) – ONLY SUBSET OF SITES

Participating Sites

112 – Boston Children's Hospital
126 – University of Illinois at Chicago
132 – National Jewish
133 – University of New Mexico
141 – University of Wisconsin
162 – Washington University
181 – University of Arizona
194 – Emory University

General Instructions

The participant's current age should be entered into the Jaeger software for each session. If a participant has a birthday during the study, his/her updated age should be used at all subsequent visits.

Since the participant's height will change throughout the study, be sure to update the participant's height at each visit. The participant's height should be measured and recorded on the Physical Exam (PHY_EXAM) form at all visits.

Visits 2-8
Perform pre-bronchodilator IOS testing (IOS_PRE)

Results are documented on the Pre-bronchodilator IOS (IOS_PRE) form. The IOS collection procedure should follow ENO, but should precede spirometry at a given visit. Clinical personnel should follow the order of procedures outlined on the visit procedure checklists. Any deviation from this order of procedures will result in the assignment of a protocol violation.

The Jaeger systems from the CARE Network will be used to measure IOS. Since there are a limited number of machines remaining, only selected sites will be performing IOS as part of the visit procedures. Any individual who participates in IOS collection must be certified in the IOS procedure. See Appendix 9 of the AsthmaNet General Manual of Operations for details regarding certification and QC procedures.

Prior to proceeding with IOS testing, participants must pass the eligibility checks on the STICS Pulmonary Procedure Checklist (P7_PULMONARYCHK). If any of the required washouts are not met, the participant should not proceed with collection of FeNO, IOS or pulmonary function testing at the visit.

Detailed instructions on performing the IOS procedure are documented in the Impulse Oscillomery Manual of Operations located in Appendix 9 of the AsthmaNet General Manual of Operations.

2.22 INFORMED CONSENT

Visit 1
Acquire signed STICS informed consent

Informed consent **must** be obtained before any study information is collected or any study procedures are performed.

The informed consent document explains the procedures and time commitment necessary to participate in the STICS trial, should the potential participant be deemed eligible. Prior to implementation of Visit 1, a summary of the studies and their complementary nature should be presented to the parent/guardian. He or she should be given an opportunity to read and sign the consent documents.

Guidelines for obtaining consent:

- At the beginning of Visit 1, provide the parent/guardian copies of the informed consent forms for the studies and ask him or her to read them thoroughly. The parent/guardian should not sign the forms until after you have discussed their contents with him or her.

- Allow ample time for the parent/guardian to read the informed consent forms thoroughly.

- If the parent/guardian is unable to read the informed consent forms or seems to be struggling, offer to read them to him or her or to help him or her with the more difficult sections.

- Be prepared to answer any questions the parent/guardian may have. If the person does not appear to understand the studies or what participation entails, or if he or she has any other doubts about enrolling, do not ask him or her to sign the informed consent forms.

- Maintain the signed informed consent forms in the participant's study folder. To ensure confidentiality, **do not send these forms to the DCC**. These documents will be reviewed during data quality site visits.

If the participant fails to qualify at Visit 1 for a reason that can be remedied (e.g., insufficient drug washout period, etc.), he or she may be re-enrolled at a later date. During the new Visit 1, the parent/guardian should be given clean copies of the consent documents to review and sign. See the Reenrollment discussion in this section for further details.

If modifications are made to the STICS consent document and approved by the local IRB while a participant is in the study, the parent/guardian must be re-consented following local IRB rules. All versions of the STICS consent documents the parent/guardian signed must be retained in the participant's study folder and are subject to audit.

The date the parent/guardian signed the study consents is recorded and tracked on Eligibility Checklist 1 (P7_ELIG1). Genetic analysis participation is tracked on the Genetic Analysis Blood Draw (GABLOOD) form which is completed at the blood draw visit.

Visit 1

Administer Genetics Consent – part of STICS Consent (if applicable)
Administer BioLINCC Consent Document
Complete BioLINCC Consent Tracking Form (BIOLINCC)

As a network funded by the National Institutes of Health, National Heart, Lung, and Blood Institute (NIH/NHLBI), AsthmaNet is expected to participate in the NHLBI's biobank which is coordinated by the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC). A biobank is a centralized collection of biological samples and health information that can be used by researchers outside of AsthmaNet for future studies in the areas of asthma and other diseases. At some time in the future, with the acceptance of BioLINCC, leftover samples from the STICS study (i.e. DNA and plasma) will be transferred to BioLINCC and made available to other researchers. A parent/guardian must be asked to give his/her consent to transfer samples to BioLINCC. Samples for participants who refuse to provide consent will be retained by AsthmaNet. Participation is voluntary. See the AsthmaNet Genetics Procedures and BioLINCC manual in appendix 4 of the AsthmaNet General Manual of Operations for further details regarding BioLINCC.

At Visit 1, after a parent/guardian provides consent for the participant to be in the STICS trial, he/she must be given the IRB-approved STICS BioLINCC consent document to review. If he/she agrees to allow the leftover samples to be transferred to BioLINCC, he/she should sign the document and indicate the level of consent he/she is providing. Two levels of consent are possible: 1) allowing consent for all types of analyses, including genetic analyses, on the transferred samples and 2) allowing analyses with the exception of genetic analyses by researchers outside of AsthmaNet. The parent/guardian should indicate his/her preference in the consent document, prior to signing it. If the parent/guardian consents to participate in BioLINCC, then his/her consent document must be retained with the STICS study consent document in the participant's study folder at the performance site. This consent document is also subject to audit during an AsthmaNet data quality site visit.

Every participant must have a BioLINCC Consent Tracking Form (BIOLINCC) completed at Visit 1. This form tracks whether or not the parent/guardian agreed to donate the leftover samples to BioLINCC and, if so, what level of consent he/she provided. Information submitted to the DCC on the BIOLINCC form must match the participant's consent document. The BIOLINCC form data will be used to determine which samples are transferred to BioLINCC in the future.

2.23 MICROBIOME MECHANISTIC STUDY

The MicroBIOME Mechanistic Study does not involve any additional procedures to the STICS study. The nasal samples from Visit 2 and the first Yellow Zone will be divided at the Madison lab and half of the sample will be sent on to the St. Louis Lab.

At Visit 1, an additional questionnaire will be completed by the parents/guardians to assess environmental factors that might affect the microbiome (P7_MEQ). At Visit 2, an additional questionnaire will be completed by the parents/guardians to capture antiobiotic use during the previous 12 months and current nasal steroid use (P7_BIOME_HX).

Also, throughout the study, the parents/guardians will be asked to report any antibiotic use and nasal steroid use. Use of either of those medications should be recorded on the Concomitant Medication Form (CMED).

2.24 MDI INHALATION TECHNIQUE ASSESSMENT

Visit 1

Instruct Use of Albuterol (Rescue) Inhaler (TECH_MDI_SP, HTMDI)

It is important that the participant demonstrate that he/she can accurately use a metered-dose inhaler (MDI). In order to assure that each participant has met the AsthmaNet standards for MDI use, an MDI Inhalation Technique Checklist (TECH_MDI) has been implemented.

Visits 2-7

Instruct Use of Albuterol (Rescue) Inhaler (TECH_MDI_SP)

The technique assessment should be reviewed at all visits for participants who are using an MDI for rescue medications.

Results of the technique assessment are recorded on the TECH_MDI_SP checklist. See Section 4 in this manual for details regarding the completion of the TECH_MDI_SP checklist. Checklists should be stored in the participant's study folder; do not submit these forms to the DCC. If you do not to complete the TECH_MDI_SP form, then there should be a note in the clinic progress notes that the technique assessment was reviewed with the participant.

2.25 MEDICAL HISTORY

Visit 1

Complete Pediatric Asthma and Allergy History form (ASTHMA_HX_PED)
Complete Prior Conditions for All Participants form (PRIOR_COND_ALL)
Complete Prior Asthma/Allergy Treatment form (PRIOR_TRT)

A comprehensive medical history is taken at Visit 1. The medical history is broken into three parts: 1) The Pediatric Asthma and Allergy History form (ASTHMA_HX_PED) collects information regarding the onset of disease and family history, recent asthma symptoms and acute episodes of asthma, asthma triggers, allergies, and smoking history. 2) The Prior Conditions for All Participants form (PRIOR_COND_ALL) collects detailed information on prior diseases, illnesses and surgeries the participant has had. 3) The Prior Asthma/Allergy Treatment form (PRIOR_TRT) collects detailed information on prior asthma/allergy medications.

The medical history is administered early in the visit so that eligibility criteria that are easy to confirm can be checked quickly. The three portions of the medical history are obtained by parent/guardian interview. Read each question to the parent/guardian in a consistent, even tone, exactly as written on the forms. Provide clarification when asked.

When available, information contained in medical records should be considered more accurate than parent/guardian reporting. If the Study Coordinator chooses to report interview information rather than information from the participant's medical record (when it is available), the affected item(s) should be dated and initialed to document this override. A notation indicating the override should also appear in the clinic notes. This documentation will be necessary when the data are audited during a site visit.

The parent/guardian should verify that information he or she reported about the participant's medical history has been recorded correctly on all forms.

When answering questions on the PRIOR Asthma/Allergy Treatment form, responses should reflect the participant's asthma treatment *prior to participating in the study*. If the participant's asthma therapy was changed just prior to Visit 1 due to study eligibility criteria (e.g., holds on long-acting beta-agonists (LABA)), responses on the form should convey the participant's medications before the change was made. For example, if a participant is switched from Advair (combination therapy with inhaled corticosteroid and LABA) to study QVAR two (or more) days prior to Visit 1 in order to meet the 48-hour washout required for the LABA, then responses should relate to the participant's use of Advair.

2.26 METHACHOLINE CHALLENGE

General Instructions

Individuals performing methacholine challenges must be AsthmaNet-certified in this procedure or, at minimum, supervised by AsthmaNet-certified personnel.

To maximize supplies, old (unexpired) stock of methacholine should be used before newer lots.

Participants must pass all of the checks on the STICS Pulmonary Procedure Checklist (P7_PULMONARYCHK) to proceed with spirometry and methacholine challenge at the visit. They must also pass all of the checks on the Methacholine Challenge Testing Checklist (METHACHK_PED).

Note that METHACHK_PED Q1050 excludes a participant from performing the challenge only if he/she used systemic corticosteroids for 4 or more days for treatment of an asthma exacerbation; if systemic steroid was used for a different indication, the question should be answered 'No.'

Note that METHACHK_PED Q1040 excludes a participant from the performing the challenge if he/she has had a respiratory infection, cold or bronchitis in the last 2 weeks. Since the methacholine challenge is not required for eligibility, if the participant has had a respiratory infection, cold or bronchitis in the last 2 weeks, the procedure should be skipped. The visit does not need to be rescheduled.

General procedures for carrying out a methacholine challenge can be found in the Methacholine Manual of Operations in Appendix 2 of the AsthmaNet General Manual of Operations.

Visit 2

Complete Pediatric Methacholine Testing Checklist (METHACHK_PED)
Perform Methacholine Challenge Testing (METHA)
Complete Additional Treatment Post Methacholine Challenge (METHA_ADD_TRT) form, if needed

Participants must pass all of the checks on the STICS Pulmonary Procedure Checklist (P7_PULMONARYCHK) and the Methacholine Challenge Testing Checklist (METHACHK_PED) before proceeding with the challenge. Results of the challenge are recorded on the Methacholine Challenge Testing (METHA) form. The methacholine challenge report generated through the MedGraphics system must be printed and submitted with the data forms.

