4 PROTOCOL SPECIFIC FORMS AND INSTRUCTIONS

This section provides specific instructions needed to correctly complete the forms for the INFANT/AVICA study. The forms are divided into two types - data collection forms and administrative forms. Data collection forms are used to collect data from the participant. These forms are entered into the AsthmaNet database and submitted to the DCC. Administrative forms facilitate the processing of the participant and the visit flow by the clinical centers and the DCC. Administrative forms are not entered into the AsthmaNet database and they are not submitted to the DCC in most cases.

The instructions are divided into two parts - instructions for data collection forms followed by instructions for administrative forms. The instructions for both parts are in alphabetical order based on the name of the form found in the header of each form. Forms with a 'P4' prefix are INFANT/AVICA protocol specific.

For each form, the following information is provided: the purpose of the form, who completes the form, when the form should be completed, and form instructions. Most forms have a comments section (Q6000) at the bottom of the form. The coordinator can record additional comments or information related to the form in this section. This information is entered into the database management system. If you are unable to find the specific information needed to complete a form for a special circumstance, please contact the INFANT/AVICA Primary Data Manager or Secondary Data Manager at (717) 531-3663.

4.1 List of Data Collection Forms Contained in the Visit Packets

Form Name	Form Code	Refer to the AsthmaNet General MOP for Instructions
Visit 1:		
INFANT Visit Procedure Checklist Visit 1	P4_VISIT1	
Registry Checklist	REG_CHK	*
BIOLINCC Consent Tracking Form	BIOLINCC	*
INFANT Eligibility Checklist 1	P4_ELIG1	
INFANT Eligibility Checklist 2	P4_ELIG2	
INFANT Eligibility Checklist 3	P4_ELIG3	
Pediatric Asthma and Allergy History	ASTHMA_HX_PED	*
Prior Conditions for All Participants	PRIOR_COND_ALL	*
Prior Asthma/Allergy Treatment	PRIOR_TRT	*
Household Socio-Economic Information	HOUSEHOLD_SEI	*
Home Environment Questionnaire	HEQ	*
Pediatric Long Physical Exam	LEXAM_PED	*
Visit 2:		
INFANT Visit Procedure Checklist Visit 2	P4_VISIT2	
INFANT Eligibility Checklist 4	P4_ELIG4	
INFANT Eligibility Checklist 5	P4_ELIG5	
Pediatric Short Physical Exam	SEXAM_PED	*
INFANT Laboratory Results	P4_LAB	
Genetic Analysis Blood Draw	GABLOOD	*
INFANT Medications	P4_INFANT_MED	
AVICA Medication	P4_AVICA_MED	
Visits 3, 5, 7:		
INFANT Visit Procedure Checklist Visits 3, 5, 7	P4_VISIT3_5_7	
INFANT Compliance Checklist	P4_INFANT_COMPLY	
AVICA Compliance Checklist	P4_AVICA_COMPLY	
AVICA Medication Diary	P4_AVICA_DIARY	
Phone/Visit Symptom Assessment	P4_PHONE_CONTACT	
Pediatric Short Physical Exam	SEXAM_PED	*
AVICA Medication	P4_AVICA_MED	

Form Name	Form Code	Refer to the AsthmaNet General MOP for Instructions
Visit 4, 6:		
INFANT Visit Procedure Checklist Visits 4, 6	P4_VISIT4_6	
INFANT Compliance Checklist	P4_INFANT_COMPLY	
AVICA Compliance Checklist	P4_AVICA_COMPLY	
AVICA Medication Diary	P4_AVICA_DIARY	
Phone/Visit Symptom Assessment	P4_PHONE_CONTACT	
Pediatric Short Physical Exam	SEXAM_PED	*
INFANT Study Treatment Questionnaire	P4_INFANT_TRTQX	
INFANT Medications	P4_INFANT_MED	
AVICA Medication	P4_AVICA_MED	
Visit 3a/3b, 5a/5b, 7a/7b:		
INFANT Phone Contacts Visit Procedure Checklist	P4_VISIT_PC	
Phone/Visit Symptom Assessment	P4_PHONE_CONTACT	
Visit 8:		
INFANT Visit Procedure Checklist Visit 8	P4_VISIT8	
INFANT Compliance Checklist	P4_INFANT_COMPLY	
AVICA Compliance Checklist	P4_AVICA_COMPLY	
AVICA Medication Diary	P4_AVICA_DIARY	
Phone/Visit Symptom Assessment	P4_PHONE_CONTACT	
Pediatric Short Physical Exam	SEXAM_PED	*
INFANT Study Treatment Questionnaire	P4_INFANT_TRTQX	
AVICA Study Treatment Questionnaire	P4_AVICA_TRTQX	
Termination of INFANT	P4_INFANT_TERM	
Termination of AVICA	P4_AVICA_TERM	

4.2 Data Collection Forms

Data collection forms are used to record data for use in the study analysis. Packet collection data forms are found only in visit-specific packets, and they are entered and submitted to the DCC as complete packets. Individual data collection forms (single forms) are entered and submitted on an as-needed basis. All concurrent forms should be submitted when the participant concludes his or her participation in the INFANT study. Some forms (example: Termination of INFANT) can be submitted as part of a visit packet or as a single form. The following is a list of the data collection forms alphabetized by form name, indicating if each is considered to be a packet form, a single form, or both for the INFANT/AVICA protocols. Instructions for all the AsthmaNet Standard Forms can be found in the AsthmaNet General MOP. For more details on packet form entry and single form entry, see Section 7 of the AsthmaNet General MOP.