Post-Methacholine Challenge Procedures

After a methacholine challenge has been completed, the participant should be reversed back to at least 90% of baseline (pre-challenge) lung function with albuterol. Baseline lung function (FEV_1) is obtained from Q1030 on the participant's Spirometry Testing (SPIRO) form completed at the visit.

Standard reversal is two puffs of albuterol. Results of standard reversal are recorded on the Methacholine Challenge Testing (METHA) form.

If a participant requires additional treatment to achieve reversal, this information should be recorded on the Additional Treatment Post Methacholine Challenge Testing (METHA_ADD_TRT) form. This form is entered as a single form.

See Section 10 of the AsthmaNet General Manual of Operations for details on the completion of these forms.

2.27 MISSED VISITS/PHONE CONTACTS

A missed visit is defined as one for which the participant is unavailable to undergo any clinic procedures for purposes of obtaining data for analysis. A missed phone contact is defined as one for which the participant is unreachable for a phone contact to collect data and follow-up on how the participant is doing.

Ideally all visits for a participant should occur at the same time of day (+/- 2 hours). When this is not possible, it is desirable for all visits to fall within a 3-hour window. Do not skip a visit if it is not possible to maintain these goals. Consistency in spacing of visits is more important for the collection of outcome data.

If a participant cannot come to the clinic at all within the visit windows and no suitable alternate arrangements can be made, the visit will be considered missed. Arrangements should be made to send any study materials that are needed (drugs, nasal collection samples, etc.) to the participant by some other means. If at all possible the participant's spirotel® device should be returned to the performance site for uploading and quality control.

If a participant can come in for a visit but the visit will occur outside the visit window, please contact the DCC for a visit window exception.

Visits 1 and 2

These visits are mandatory; they cannot be missed due to the procedures that take place at the visits which could compromise the study if not carried out completely. Contact the STICS Scientific Coordinator at the DCC if scheduling issues arise for these visits.

Visit 3-8

These visits occur post-randomization. While it is not ideal for these visits to be missed since drugs may need to be dispensed, these visits may be skipped if absolutely necessary. Contact the STICS Scientific Coordinator at the DCC to discuss possible options to prevent missed data for these visits.

If one of these visits must be missed, the participant should be asked to return his/her spirotel® device to the performance site for upload and quality control around the time of the ideal visit date for the applicable visit, if at all possible.

2.28 NASAL SAMPLING PROCEDURES

Visit 2 AND Day 1 of each Yellow Zone

Nasal blows will be taken by the coordinator during Visit 2 AND Day 1 of each yellow zone (by parent/guardian at home). Please note: a nasal blow can be obtained up to a maximum of 3 days after the onset. Ideally the samples should be collected on Day 1. However, if the parent/guardian forgets on that day, the samples can still be collected within a few days of the ideal date (up to 3 days as stated above). Nasal blows should be collected for all yellow zones.

If the sample is collected > 3 days after starting the Yellow Zone, it should still be processed. Please add a comment in Biological Sample Tracking when scanning the samples noting that the given sample was obtained more than 3 days after starting the Yellow Zone.

Parents/guardians should be given 2 nasal kits to take home. Additional kits can be distributed at visits or mailed to the parents/guardians, as needed throughout the study. Sites should inquire at all visits and phone contacts if any nasal samples have been collected and mail additional kits as needed. Two nasal mucus sample kits should be maintained at the participant's home during the study.

The 'Daily Activities' Guide on the back of the STICS Action Plan will serve as a reminder to collect nasal blows on Day1 of each Yellow Zone. For the in-clinic samples that are obtained at Visit 2, the P7_LAB form is part of the visit packet and includes questions regarding whether the nasal blow was collected.

The nasal sample can be **only** obtained by nasal blow technique for the STICS study. This is different from the APRIL and INFANT studies, where the parents/guardians had the choice of a blow or a swab. Written instruction should be provided to parents/guardians at Visit 2 and reviewed at visits thereafter.

Coordinators will teach and demonstrate the procedure at the study visits. Coordinators need to apply AsthmaNet collection labels to the transport solution baggie prior to dispensing; assuring the appropriate ID is applied. Parents/guardians should be instructed to write the date collected on the baggie.

There are 2 labels that should be placed on the nasal blow kit prior to dispensing to the participant. The first label contains the nasal blow number, participant ID and date collected. The coordinator should complete the nasal blow number and participant ID. The parent should be instructed to complete the date collected when the sample is obtained. The second label contains instructions for the parent. The label templates are located on the AsthmaNet website – Forms: STICS: Admin Forms.

As part of the Biome mechanistic study, additional analyses will take place on the Visit 2 nasal sample and the nasal sample obtained during the **first** Yellow Zone. Therefore, it is extremely important that the **first** Yellow Zone sample be correctly identified. Please be sure to remind parents that it is important to complete the 'Date Collected' on the nasal sample label. If a nasal sample is not obtained for the first Yellow Zone, the second Yellow Zone sample will be processed as part of the Biome mechanistic study. Please add a comment in Biological Sample Tracking noting that the first sample was missed and the second sample should be processed for the Biome mechanistic study.

Contents of Nasal Blow Kit:

- Saline Spray Bottle
- Ziplock Baggie
- Transport Solution
- Biohazard bag (orange)
- Koldtogo Bag
- Ice Pack

Ordering additional Nasal Blow Kits:

To order additional nasal blow kits, please send an email to pediatricasthma@medicine.wisc.edu.

Receiving Nasal Samples from home:

Parents/guardians should be instructed to bring the frozen nasal samples into the site at the next visit. Samples must remain frozen. Therefore, the samples should be transported in the "Koldtogo" freezer bag with the ice pack provided. If the samples are thawed, include a note with the samples when shipping to the lab.

Specimen Tracking – Collection Day

Site coordinator will label each V2 and yellow zone sample with a barcode label generated through the AsthmaNet Biological Sample Tracking (BST) module.

Label specifications: Avery 5160 labels

V2 Collection	Yellow Zone Collection
Part.ID: 7 - _ _ _ - _ _ _ Date Collected:_ _/_ _/_ _ Visit: 2 P7V2NB0244	Part.ID: 7 - _ _ _ - _ _ _ Date Collected:_ _/_ _/_ _ Visit: _ _ P7YNB00277

Each sample is scanned into the BST module and stored in a -80 freezer until shipping.

For the Yellow Zone samples, please record the visit number of the return visit. That is, if the sample is collected between Visits 3 and 4, a visit number of 4 should be recorded on the sample. If the parent forgets to bring the sample to the next visit (i.e. Visit 4), but brings it to the following visit (i.e. Visit 5), please record the visit number when the sample should have been brought to the clinic (i.e. Visit 4).

Specimen Tracking – Shipping Day

Each site will be assigned a designated shipment day at the beginning of each month.

Monday: Boston, Chicago, Denver
Tuesday: Madison, Pittsburgh, St. Louis
Wednesday: San Francisco, Tucson*/Durham, Winston-Salem/Charlottesville

On the first designated shipment day of the month, the site coordinator will scan each sample to build a shipment list for each sample type (V2 samples and yellow zone samples). When the shipments are created in the BST module an export file will be emailed to the University of WI – Madison Lab and the DCC.

Example of a yellow zone shipment export file

A	B	C	D	E	F	G
Sample Barcode	Participant ID	Initials	Visit ID	Collection Date	Sample Type	Ship To Lab
P7YNB00272	7-162-001	JDF	3	5/1/2014	STICS_NB_YELLOW_DAY1	992
P7YNB00274	7-162-002	JGD	3	5/5/2014	STICS_NB_YELLOW_DAY1	992
P7YNB00275	7-162-003	PLE	3	5/10/2014	STICS_NB_YELLOW_DAY1	992
P7YNB00276	7-162-004	ACC	3	5/15/2014	STICS_NB_YELLOW_DAY1	992
P7YNB00277	7-162-005	COW	3	5/22/2014	STICS_NB_YELLOW_DAY1	992

The samples will be shipped on dry ice per AsthmaNet shipment MOP.

Packaging Instructions

Note: The instructions below meet the minimum federal standards. Each site's institution may have additional guidelines. Sites should follow their institutional guidelines as long as they are in compliance with these minimum federal standards.

1. Place samples and absorbent material (see below for absorbent material information) into the recommended plastic transport bags and seal.

    a. VWR Scientific Co
    1-800-932-5000

These are 9 x12 liquid tight clear plastic bags, suitable for most shipments (this size will hold approximately 10-15 bags). Other sizes are available also.

-Infecon Transport Bags 11217-194 250/case $204.59

-or-

-Bitran Specimen Bags 11217-126 250/case $224.69

b. Samples should be packed in the bags so that they lie flat and will have as much contact with the dry ice as possible

2. Include the absorbent material (absorbs up to 250ml) in the plastic transport bag.

   a. Fisher Scientific Co.
      1-800-926-1166
      sheets 19-075-383C 100/case $20.36

   b. If shipping more than 25 samples use additional sheet. If shipping fewer than 12 samples half sheets may be used.

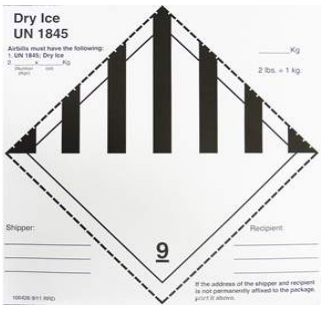
3. Use bubble wrap or cardboard to keep the samples stable should the dry ice dissipate.
   NOTE: There should be sufficient dry ice to keep the samples frozen until they reach the Madison lab.
   a. Suggestions:
      i. Plastic bubble wrap can be used at the bottom and top of the shipping container.
      ii. Plastic bubble wrap can be reused if there is no leakage
      iii. Cardboard can also be used to stabilize samples.

4. Fill bottom of shipping box with dry ice

   a. The Styrofoam boxes should be sufficient in size and must be shipped in a cardboard carton.

   b. Boxes must have the label “Exempt Human Specimen” attached. (Fisher Scientific, Catalog #22-130-070: Therapak “Exempt Human Specimen” label)

c. Affix the dry ice label "DRY ICE – UN 1845" to the carton. Mark the approximate weight of dry ice in kg for each shipment. (Air Sea Containers, http://www.airseacontainers.com, Product name: Dry Ice UN 1845 Label, Roll of 500 (No product number),1-866-272-9880)



d. The name, address, and telephone number of a person responsible for the shipment is required on the box.
e. Boxes of various sizes have been subjected to the required drop test.

Shipping Specimens

The samples should be placed into a shipping box containing a sufficient amount of **cubed/chipped dry ice**. Put 1 inch of crushed dry ice in the bottom of the shipping box. Add a plastic transport bag containing the samples. Lay flat on top of the first ice layer. Layer more crushed dry ice so that the bag of samples cannot be seen – at least one inch. If there is additional space in the box, add another plastic transport bag containing samples. Make sure there is room for 2 inches of dry ice at the top. There is no limit for the number of samples per box. Just make sure that the box is large enough to include enough dry ice. (Close the box in such a way that the lab address is showing.) The box is then sealed with tape. Please do not completely seal the stryrofoam box so that it is airtight because the carbon dioxide from the dry ice must be allowed to escape. The dry ice poundage should be marked on the dry ice label on the box.

All samples should be sent FedEx Priority Overnight. No other form of shipping is acceptable.

Samples will be shipped on the same day of the week that the genetic samples are shipped to Tucson. The samples will be shipped every other month, on the first day that each site ships genetic samples to Tucson, beginning in June 2016.

- Ship to:

COAST Lab/Tressa Pappas
H4/469 CSC
600 Highland Ave.
Madison, WI 53792
FAX: (608) 263-9833
Phone: (608) 263-8539 (Tressa)
Email: tep@medicine.wisc.edu

It must be noted to have "COAST Lab" as the main recipient.

- Samples should *never* be shipped on a Friday or Saturday; shipment for weekend receipt is unacceptable, as the lab is not staffed to receive such shipments, and the samples may thaw. Also note that anything other than overnight shipment for AM receipt is unacceptable due to possible thawing of samples (i.e., Do not ship on Friday for Monday delivery).

2.29 PARTICIPANT ASSIGNMENT LOG/PROTOCOL ENROLLMENT

Visit 1

Assign participant ID number (P7_LOG)

A Participant Assignment Log (P7_LOG) has been developed for each performance site. This log includes columns for unique participant ID numbers, participant initials, participant's name, and whether he/she is randomized.

Participant ID numbers are preprinted on P7_LOG and are comprised of 8 digits:

- The first two digits are the number of the AsthmaNet protocol. For the STICS protocol the first two digits are 07.

- The next 3 digits are the AsthmaNet performance site identifier (112=Boston Children's Hospital, 122=Children's Memorial - Chicago, 125=Stroger Hospital/Rush Univ., 126=University of Illinois – Chicago, 132=National Jewish – Peds, 133=University of New Mexico, 141=University of Wisconsin – Peds, 152=University of Pittsburgh - Peds, 153=Case Western, 154=Allegheny, 162=Washington University-Peds, 172=University of California (SF)-Peds, 173=Children's Hospital Oakland, 181=University of Arizona, 191=Wake Forest, 194=Emory University, 195=Nemours – Jacksonville, 196=Nemours - Orlando)

- The last 3 digits constitute the participant identification (ID) number that is unique within the performance site. Participant IDs start with 001 and increase sequentially for the number of participants who are screened at Visit 1 at a given site.

To assign an individual a participant ID number, select the next available blank entry on the STICS Participant Assignment Log. This number will be the primary participant identifier used during the STICS study; it should be used in all communications with the DCC. The participant ID number also should be used to label the participant's study folder at the performance site.

Once issued, a participant ID number cannot be re-assigned to any other person.

If a participant re-enrolls at Visit 1, a new participant ID number should be assigned. See the Re-Enrollment discussion in this section for further details.

In order to maintain participants' confidentiality, do NOT use participants' names in any communications with the DCC, either written or oral. Provide only participant ID numbers and initials.

The Participant Assignment Log (P7_LOG) is a confidential document because it ties a participant ID number to a name. This document is required when it is necessary to verify a participant's actual treatment assignment, either during or after the study. For this reason, this log should be stored in a secure location and retained indefinitely at the performance site following the close of the study.

Visit 1

Assign participant ID number (P7_LOG)

Following assignment of the participant's ID number on the STICS Participant Assignment Log (P7_LOG), the protocol enrollment module should be accessed to enroll the participant formally in the database. Close attention should be paid when entering the participant's information to ensure that the correct ID is entered. If a participant is enrolled mistakenly under an incorrect participant ID, the DCC should be contacted immediately for assistance in correcting the error.

Visits 2-7

Record the drug assignments if the participant has been randomized.

2.30 PARTICIPANT HANDOUTS

At Visit 1 each participant is several handouts that cover topics related to study procedures. Additional handouts will be dispensed at Visit 2 to those participants who are randomized. Each handout contributes to increased adherence in areas such as using the spirotel® device, how to collect a nasal sample, etc. The parent/guardian should store the handouts in a convenient location, as it will serve as a reference throughout the trial. The handouts should be brought to each study visit so that clinical personnel can review and/or update handouts, as necessary. The following handouts are used in the STICS study:

Handouts Distributed at Visits

Visit 1	Run-In Action Plan Asthma Triggers (Asthma_Triggers) – optional How To Use the spirotel® Device (P7_HTSPIROTEL®) SPIROTEL® Reference Card (P7_SPIROTEL®_REF) How To Use Your albuterol RESCUE Inhaler (HTMDI_FACE)
Visit 2	STICS Action Plan Card / Daily Activities Guide STICS Action Plan tri-fold ID Card Nasal Blow (P7_HTNASAL_BLOW) STICS Visit Preparation Checklist (P7_VISPRP)

Run-In Action Plan, STICS Action Plan Card, and STICS Action Plan tri-fold ID Card

See “Action Plans and Identification Cards” for further details.

Asthma Triggers Handout - optional

The purpose of the optional Asthma Triggers Handout (Asthma Triggers) is to educate the parent/guardian about various aspects of the participant’s home life that could potentially be improved in terms of the participant’s asthma control. The information that is covered in the Asthma Triggers Handout includes:

Getting Rid of Cockroaches
Getting Rid of Mold
Pets
Tobacco Smoke

How to Use the spirotel® Device (P7_HTSPIROTEL®)

These instructions can be used as a tool to introduce the spirotel® Device (P7_SPIROTEL®) to the parent/guardian at Visit 1. See "spirotel® Device" for further details.

spirotel® Device Reference Card (P7_SPIROTEL®_REF)

This reference card serves as a quick guide to using the spirotel® Device and is dispensed to the parent/guardian at Visit 1. See "spirotel® Device" for further details.

How to Use Your albuterol RESCUE Inhaler (HTMDI_FACE)

These handouts provide general instructions for proper inhalation technique for home use of the rescue inhalers. Participants must demonstrate proper inhalation technique with each of these devices as assessed through the appropriate Technique Checklist before leaving Visit 1.

Nasal Blow (P7_HTNASAL_BLOW)

This handout demonstrates the blow technique for obtaining a nasal sample.

STICS Visit Preparation Checklist (P7_VISPRP)

This handout reminds the parents/guardians of food and medications that should be avoided prior to visits, and what study items need to be brought to all visits.

2.31 Participant Status Report

A Participant Status Report has been developed to communicate important information from the STICS database to the performance sites on a participant-specific basis. The report lists all drug assignments that have been made by participant ID and date.

The Participant Status Report is accessed through the AsthmaNet secure website by clicking on the 'Participant Status Reports' link on the homepage and then choosing STICS from the protocol list. If a coordinator has access to data from more than one performance site, he/she will need to choose the site for which the report is requested from a dropdown list. If a coordinator has access to data from only one performance site, the report request will be submitted automatically.

The Participant Status Report runs in real-time, accessing the current data in the database each time a request is submitted. Because the report is running a program in the background, it may take several seconds (or minutes as the database grows) for the results to appear.

2.32 PHONE CONTACTS

4 weeks after Visits 2-7

Complete Visit Procedure Checklist (P7_VISIT_PC)

Scheduled phone contacts during the STICS study assist in the early identification and documentation of lack of asthma control and new medical problems. It is preferred that the parent/guardian is the contact person for the phone call, but if necessary, an adult relative may answer the questions. Any questions the parent/guardian has may be answered during the phone calls rather than waiting until the next clinic visit.

Phone contacts provide an opportunity to:

- Monitor the participant's asthma symptoms and ensure the participant's safety.
- Determine whether the participant is using his or her rescue drugs appropriately.
- If participant has had any yellow or red zones, assure that procedures are being followed correctly. Plan to mail additional nasal kits as needed.
- Review Action Plan.
- Answer any questions the parent/guardian may have.

Prior to Study Visits

Families should be called prior to study visits to remind participants to bring items as described on the Daily Activities handouts. Please emphasize the following:

It is extremely important that participants remember to bring all study materials, including used STICS medications, the spirotel® device, and collected nasal samples.

CACT Form

Parents/guardians should be instructed to complete the CACT form that was given to them at the last regularly scheduled visit. They should have also received a pre-addressed, postage-paid envelope. After completing the form with the participant, they should mail the form back to the site.

2.33 PHYSICAL EXAMS

Visit 1 and Red Zone Visits
Perform Long Physical Exam (LEXAM_PED)

A long physical exam by a licensed medical practitioner is required at Visit 1 in order to ensure that it is safe and appropriate for each participant to enroll in the STICS studies. A Long Physical Exam (LEXAM_PED) form should be completed.

- See Section 3 of the AsthmaNet General Manual of Operations for information regarding the physical exam clinical procedures.
- Long physical exams should be performed by a licensed medical provider.
- The person conducting the physical exam should sign, date and note the time in the gray box on the Long Physical Exam (LEXAM_PED) form as source documentation.

Visit 2-8
Perform Short Physical Exam (SEXAM_PED)

A brief physical exam is conducted at Visits 2-8. Results of the exam are recorded on the Short Physical Exam (SEXAM_PED) form.

- See Section 3 of the AsthmaNet General Manual of Operations for information regarding the physical exam clinical procedures.
- Short physical exams may be carried out by the Study Coordinator, study physician, nurse practitioner, registered nurse, or physician's assistant.
- The person conducting the physical exam should sign, date and note the time in the gray box on the Short Physical Exam (SEXAM_PED) form as source documentation.

2.34 PREDNISONE/RED ZONE

General Instructions

The following are scenarios for which prednisone may be administered:

- The participant used more than 3 nebulizer treatments with albuterol or comparable beta-agonist bronchodilator or 6 puffs of albuterol (3 treatments of 2 puffs each) in the prior 4 hours for relief of asthma symptoms OR
- The participant used 12 or more puffs of albuterol in the last 24 hours for relief of asthma symptoms OR
- The participant awakened due to cough, shortness of breath, chest tightness, or wheezing AND needed to use albuterol at least 2 of the previous 3 nights OR
- The participant used 8 or more puffs of albuterol per day during 2 of the previous 3 days for relief of asthma symptoms.
- Physician discretion - If physician discretion is utilized, a specific reason for initiation of prednisone will be recorded.

Prednisone course. Parents/guardians will be instructed to call the AsthmaNet Clinical Center or the AsthmaNet on-call medical provider if, according to the action plan, they have followed instructions and believe that prednisone is indicated for the treatment of their child's asthma symptoms. The prednisone course will consist of a 4 day course of prednisone: 2 mg/kg/day for 2 days (maximum 60 mg/day) taken as a single morning dose, followed by 1 mg/kg/day for 2 days (maximum 30 mg/day) taken as a single morning dose. All administered will be rounded down to the nearest 5 mg.

In general, prednisone should be prescribed in tablet form for use as a rescue medication during the STICS study. Parents may crush prednisone tablets and administer them in applesauce or pudding if their child cannot swallow them. In cases where the child absolutely cannot or will not take the prednisone tablets, liquid may be prescribed as an alternative. Record the correct formulation on the CMED form. Liquid prednisone should only be prescribed if absolutely necessary. No formal exception from the DCC is required to substitute the liquid formulation. Since dosing instructions indicate that the dose should be rounded down to the nearest 5 mg, it may be necessary to split the tablets into quarters. In the event that is too difficult, liquid prednisolone can be substituted instead.

The participant's weight at the visit should be used to determine the dose. Therefore, the dose may change throughout the study as the participant's weight increases as new prescriptions are dispensed.

Visit 1

If the participant requires prednisone during the Run-In, he/she should be termed. The participant must wait 4 weeks after the prednisone course is complete to be re-enrolled. The P7_ELIG3 form and the P7_TERM form should be completed. In addition, the prednisone course should be recorded on the CMED form. (Do not complete the P7_PRED form or the P7_TRK form).

Visits 2-8

If prednisone is recommended by AsthmaNet Clinical Center medical personnel, these personnel will telephone the parents/guardians within 48-96 hours after the initiation of the prednisone. The purpose this telephone call is to reassess the child's condition and determine whether additional prednisone courses may be warranted.

If the child is still symptomatic during the 48-96 hour phone call and the AsthmaNet Clinical Center medical personnel are comfortable with telephone management of the child (based on their medical judgment), the prednisone course will be repeated (i.e., 2 mg/kg/day for 2 days [maximum 60 mg/day], followed by 1 mg/kg/day for 2 days [maximum 30 mg/day]). However some AsthmaNet medical personnel may not be comfortable assessing the child over the telephone and may wish to evaluate the child in the outpatient setting. If those personnel feel that additional prednisone is warranted, the prednisone course will be repeated as described above.

If the child's symptoms worsen <u>at any time</u> after the initiation of prednisone, the child will be referred to urgent care or the emergency department for additional evaluation. The treatment of these children will be at the discretion of the attending physician at those locations. Children requiring hospitalization for >24 hours are considered treatment failures.

If the participant is using the Yellow Inhaler while starting prednisone, the Yellow Inhaler should be continued for the full 7 days.

If a child experiences an exacerbation within 2 weeks of completing a course of oral corticosteroids, a second course of oral corticosteroids will be recommended. Any child receiving two courses of prednisone during a 6 month period (separated by at least 1 week) will be considered a treatment failure. Any child receiving 3 courses of prednisone during a 12 month period (separated by at least 1 week) will be considered a treatment failure. A course that gets extended to 8 days should only be counted as 1 course.

Complete the STICS Prednisone Medication Form (P7_PRED) and record the course on the STICS Prednisone and Yellow Zone Tracking Form (P7_TRK). In addition, record the course on the Concomitant Medication form (CMED) by recording the dose as one record with the starting dose and frequency listed as tapered dose.

Corticosteroids prescribed by non-AsthmaNet personnel

If a prednisone course is prescribed by someone not at the AsthmaNet site (i.e. ER, PCP, etc.), please complete the P7_PRED form, mark '5. Physician discretion' as the response to Q1010 and provide a brief explanation in the comments section.

It is a growing trend for EDs to give a treatment of 1 dose of dexamethasone to patients. It eliminates the requirement of the patients to fill prescriptions. Treatments of that nature should be counted as equivalent to a prednisone course. Please contact the DCC if you have any questions about a particular dose.

Red Zone Phone Contacts

All participants who take prednisone for an asthma exacerbation should have a Red Zone Phone Contact. This call should take place approximately 5 days after starting the prednisone course (+/- 2 days). The purpose of the call is safety. The Red Zone Phone Assessment Form (P7_RED_PC) should be completed. If the participant is not improving on the prednisone therapy, a follow-up phone call or Red Zone Study Visit should be scheduled.

Red Zone Study Visits

Visits 90, 91, 92

This visit should be performed at the discretion of the site PI/coordinators. If the participant is not improving on prednisone therapy, the Red Zone Study Visit should be scheduled. The Red Zone Visit Checklist (P7_VISIT_RED) should be completed. Red Zone Visits should be numbered 90, 91, 92.

Procedures that should be performed at Red Zone Visits are spirotel procedures, long physical exam, spirometry, collection of nasal samples and replacement of any used medications (i.e. prednisone, albuterol).

2.35 Pregnancy Test

At protocol-defined visits, urine samples will be obtained from female participants of child-bearing potential for assessment of pregnancy by the presence of the beta subunit of human chorionic gonadotropin (HCG). Testing will be performed at the performance site during the participant's visit using the HCG combo stick test approved by each institution. The results of the pregnancy test should be recorded on the Urine Pregnancy Test (PREG_TEST) form and the participant should initial and date the source documentation box to acknowledge the results. If a participant is found to be pregnant at any point during the STICS study, she must be terminated from study participation immediately. See additional instructions below.

Visits 1 and 2

Complete Urine Pregnancy Test form (PREG_TEST) form for all female participants age 6 and older; administer urine pregnancy test, if necessary

At the designated visits, the PREG_TEST form is required for all female participants age 6 and older, regardless of their child-bearing potential. A urine pregnancy test must be administered if the participant is deemed to be of child-bearing potential.

At all relevant visits, if the participant is potentially able to bear children by the information supplied on the PREG_TEST form, the pregnancy test must be performed and results reported to the participant and to the DCC. Follow local and state regulations regarding reporting of pregnancies to parents/guardians/guardians in the case of participants who are minors.

Juvenile participants who are pre-menarche also do not need to be tested. The parent/guardian should provide source documentation for pre-menarche individuals. This information is documented on the PREG_TEST form.

Female participants who are of child-bearing potential must use birth control and provide urine for pregnancy tests as required by the protocol.

After performing a urine pregnancy test, the participant should be shown the results and asked to initial and date the source documentation box at the bottom of the form as verification that the information on the form is correct and acknowledged by her.

Source documentation should be completed even if a pregnancy test was not performed at the visit. In most cases the participant will provide the source documentation. If a participant is pre-menarche, the parent/guardian should provide the source documentation.

If a participant is considered able to bear children, results of the pregnancy test must be known before she proceeds with the diluent stage of the methacholine challenge at Visit 1. Pregnant participants should not perform methacholine challenges. In addition, pregnant or nursing participants are ineligible for the STICS protocol.

Pregnancies Discovered during Study Participation

If a participant is found to be pregnant at any time during the study, either through a pregnancy test performed at a study visit or through another means, she is ineligible for continued participation. Pregnant participants should be seen at the performance site and terminated from further study participation immediately. Participants who become pregnant during the study should have a STICS Termination of Study Participation (P7_TERM) form submitted to the DCC as soon as possible recording pregnancy as the primary reason for study termination (Q1050 should be answered '1=Pregnancy'). Pregnancy should not be reported as an adverse event or as a serious adverse event in the STICS database.

See Section 10 of the AsthmaNet General Manual of Operations for further details on the completion of the Urine Pregnancy Test (PREG_TEST) form.

2.36 RANDOMIZATION MODULE

Visits 2-7

The randomization module may be accessed for two reasons during the STICS study: Visit 2-7 for the yellow inhaler assignment and to obtain lost/replacement drugs.

The randomization will be stratified by the 9 performance sites.

Two copies of the randomizations should be printed. One copy should be used for drug dispensation (i.e. give to pharmacy if applicable); the other copy should be stored in the participant folder.

Visits 2-7: Regular Dispensation

At visits 2-7, the randomization module will provide a yellow zone inhaler number. The code for the YELLOW Inhaler will have the format __ __ __ __. At each visit, the old YELLOW Inhaler should be collected and replaced with a new YELLOW Inhaler obtained from the randomization module regardless of whether it was used.

Visits 2-7: Lost/Replacement Drugs

If the participant loses the STICS yellow zone inhaler or the inhalers are expiring, the randomization module can be used to obtain replacement supplies. This feature should only be utilized when absolutely necessary since drug supplies are limited. A detailed description of the reason for needing replacement drugs will need to be provided.

Visits 3-7: Randomizations prior to Visit

Since many sites are using a pharmacy which makes the process of getting study drugs more difficult and time consuming (and the pharmacy may not be open at the time of the visit), the randomization application can be accessed up to 3 days prior to the scheduled visit for Visits 3-7. **For Visit 2, the randomization can only be accessed on the day of the visit once eligibility has been determined.**

2.37 RECRUITMENT

STICS visits will commence in May 2014. A total recruitment period of approximately 12 months has been set. Each site should strive to maintain Visit 1 enrollment percentages of 50% female participants and at least 33% minority participants over the recruitment period. The gender and minority status of individuals enrolled at Visit 1 and individuals randomized in each protocol will be summarized by site on the STICS accrual report. This report will be available on the secure website shortly after commencement of the studies.

Target sample sizes for each site are based on the number of participants who are successfully screened, entered into the run-in, and subsequently randomized in the STICS protocol. Each of the 9 participating performance sites should have a goal of randomizing approximately 27-28 participants. However, sites will not be stopped at 28 randomized participants and should continue recruiting beyond that goal. Recruitment will end when the Network total reaches 250 randomized participants.

2.38 REENROLLMENT

Participants who do not qualify for randomization at Visit 2 for reasons that may be overcome with time or training may be allowed to re-enter the Run-In period of the study for a second try. Only participants who have a high probability of success on the second try should be afforded this option. Participants can be re-enrolled immediately (i.e. new Visit 1 can take place on the same day as old Visit 2).

Participants may not be reenrolled for the following reasons:

1. Concurrent medical conditions other than asthma that are likely to require oral or injectable corticosteroids during the study (i.e. thyroid disease, diabetes mellitus, Cushing's disease, Addison's disease, hepatic disease)
2. A history of cataracts, glaucoma, or any other medical disorder associated with an adverse effect to corticosteroids.
3. History of significant adverse reaction to any study medication ingredient (fluticasone, oral corticosteroids and albuterol).
4. Gestation less than late preterm as defined as birth before 35 weeks gestational age.
5. Pregnancy or lactation.
6. If of child bearing potential, failure to practice abstinence or use of an acceptable birth control method
7. Chronic or active lung disease other than asthma.
8. Presence of other significant medical illnesses (cardiac, liver, gastrointestinal, endocrine) that would place the study participant at increased risk of participating in the study (See P7_EXCLMED).
9. History of life-threatening asthma exacerbation requiring intubation, mechanical ventilation or resulting in a hypoxic seizure.
10. The participant has significant developmental delay/failure to thrive as defined by the participant's height or weight is < 2nd percentile for age and gender.

If a participant re-enters the study, he/she must be given a new Participant ID number from the Participant Assignment Log (P7_LOG). However, specific data can be reused:

- A new copy of the STICS informed consent must be read and signed. The document signed at the initial enrollment should reside in the folder created for the participant's original participant ID number. The new signed consent should reside in the participant's current study folder. The informed consent should not be updated with initials and the date, as this practice violates institutional procedures at some of the sites.

The following forms may be reused from the original Visit 1: Participant Contact (CONTACT), Household Socio-Economic Information (HOUSEHOLD_SEI), the STICS Microbial Exposure Questionnaire (P7_MEQ), and the Home Environment Questionnaire (HEQ). These forms should be reviewed and updated, as necessary, with

the parent/guardian upon re-entry. The forms must also be updated with the new Participant ID and Visit 1 date and initialed by the Study Coordinator. Copies should be placed in both the old and new participant study folders.

All other labs and procedures must be repeated for each reenrolled participant in STICS.

2.39 REGISTRATION

Visit 1 or Prior

Register participant in AsthmaNet Registry

Before a participant can be enrolled in the STICS study, he or she must be entered into the AsthmaNet Registry. Complete Registry procedures are documented in section 9 of the AsthmaNet General Manual of Operations.

Visit 1

Complete Registry Checklist (REG_CHK)

Follow the procedures for completing the Registry Checklist (REG_CHK) as outlined in section 9 of the AsthmaNet General Manual of Operations. Attach one of the participant's "Registry Checklist" labels to the gray box at the bottom of the checklist before submitting the form to the DCC. This label contains the participant's master ID number and serves as a reference during the protocol enrollment process.

Include REG_CHK behind the Visit Procedure Checklist (P7_VISIT1) in the participant's Visit 1 packet.

2.40 SATISFACTION QUESTIONNAIRE

Participant's Termination Visit

Give parent/guardian AsthmaNet Satisfaction Questionnaire (SATQX) with preaddressed, postage-paid envelope

The AsthmaNet Satisfaction Questionnaire (SATQX) is a quality control tool that was developed by the AsthmaNet Quality Control Committee (QCC) to solicit feedback from participants when they leave AsthmaNet studies. The questionnaire is anonymous in that no participant or master ID number or other identifying information is recorded on the form. In addition, the participant returns the form directly to the DCC in a pre-addressed, postage-paid envelope. Performance site staff does not review the data on the form, does not see individual results, and does not data enter the information on the form. Data entry takes place solely at the DCC.

The Satisfaction Questionnaire (SATQX) is posted on the secure AsthmaNet website in the visit packet corresponding to the final study visit for a given protocol. For STICS, it is present in the Visit 8 packet. In addition, the questionnaire is also posted appended to the single STICS Termination of Study Participation (P7_TERM) form for use with participants who terminate from the study before Visit 8.

Postage-paid envelopes that are pre-addressed to the DCC may be obtained from the DCC as supplies are needed. At least one month's lead time should be allowed for shipment and receipt of the envelopes to ensure an adequate supply at the performance site at all times.

Process: The following steps should be carried out to ensure that all participants who terminate from the STICS trial have an equal opportunity to provide feedback on their experiences.

1. Distribute a copy of the questionnaire to any participant who successfully completes Visit 2, then terminates, whether he/she completes the study or terminates early.

2. Download the questionnaire from the secure AsthmaNet website along with the STICS Termination of Study Participation (P7_TERM) form. Questionnaires in visit packets will have protocol number and site ID pre-completed in the key fields area of the form. Questionnaires appended to single P7_TERM forms will have only protocol number completed. Coordinators should complete the site number before distributing the questionnaire to a participant.

3. Print the questionnaire double-sided and staple the pages together to avoid loss.

4. Complete the participant's final study status in the gray box at the top of page 1 of the form.

5. Give the questionnaire to the participant at the conclusion of his/her final study visit. The participant should be given a pre-addressed, postage-paid envelope with the questionnaire.

6. Instruct the participant to complete the questionnaire, put it in the envelope, seal it, and place it in the US postal mail. If a participant elects to complete the questionnaire at the performance site, clinic personnel should not interact with him/her as the form is completed. In this case, it is preferable for the participant to drop the questionnaire in any postal box himself, but he/she may seal the questionnaire in the envelope and ask clinic personnel to mail it.

Note: If an individual is not present at the time he/she withdraws from the study, and he/she is unwilling to come to the performance site for a final visit, the Satisfaction Questionnaire should be mailed to his/her home address. Include instructions for completion with the questionnaire and prepaid envelope.

The DCC will provide periodic reports of the data from the questionnaire for the QCC and the coordinators/investigators to review. Response rates will be compared across the performance sites to ensure that all sites are participating fully in the survey process.

2.41 SCREEN FAILURES

Visit 1

If an STICS participant is discovered to be ineligible at Visit 1, the following directions apply:

- If the participant was deemed ineligible before a participant id number was assigned, there is nothing more to do.

- All data collected at Visit 1 for this type of participant should be kept on file at your site and should not be entered into the database. Data should be entered and submitted to the DCC for Visit 1 only for participants who meet all criteria on Eligibility Checklist 1 and Eligibility Checklist 2.

2.42 SPIROMETRY

Spirometry procedures are carried out at all STICS visits. Pulmonary function data are very important, as they confirm the participant's eligibility for the study and provide important data for study analysis.

General Instructions

AsthmaNet utilizes the MedGraphics spirometry system. The Spirometry Manual of Operations is located in Appendix 1 of the AsthmaNet General Manual of Operations.

Individuals performing spirometry must be AsthmaNet-certified in pulmonary function testing or, at a minimum, observed and supervised by an AsthmaNet-certified technician. If an uncertified individual is performing any spirometry procedures at a visit, a supervisor ID must be recorded on the applicable form(s), including the Spirometry Testing (SPIRO) form and the Post-Albuterol (4 puffs) Spirometry Testing (PALB4_SPIRO) form, as applicable at a given visit.

A participant's prior spirometry results should not be reviewed with him/her at the current visit. Knowledge of past test results can influence current expectations and bias the resulting data.

In general, before a participant can proceed with spirometry testing, he/she must meet all of the medication and substance holds specified on the STICS Pulmonary Procedure Checklist (P7_PULMONARYCHK) with "gray box" exclusions. If a participant has taken any of the listed substances within the specified washout period prior to a visit, he/she generally may not proceed with spirometry testing at the visit. In this case, the visit should be rescheduled within the visit window for appropriate washouts to be met. If the participant has almost met a required washout period, contact the STICS scientific coordinator at the DCC.

If an exception is granted through the DCC, Q1140 on P7_PULMONARYCHK should be marked 'Yes' even though one or more of the 'gray boxes' corresponding to drug or substance washouts is completed. This conflict will result in a data error which the coordinator should mark unresolvable; the exception should be explained in a comment.

eNO Testing in Relation to Spirometry

Since spirometry testing is known to affect eNO measures, eNO testing must be performed after the STICS Pulmonary Procedure Checklist is completed and prior to spirometry at Visits 2-8. See the Exhaled Nitric Oxide discussion in this section for further details.

Demographics

Care must be taken to enter the participant's identification (i.e., participant ID number with leading '0', initials, etc.) and demographic information into the spirometry software correctly. A technician ID must also be included for each test that is performed.

Height

Heights will be measured at each visit and recorded on the applicable Physical Exam form (LEXAM_PED or SEXAM_PED) at the visit. These forms are data entered. Height values should be verified and updated in the spirometry system each time spirometry is performed on participants.

Race/Ethnicity

The participant's spirometry race/ethnicity designation should be retrieved from his/her AsthmaNet Registry Report. The participant's spirometry race/ethnicity category corresponds to the primary racial designation that he/she supplied in Q1150 on the Registry (REGISTRY) form. Individuals who specified 'American Indian/Alaskan Native' or 'Other' will use Caucasian predicted lung function equations. Always use the spirometry race/ethnicity designation listed on the participant's Registry report in the MedGraphics software. Race/ethnicity has a large influence on a participant's predicted lung function values.

Gender

Biological sex should be entered into the MedGraphics software for purposes of calculating predicted lung function values.

Visit 1

Complete Pulmonary Procedure Checklist (P7_PULMONARYCHK)
Perform Spirometry Testing (SPIRO)

Baseline spirometry at Visit 1 is used to determine study eligibility. These results are recorded on the Spirometry Testing (SPIRO) form and are referenced on STICS Eligibility Checklist 1 (P7_ELIG1).

Visits 2-8

Complete Pulmonary Procedure Checklist (P7_PULMONARYCHK)
Verify/update height on MedGraphics machine (using height recorded on SEXAM_PED)
Perform Spirometry Testing (SPIRO)

Baseline spirometry at Visit 2 is used to determine study eligibility. These results are recorded on the Spirometry Testing (SPIRO) form and are referenced on STICS Eligibility Checklist 3 (P7_ELIG3).

Visit 1

Administer 4 puffs of albuterol, wait 10-15 minutes, and perform post-bronchodilator testing
Complete Post-Albuterol (4 puffs) Spirometry Testing form (PALB4_SPIRO)

To qualify the participant, he/she should perform baseline spirometry, then be given 4 puffs of albuterol and be allowed to rest for **10-15 minutes**. After the 10-15-minute wait, spirometry should be repeated and the results recorded on the PALB4_SPIRO form. All participants should complete the pre/post spirometry sessions at Visit 1, regardless of whether or not they provided source documentation from a previous pre/post spirometry test to support their eligibility.

For pre/post spirometry, participants should dose from albuterol (Ventolin®) inhalers taken from bulk supply at Visit 1. This should be logged on STICS Drug Dispensing Log: Ventolin® (RESCUE) Inhaler (P7_ALB_LOG). Actuators should be sterilized between participants, allowing for multiple participant use.

Albuterol puffs taken as part of the pre/post spirometry testing procedure should not be included in the RESCUE puffs the participant records in his/her spirotel® device the evening after the visit.

2.43 SPIROTEL® DEVICE

The spirotel® is an electronic diary (e-diary). Parents/guardians will be given a device and trained in its use at the beginning of the run-in period. Parents/guardians will be expected to complete the scheduled PM session daily for the duration of the study. A scheduled session includes answering a set of questions in the e-diary, followed by 3 peak flow blows by the participant. The peak flow values will not be displayed on the device or on the reports. They will be hidden throughout the study and used during analyses. Data collected in the device between visits will be uploaded to the MedGraphics database during each visit to the performance site. After the most recent data have been uploaded, clinical personnel will generate and print reports to review with the parent/guardian.

This section covers STICS-specific spirotel® information. For additional information on the spirotel® device, refer to appendix 6 of the AsthmaNet General Manual of Operations.

Parent/guardian Instruction

Visit 1
Instruct **parent/guardian** in use of spirotel® (use demo device) (P7_HTSPIROTEL®, P7_SPIROTEL®_REF). While the participants in the STICS study might be old enough to answer some of the daily questions, the intention of this study is to have the spirotel® sessions completed by parents/guardians only. It should be strongly discouraged to have the participants completing the spirotel® sessions.

The DCC will provide each performance site 1 or 2 demonstration (demo) devices loaded with the STICS demo program. These devices are only for instructional purposes; they should not be dispensed to parents/guardians for use during the trial. Demo devices do not store data.

Demo devices that have been programmed with the STICS e-diary questions may present alerts following the scheduled PM session. The “Medication” alert will be presented for all sessions. The “Yellow Zone” alert will be presented if Q2 (child awake last night with symptoms requiring albuterol) =1 and/or Q9 (number of puffs from RED RESCUE albuterol inhaler taken for asthma symptoms in past 24 hours)≥ 6 and/or Q10 (there was a 6 hour period in the past 24 hours when the RED RESCUE albuterol was used for symptoms two times)=1. The “Red Zone” alert will be presented if Q2=1 for 2 out of 3 days and/or Q9≥8 for 2 out of 3 days and/or Q9≥12.

At Visit 1 when the spirotel® is first introduced to the parent/guardian, clinical personnel should review the information on the How to Use Your STICS spirotel® Electronic Diary (P7_HTSPIROTEL®) handout. The parent/guardian should be educated on the steps for

completing scheduled evening assessments and on the expectation that these sessions are to be completed every day throughout the study.

After the parent/guardian has reviewed the P7_HTSPIROTEL® handout, clinical personnel should introduce the parent/guardian to the demo device. Reinforce to the parent/guardian that all data entered into the device will be stored for upload and review at his/her next visit to the site.

In addition to the P7_HTSPIROTEL® handout that covers the spirotel® procedures in general, an STICS-specific handout (STICS spirotel® Reference Card (P7_SPIROTEL®_REF)) has been created to fit into the spirotel®'s case for quick reference by the parent/guardian at home during a session. This reference includes each question abbreviation (i.e., the up to 18 character representation on 3 lines the parent/guardian sees on the device), along with the longer text question that it represents. The reference also supplies clarification for certain questions, explanation of alerts they may receive, as well as explanations for the symptom scores. Clinical personnel should show the parent/guardian this reference and review it upon dispensing his/her device. It should also be emphasized that pre-exercise puffs taken from the Red Albuterol inhaler should not be counted when reporting rescue use values.

spirotel® Performance Check

Visit 1
Complete STICS spirotel® Performance Checklist (P7_SPIROTEL®_PERF, P7_ELIG1) (use demo device)

After the parent/guardian has had a chance to experiment with the STICS demo device, he/she should undergo a formal spirotel® performance assessment using the steps on the STICS spirotel® Performance Checklist (P7_SPIROTEL®_PERF). He/she must pass the performance check with a score of 4 to remain eligible for the study.

If a parent/guardian fails to perform all the steps on the performance checklist correctly, he/she may be retrained and undergo another assessment. There is no limit on the number of times the parent/guardian may attempt to pass the checklist. Store all completed P7_SPIROTEL®_PERF forms in the participant's STICS study folder at the performance site; they should not be forwarded to the DCC.

Loading the STICS Program and Preparing Device for Participant Use

Visit 1
Load STICS program into participant's assigned spirotel® device

Determine which spirotel® device will be assigned to the participant. Load the STICS program into the device. The following setup screen will appear with the protocol name

(STICS), device serial number, software version number, first digit of the participant ID (7), and the choice between English language (default) or Spanish language.

Visit 1
Program the spirotel® with the participant's information.

After the STICS program has been loaded into the participant's device, several participant-specific pieces of information must be entered by clinical personnel, including:

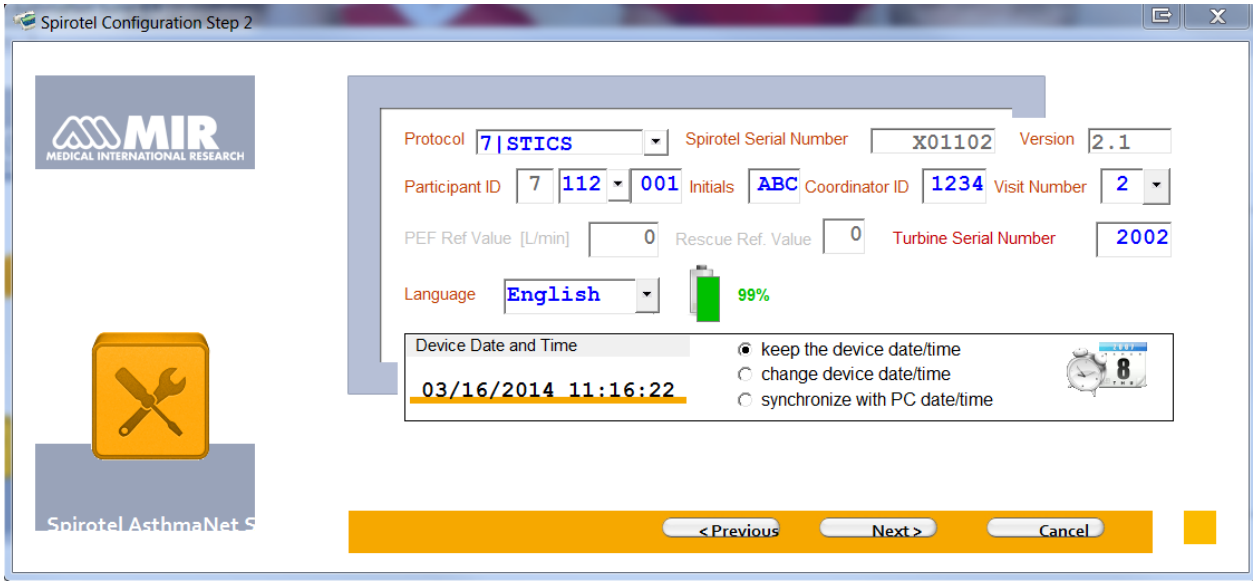
Participant ID: This is the participant's assigned STICS ID number. The ID is broken into three sections: protocol number (7 pre-completed), performance site number, and ID number. Clinical personnel must complete the site number and ID number portions.

Coordinator ID: This is the 4-digit identification number belonging to the person who is setting up the participant's device

Visit Number: The return visit number should be entered. At Visit 1 the return visit number should be specified as 2. This value will be updated by clinical personnel at each regular visit.

The PEF Ref Value and Rescue Ref Value fields have been disabled for STICS.

A sample completed setup screen with information for participant 7-112-001 at Visit 2 follows.



Visits 2-7
Update return visit number in spirotel® device

When a participant returns to the performance site and completes a visit, the Visit Number in his/her device must be manually changed to the next return visit number. Choose the appropriate return visit number from the dropdown menu. For example, if a participant is at the site and completes Visit 3, the visit number setting in his/her device must be incremented to 4 before he/she leaves the visit. This setting ensures that all stored data will be associated with the correct return visit number.

Note: If a participant is discharged from the performance site and the visit is postponed for any reason (i.e. not yet eligible for randomization at Visit 2), he/she will be returning to complete the visit at a later date. In that case the return visit number in his/her device should not be updated until the return visit. All accumulated data should register in the device under the visit he/she is in the process of completing.

Logging Dispensation and Return of spirotel® Equipment

Visit 1
Log/dispense spirotel® (SPIROTEL®_DEVICE)

Visits 2, 8 or whenever a participant leaves the study
Collect/Log spirotel® SPIROTEL®_DEVICE)

Each time a spirotel® device is assigned to a participant, the spirotel® Device Log (SPIROTEL®_DEVICE) must be completed. At the time of dispensation, complete the device number, the participant's STICS ID number, the date the device is being dispensed, and the initials of the person dispensing the materials to the participant.

Each time a spirotel® device is returned by a participant at the end of his/her study participation, SPIROTEL®_DEVICE must be updated to reflect receipt of these items. At the time of the termination visit, complete the date the device is being returned, the initials of the person collecting the materials.

If a device is lost during the study, enter this information into the logs in the comment column. All devices must be accounted for at all times.

Uploading the spirotel®

Visits 2-8
Upload spirotel®

At each visit to the performance site, the data stored in the participant's spirotel®'s memory will be uploaded to the MedGraphics database. Once the data have been uploaded successfully, they will no longer be available on the participant's device.

Note that data must be uploaded prior to generating reports at a visit. If the participant forgets to bring his/her spirotel® to a visit, the visit must be rescheduled. Participants must be reminded to bring their devices with them to every study visit.

Compliance Assessments

Visit 3-8

Print and review spirotel® Participant Compliance Report (P7_COMPLY)

The e-diary questions serve as a daily log that should be completed by the participant every day starting with the Visit 1 date, during his/her study participation. Participants who do not meet high standards of compliance with completion of e-diary questions will not be eligible to continue in STICS at Visit 2. If a participant's compliance begins to decline during the trial, he/she should be counseled regarding the importance of carrying out his/her home procedures, including e-diary procedures. Compliance percentages less than 75% are considered unacceptable.

At each visit 3-8, the participant's spirotel® device will be uploaded to the MedGraphics database. The spirotel® Participant Compliance Report for the current visit should be generated through the Breeze software. This report includes all data collected between the previous visit number and the current visit number. If multiple uploads were performed between visits and the return visit number was correctly specified, all data from the combined uploads will be used in the compliance assessment.

The spirotel® Participant Compliance Report (P7__COMPLY) contains the following:

- Number of full days since the last visit: This value includes the start date but not the end date. Only days since the last visit when the participant should have completed the PM scheduled session are included/counted. This value is recorded in Q1000 on P7_COMPLY.

- Number of days where the PM scheduled session is complete: A complete session is defined as a scheduled session where all e-diary questions presented to the parent/guardian were answered. This value is recorded in Q1010 on P7_COMPLY.

- Percent compliance: This value is computed as the number of e-diary complete days divided by the number of full days x 100. This value is recorded in Q1020 on P7_COMPLY.

The rest of the fields on the P7_COMPLY form Q1030-Q1100 will get completed by the coordinator based on the Inhaler counters. At Visit 2, Q1030-Q1060 should be completed based on the Green Inhaler used during the Run-In. At Visits 3-8, Q1070-

Q1100 should be completed based on the Green Inhalers and Yellow Inhaler used since the last visit.

STICS spirotel® Reports

Visit 2
Print and review spirotel® Participant Visit Report (P7_SPIROTEL®_RPT)
Print and review spirotel® Participant Compliance Report (P7_COMPLY) – on STICS Eligibility Checklist 3 (P7_ELIG3) answer Q1030-Q1040

Visits 3-8
Print and review spirotel® Participant Visit Report (P7_SPIROTEL®_RPT)
Print and review spirotel® Participant Compliance Report (P7_COMPLY)

Two spirotel® reports will be generated and consulted during the STICS trial. Reports are accessed through the MedGraphics Breeze Suite software after a participant's spirotel® data are uploaded at a given visit by doing the following: 1) Open the Breeze Suite software. The 'Open Patient' screen will display. 2) Select the applicable participant ID and hit the 'Open' button. A list of visits for this participant will appear. 3) Select the desired visit and hit the 'Open Visit' button. 4) Select 'Quick Print' from the toolbar. 5) Select STICS spirotel® Reports. 6) Three options are available for printing: All Reports, the Participant Visit Report or the Participant Compliance Report.

Descriptions of the STICS reports follow.

- spirotel® Participant Visit Report: This report serves as a 'data dump' of all the information the participant entered into his/her e-diary device between visits.

  The top part of the report shows device configuration data. Variables include: participant ID and initials, visit number, coordinator ID, device serial number, turbine serial number and upload date. If multiple uploads occur between visits, data from each upload are summarized separately.

  The body of the report shows all the data entered into the device sorted by trial date and time each trial started. Variables include: trial date, time trial started (military time), STICS diary questions Q1-Q15, Yellow and Red Alert Flags, and whether the Yellow Inhaler was used. STICS diary questions correspond to the order in which the participant answers them in the device. Refer to the STICS spirotel® Coordinator Reference Card (P7_SPIROTEL®_CREF) when reviewing the report with a participant. Questions and their possible responses are listed below:

  Q1: Did your child have asthma symptoms in the past 24 hours? (0=No, 1=Yes)
  Note: A 'No' response skips to Q11
  Q2: Did your child awaken last night with symptoms requiring albuterol? (0=No, 1=Yes)

Q3: How severe was your child's cough today? (0,1,2,3)
Q4: How severe was your child's wheezing today? (0,1,2,3)
Q5: How severe was your child's trouble breathing today? (0,1,2,3)
Q6: How much did your child's asthma interfere with your child's activities today? (0,1,2,3)
Q7: Was your child absent from daycare or school today due to asthma symptoms? (0=No, 1=Yes)
Q8: Was your child seen by a healthcare provider (doctor's office, ER, urgent care, study site) for an unscheduled visit today due to asthma symptoms? (0=No, 1=Yes)
Q9: Number of puffs your child took from the RED RESCUE albuterol inhaler for asthma symptoms in the past 24 hours (0-40)
Q10: Was there a 6 hour period in the past 24 hours when RED RESCUE albuterol was used for asthma symptoms two times (i.e. 4 puffs)? (0=No, 1=Yes)
Q11: Number of albuterol puffs taken in the past 24 hours to prevent symptoms (for example: before exercise, before smoke exposure, or before exposure to pets)? (0-40)
Q12: What type of inhaler was used during the AM dose today? (0=NONE, 1=GREEN, 2=YELLOW)
Note: A 'NONE' response skips to Q14
Q13: Number of puffs taken in the AM? (1-9)
Q14: What type of inhaler was used during the PM dose today? (0=NONE, 1=GREEN, 2=YELLOW)
Q15: Number of puffs taken in the PM? (1-9)

The spirotel® Participant Visit Report should be reviewed with the participant at each visit, starting with Visit 2.

- spirotel® Participant Compliance Report: This report summarizes a participant's compliance with completing his/her e-diary questions in the interval between visits. If multiple uploads are done between visits, all data corresponding to a given visit number will be included in one summary report.

  See the compliance section above for further details on this report.

STICS spirotel® Alerts

Several alert messages have been programmed into the STICS spirotel® device in an effort to improve participant compliance with taking study medications, recognizing high rescue use, and identifying moderate/severe symptoms. Alerts other than the Timing Alert appear following a completed scheduled PM session when certain criteria are met. Alert definitions follow.

- Medication Alert

  This alert appears for all sessions as a reminder to take the study medications. The following message will be displayed – 'Have child take puffs from study inhaler'.

- Yellow Zone Alert

  This alert appears after a completed scheduled PM session when the participant meets the yellow zone criterion. The "Yellow Zone" alert will be presented if Q2 (child awake last night with symptoms requiring albuterol) =1 and/or Q9 (number of puffs from RED RESCUE albuterol inhaler taken for asthma symptoms in past 24 hours)≥ 6 and/or Q10 (there was a 6 hour period in the past 24 hours when the RED RESCUE albuterol was used for symptoms two times)=1. The following message will be displayed after all the diary questions have been answered – 'Based on your answers child may be in Yellow Zone refer to your Action Plan'.

- Red Zone Alert

  This alert appears after a completed scheduled PM session when the participant meets the red zone criterion. . The "Red Zone" alert will be presented if Q2=1 for 2 out of 3 days and/or Q9≥8 for 2 out of 3 days and/or Q9≥12. The following message will be displayed after all the diary questions have been answered – 'Based on your answers child may be in Red Zone Call site ASAP.

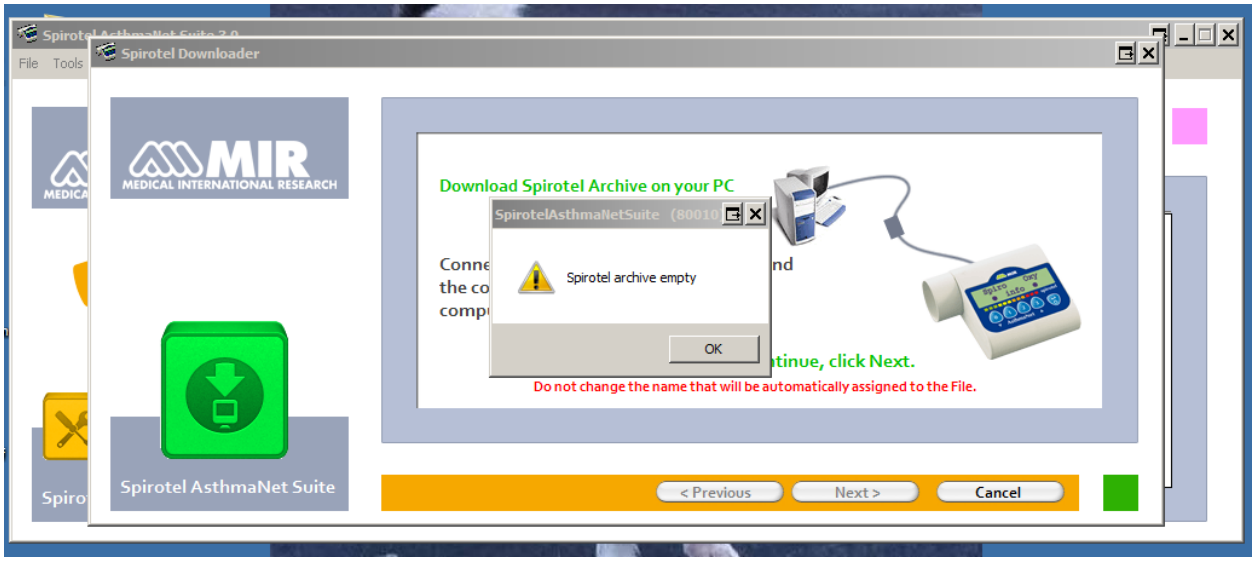
Handling participant travel

If a participant takes a trip during his/her study participation that requires sleeping for one or more nights in a new time zone, e-diary answers should be made within the specified time windows using "local" time. For example, if a participant from the Boston performance site travels to San Francisco for a five-day vacation, then he/she should perform e-diary procedures in the protocol time windows using local San Francisco time. This assumes that the participant will adjust his/her sleep/wake habits from Eastern Time to Pacific Time.

To assure that the spirotel® device will accommodate the participant's measurements in the alternate time zone, and to ensure that times reflect when activities were actually performed during the participant's day, the time setting in the device must be changed by clinical personnel just prior to the participant leaving on the trip. Refer to the spirotel® Manual of Operations in appendix 6 of the AsthmaNet General Manual of Operations for options and instructions for handling participant travel.

Identifying when a device wasn't used at all

If a parent/guardian hasn't used the device at all, the following error will be displayed when the data is downloaded:



2.44 STUDY MEDICATIONS

A general description of the STICS study medications is given below. See the STICS Pharmacy MOP for procedures related to drug preparation, logging, and dispensation for clinic staff and pharmacists.

Please be sure that inhalers are primed prior to dispensation. Prime the inhalers by releasing 4 test sprays into the air away from the face, shaking well for 5 seconds between each spray.

Rescue medications

All participants will receive the following study rescue medications:

- Albuterol rescue drug (Ventolin), an inhaled beta-agonist to be used as-needed throughout the STICS trial to treat asthma symptoms.

  Albuterol rescue drug will be labeled with a red label and will be dispensed from bulk supplies provided by the DCC. This inhaler will be referred to as the RED inhaler (color of label) on participant handouts and in the spirotel®.

- Rescue prednisone, an oral corticosteroid to be used only in emergencies and under the direction of clinical staff to treat an asthma exacerbation.

  Rescue prednisone will be obtained through the individual performance site pharmacies and dispensed to each participant at their first visit. Packaging should be childproof. See the Prednisone/Red Zone discussion in this section for further details regarding use of prednisone for treatment of asthma exacerbations.

Visit 1: Run-in medication

During the Run-In, participants will use a fluticasone Inhaler (Flovent 44 mcg/puff) 2 puffs/twice a day. This inhaler will be referred to as the GREEN inhaler (color of label) on participant handouts and in the spirotel®.

Visits 2-8: GREEN Zone medications (open-label)

Treatment period medications are double-blind. Participants, performance site staff, and DCC personnel involved in day to day decision-making for the study and statisticians on the project will not know what treatment regimen the participant is receiving during any of the three treatment periods.

Participants will use a fluticasone Inhaler (Flovent 44 mcg/puff) 2 puffs/twice a day. This inhaler will be referred to as the GREEN inhaler (color of label) on participant handouts and in the spirotel®. Since the participant will receive 3 GREEN inhalers to use between visits, the GREEN Inhaler Dates-of-Use Worksheet (P7_GREEN_DOU) should be used to complete the 'Do not use after MM/DD/YY' date that is recorded on the GREEN Inhaler labels.

Visits 2-8: YELLOW Zone medications (blinded)

Participants will be randomized to receive either fluticasone 44 mcg/puff or fluticasone 220 mcg/puff for their Yellow Zone treatment. This inhaler will be referred to as the YELLOW inhaler on participant handouts and in the spirotel®.

When participants meet the criteria for the Yellow Zone, they should be instructed to stop using the GREEN Daily Inhaler, and begin using the YELLOW Inhaler for 7 days. See the Yellow Zone discussion in this section for further details regarding starting YELLOW Zone treatment.

Individual blinded YELLOW Zone Inhalers will be identified by a code number that is associated with their randomized treatment assignment in the STICS database. Codes for the YELLOW Inhaler will have the format __ __ __ __. This inhaler will be referred to as the YELLOW inhaler on participant handouts and in the spirotel®.

2.45 STUDY MEDICATION COMPLIANCE

Visit 2

Complete the Compliance Checklist (P7_COMPLY)

This form/report should be printed after the spirotel® data has been uploaded. Q1000-Q1020 assess overall Diary Compliance and will be pre-populated based on the spirotel® data. Adherence with the STICS medications at Visit 2 is assessed in Q1030-Q1060 on the STICS Compliance Checklist (P7_COMPLY). Q1030-Q1060 should be completed by the coordinator from the GREEN Inhaler counter.

Compliance must be >75% for the participant to be randomized. If compliance <75% at Visit 2, the participant is ineligible.

Visits 3-8

Complete the Compliance Checklist (P7_COMPLY)

This form/report should be printed after the spirotel® data has been uploaded. Q1000-Q1020 assess overall Diary Compliance and will be pre-populated based on the spirotel® data. Adherence with the STICS medications at Visits 3-8 is assessed in Q1070-Q1100 on the STICS Compliance Checklist (P7_COMPLY). Q1070-Q1100 should be completed by the coordinator from the GREEN and YELLOW Inhaler counters.

Compliance should be >75%. If compliance <75% at Visit 3-8, discuss with the parent/guardian the reasons why compliance is low and try to find an agreeable solution to improve compliance.

If you know that the calculated adherence is not correct, please provide a comment in the comment field.

Nightly Routine

Coordinators should train and encourage the parent/guardian to get in an evening routine.

An ideal routine would be:

1. Complete the spirotel® session. Parent/guardian should complete Questions 1-15. Participant should perform 3 required Peak Flow Maneuvers
2. Give the participant the required puffs from the GREEN or YELLOW inhaler
3. Put participant to bed.

2.46 TERMINATION OF STUDY PARTICIPATION

Early Study Withdrawal

The parent/guardian of the participant has the right to withdraw consent for study participation at any time and for any reason. The study investigator may also determine by physician discretion that it is in the best interest of the participant to discontinue participation in the trial.

Screen Failures

If an STICS participant is discovered to be ineligible at Visit 1, any forms that were completed should be filed in the participant folder and should not be entered into the database.

See “Reenrollment” for instructions in reenrolling participants.

Terminations and Withdrawals During the Run-In Period

The primary purpose of the Run-In period is to identify an appropriate group of participants for entry into the STICS study. It provides an opportunity to review the eligibility criteria for each participant thoroughly before he or she is randomized and starts the blinded treatment phase. For the STICS study it is extremely important to gauge the participant's ability to maintain high levels of adherence. Participants who cannot accommodate the date/time of the visits, who take exclusionary medications, do not take study medications regularly, or who fail to record information in their spirotel® devices are non-compliant. These participants should not be randomized at Visit 2, as their lack of adherence can seriously affect the results of the study. Thus, the Run-In period is the time to identify and withdraw inappropriate participants. If the clinic coordinator feels the participant may qualify to be reenrolled, the participant must begin again at Visit 1. See “Reenrollment” for these details.

When a participant is withdrawn from the Run-In period or withdraws consent during this period, a STICS Termination of Study Participation (P7_TERM) form should be submitted to the DCC along with any study data that have been collected. See Section 2 for what to do with study medications.

In addition to the P7_TERM form, any spirotel® data collected between visits should be downloaded and transmitted to MedGraphics for inclusion in the STICS dataset.

Minimum data requirements for participants terminated between Visits 1 and 2 include:

- Participant Compliance Report (P7_COMPLY)
- Spirotel® Quality Control (SPIROTELQC)
- Spirotel® Reports
- Termination of Study Participation form (P7_TERM)

Minimum data requirements for participants terminated at Visit 2 include:

- Participant Compliance Report (P7_COMPLY)
- Spirotel® Quality Control (SPIROTELQC)
- Spirotel® Reports
- Termination of Study Participation form (P7_TERM)

There are 2 required forms included in the Visit 2 packet (CACT and P7_PULMONARYCHK) which cannot be set to missing during entry of the visit packet. The coordinator will need to enter these forms into the database completing only the header information. Please leave all data fields missing, and leave all entry errors open. When the forms arrive at the DCC, the data managers will mark the required forms as missing.

Terminations and Withdrawals After Randomization

Once a participant has been randomized, all efforts should be made to follow the participant and to collect data on his or her progress for the duration of the study. This even applies to participants who are discovered to be ineligible or who fail to comply with study procedures following randomization. Once a participant leaves the site with his or her randomly assigned drugs at Visit 2, he or she must be followed. Situations in which participants or parents/guardians are unresponsive to phone calls or lost to follow up will need to be dealt with on an individual basis.

If a randomized participant or his/her parent/guardian withdraws consent during a visit, any data already collected at that visit should be reported on the data collection forms and forwarded to the DCC. If the parent/guardian is willing to complete the STICS Participant Study Treatment Questionnaire (P7_PART_TXQX), please ask him/her to do so. Parents/guardians should also be asked to complete the Study Satisfaction questionnaire (SATQX). The goal of this questionnaire is to assess the parent/guardian satisfaction with the STICS study. A STICS Termination of Study Participation form (P7_TERM) should also be submitted.

Exceptions occur for participants who are assigned drop-out status. These participants will be terminated from study participation. Reasons for dropouts are listed below.

Criteria for Assigning Drop-out Status During Treatment Period

- Parent/guardian withdraws consent

- Study physician determines that continuation in the study is not in the best interest of the participant

Data Requirements for Participants Terminated during Treatment Period

The minimum data requirements are:

- Termination of Study Participation form (P7_TERM)
- STICS Coordinator Study Treatment Questionnaire (P7_CC_TXQX)

The data requirements for participants who are terminated from the study during the treatment period may vary quite a bit, and should be handled on a case-to-case basis. A participant who withdraws consent may not be willing to return to the site for a brief close-out visit. However, a participant who is deemed a treatment failure, may be glad to return to the site for a brief close-out visit.

If it is preferred to have a brief 'close-out' visit with the participant, the next Visit Checklist can be used as a reference for procedures/forms which may be performed (i.e. If the participant terms between visits 4 and 5, visit 5 should be performed). If a phone contact is missed, it will need to be set to missing in the database. Enter any completed forms as part of the visit packet. Any forms that you did not complete can be set to missing with the exception of the CACT, P7_TRTFAIL and P7_PULMONARYCHK forms, since they are required. If you did not complete the P7_PULMONARYCHK form at the visit, you will still need to fill out the header information, answer Q1140 as 'Yes', and add a comment to Q6000 indicating that spirometry was performed as part of the close-out visit. Similarly, if you did not complete the CACT form at the visit, you will need to fill out the header information and leave all other fields blank. It is not necessary to complete all of the procedures/forms listed on the Visit Checklist, and will depend on the situation/reason for termination. In addition, the P7_TERM, P7_PART_TXQX and P7_CC_TXQX forms should be completed and entered as single forms with the visit number of the packet that was completed as the close-out visit.

If it is not possible to have a brief 'close-out' visit, arrangements should be made to have the participant ship the spirotel® device and study medications back to the site. The data should be downloaded and the spirotel® Participant Compliance Report (P7_COMPLY) should be completed. In addition, it is important to QC the spirotel® device. With the exception of the spirotel® reports, all single forms completed should be entered with a visit date of the day that they were actually completed (not the previous packet's visit date) but with the visit number of the most recent visit completed, including phone contacts. The P7_COMPLY and P7_SPIROTEL_RPT should keep the visit number of the next scheduled visit (i.e. if the participant terms after visit 4, the spirotel® data will have a visit number = 5). Even if the participant does not complete the P7_PART_TXQX, the P7_CC_TXQX should be completed. The participant should be mailed an AsthmaNet Satisfaction Questionnaire (SATQX) with a return envelope and instructions for completion.

2.47 TREATMENT FAILURES

Visits 2-8
Complete the STICS Treatment Failure Form (P7_TRTFAIL)

A participant will be deemed a Treatment Failure for STICS if any of the following criteria are met:

- 6 yellow zones are required since randomization.
- 2 courses of prednisone for treatment of asthma exacerbations in a 6 month period since randomization.
- 3 courses of prednisone for treatment of asthma exacerbations in a 12 month period since randomization.
- Hospitalization >24 hours is required for an acute asthma exacerbation.

2.48 TREATMENT QUESTIONNAIRES

Visits 8 or last visit

Complete the STICS Coordinator Study Treatment Questionnaire (P7_CC_TXQX) and STICS Participant Study Treatment Questionnaire (P7_PART_TXQX)

Parent/guardian – P7_PART_TXQX

The STICS Participant Study Treatment Questionnaire is used to assess how well the masking of the medications was carried out and to assess any side effects of the medication. The parent/guardian should complete the questionnaire.

If a participant withdraws from the STICS study following randomization and prior to Visit 8, the STICS Participant Study Treatment Questionnaire should be completed at the time of the participant's final contact with the site.

Coordinator – P7_CC_TXQX

The STICS Coordinator Study Treatment Questionnaire is used to assess how well the masking of the medications was carried out. The coordinator who was primarily in charge of the participant's study visits should complete the questionnaire.

If a participant withdraws from the STICS study following randomization and prior to Visit 8, the STICS Coordinator Study Treatment Questionnaire should be completed at the time of the participant's final contact with the site.

2.49 VISIT SCHEDULE AND VISIT WINDOWS

Visit Scheduler

The online Visit Scheduler (Applications > Application Reports > Visit Scheduler Report) provides a list of ideal visit dates along with the acceptable range for each visit. It should be run 2 times during the study: Visit 1 (start of Run-In) and Visit 2 (start of Treatment Period).

Visit 1

Run the Visit Scheduler. It will determine the optimal date for Visit 2. The Run-In period may be repeated or extended, based on the participant's symptoms during the Run-In. See Eligibility Section for further details.

Visit 2

At Visit 2, run the Visit Scheduler to determine the schedule for the treatment period (Visits 2-8).

The table below describes the STICS visit windows for Visits and Telephone Contacts. The ideal visit date is listed as the number of days from a particular visit, along with upper and lower windows.

When the visit cannot be scheduled on the ideal visit date, schedule the visit within the visit window. If a situation arises where a visit cannot take place within the visit window, please contact the scientific coordinator at the DCC for further instructions.

Note that in addition to the visit windows, the time of day of the visits should also be considered. Because of the circadian variability associated with lung function, all subsequent post-randomization visits should be scheduled such that baseline spirometry at the visit occurs within +/-3 hours of baseline spirometry at Visit 2 (randomization visit). Timing of spirometry at Visit 1 is flexible, as the collected data are being used for characterization and eligibility assessment and will not be analyzed longitudinally. If a participant cannot be scheduled in the spirometry windows, contact the STICS scientific coordinator at the DCC to seek an exception.

Run-In Phase:

Visit at which the Visit Scheduler is run.	Visit Number	Ideal Date	Lower Window	Upper Window
Visit 1	2	28 days	-5 days	+5 days

Treatment Phase:

Visit at which the Visit Scheduler is run.	Visit Number	Ideal Date	Lower Window	Upper Window
Visit 2	PC	28 days	- 5 days	+ 5 days
	3	56 days	- 5 days	+ 5 days
	PC	84 days	- 5 days	+ 5 days
	4	112 days	- 5 days	+ 5 days
	PC	140 days	- 5 days	+ 5 days
	5	168 days	- 5 days	+ 5 days
	PC	196 days	- 5 days	+ 5 days
	6	224 days	- 5 days	+ 5 days
	PC	252 days	- 5 days	+ 5 days
	7	280 days	- 5 days	+ 5 days
	PC	308 days	- 5 days	+ 5 days
	8	336 days	- 5 days	+ 5 days

2.50 YELLOW ZONES

Parent/guardian Instructions – When to Start Yellow Zones

Parents/guardians should be instructed to Start Yellow Zones if any of the following occur:

- Rescue albuterol is used twice (i.e. 4 puffs) in 6 hours
- Rescue albuterol is used three times (i.e. 6 puffs) in 24 hours
- 1 nighttime awakening due to asthma with albuterol use

Parent/guardian Instructions - What to do during Yellow Zones

Parents/guardians should be asked to review the action plan and reminded to collect nasal samples on Day 1 the illness. The nasal samples should be brought to the clinic at the next scheduled study visit. In addition, parents/guardians should be reminded to call the study site within 72 hours of starting the yellow zone.

Remind parents/guardians that they must use the yellow inhaler for exactly 7 days, no fewer than 7 days, no longer than 7 days. The green inhaler should be **stopped** while using the yellow inhaler. Once a yellow zone has occurred, the parent/guardian should wait at least 7 days before starting another yellow zone. If the parent/guardian has concerns that the participant's asthma isn't controlled, he/she should contact the site.

While there are alerts programmed to detect starting the yellow zone**, the Action Plan should be used as the primary resource for starting Yellow Zones.** Remind the parent/guardian to start the Yellow zone as soon as the participant qualifies. Do not wait for the spirotel® to tell them to do so.

Counting Yellow Zones

While parent/guardian instructions are that any 2 illnesses should be separated by at least 7 days to be considered 2 different illnesses (and necessitating collection of 2 nasal samples), mistakes are still possible. If parents/guardians do not follow directions and there are less than 7 days between 2 yellow zones, they should be reminded that 7 days should go by before starting another yellow zone next time the participant has symptoms. In terms of counting the number of yellow zones, if the difference between 2 yellow zones is 3 or more days, then they should be counted as 2 separate yellow zones. (If the difference is only 1 or 2 days, it should be counted as 1 yellow zone.)

Usage of the yellow inhaler for 2 or more consecutive days (regardless of the number of doses) should count as a yellow zone. Record the yellow zone on the STICS Prednisone and Yellow Zone Tracking Form (P7_TRK).

If you have any questions or concerns about counting the number of yellow zones, please contact the DCC for further assistance.

Yellow Zone Phone Contacts
Complete Yellow Zone Phone Assessment (P7_YELLOW_PC)

Parents/guardians should call the study site within 72 hours of starting the yellow zone. During the call, the Yellow Zone Phone Assessment Form (P7_YELLOW_PC) should be completed. The purpose of the call is to capture details about the yellow zone, determine if the participant has met the criteria for the red zone (i.e. prednisone), and make sure that the participant is following the correct procedures for the Yellow Zone.

Yellow Zones close to Visit 8

If a Yellow Zone is started within 7 days of Visit 8, Visit 8 should be rescheduled. The Yellow Zone must be completed prior to Visit 8.