Form Name	Form Code	Packet	Single	Concurrent
AVICA Compliance Checklist	P4_AVICA_COMPLY	*	*	
AVICA Medication	P4_AVICA_MED	*	*	
AVICA Medication Diary	P4_AVICA_DIARY	*	*	
AVICA Study Failure	P4_AVICA_FAIL		*	
AVICA Study Treatment Questionnaire	P4_AVICA_TRTQX	*	*	
Biolincc Consent Tracking Form	BIOLINCC	*		
Clinical Adverse Events	AECLIN			*
Concomitant Medications for Asthma/Allergy Related Drugs	CMED			*
Genetic Analysis Blood Draw	GABLOOD	*	*	
Home Environment Questionnaire	HEQ	*	*	
Household Socio-Economic Information	HOUSEHOLD_SEI	*		
INFANT Compliance Checklist	P4_INFANT_COMPLY	*	*	
INFANT Eligibility Checklist 1	P4_ELIG1	*		
INFANT Eligibility Checklist 2	P4_ELIG2	*		
INFANT Eligibility Checklist 3	P4_ELIG3	*		
INFANT Eligibility Checklist 4	P4_ELIG4	*		
INFANT Eligibility Checklist 5	P4_ELIG5	*		

Form Name	Form Code	Packet	Single	Concurrent
INFANT Laboratory Tests	P4_LAB	*	*	
INFANT Medications	P4_INFANT_MED	*	*	
INFANT Prednisolone Medication	P4_PRED		*	
INFANT Study Failure	P4_INFANT_FAIL		*	
INFANT Study Treatment Questionnaire	P4_INFANT_TRTQX	*	*	
INFANT Treatment Arm Failure	P4_INFANT_TRTFAIL		*	
Pediatric Asthma and Allergy History	ASTHMA_HX_PED	*		
Pediatric Long Physical Exam	LEXAM_PED	*		
Pediatric Short Physical Exam	SEXAM_PED	*		
Phone/Visit Symptom Assessment	P4_PHONE_CONTACT	*		
Prior Asthma/Allergy Treatment	PRIOR_TRT	*		
Prior Conditions for All Participants	PRIOR_COND_ALL	*		
Registry Checklist	REG_CHK	*		
Serious Adverse Event Reporting Form	SERIOUS		*	
Termination of AVICA	P4_AVICA_TERM	*	*	
Termination of INFANT	P4_INFANT_TERM	*	*	
Termination of INFANT Run-In	P4_TERMR		*	

4.2.1 AVICA Compliance Checklist (P4_AVICA_COMPLY)

Purpose: To record participant's adherence for the AVICA therapy.

Who: An AsthmaNet Coordinator completes the form.

When: As a packet form at Visits 2 – 8, or as a single form at Visits 2 – 7.

Form Instructions:

If completed between scheduled visits, record the last completed visit in the **Visit Number** field and the current date in the **Visit Date** field. If the last completed visit was a phone visit, enter the form with the visit number of the last in clinic visit (i.e. if the participant terminates at Visit 5a, enter the form at visit 5).

Question 1000. Indicate if the participant has used AVICA therapy since the last visit. If Q1000 is answered 'No', ***stop*** completion of the form. Otherwise complete Q1010.

Question 1010. Indicate if the parent/guardian completed and returned the Parental AVICA Study Medication Diary.

Question 1020. Indicate if the parent/guardian returned the AVICA medication bottle. If Q1020 is answered 'No', ***stop*** completion of the form. Otherwise complete Q1030.

Questions 1030 - 1040. Record the bottle number and bottle weight in grams. Round to the closest whole gm when completing Q1040 for the weight of the bottle. The change in adherence is less than 1% due to rounding and it has been determined that this is acceptable. We are attempting to ensure the parent is giving the correct dose and following directions when giving the medications to the participant.

If more than one AVICA bottle was used since the last visit, please complete a P4_AVICA_COMPLY form for **each** AVICA bottle used. One bottle should be recorded on the P4_AVICA_COMPLY packet form and the second should be recorded on a P4_AVICA_COMPLY single form.

4.2.2 AVICA Medication (P4_AVICA_MED)

Purpose: To record the dispensation of AVICA study drugs.

Who: An AsthmaNet Coordinator completes the form.

When: Packet form at Visits 2 – 7, single form at Visits 2 – 7.

Form Instructions:

The AVICA Medications form must be completed ***every*** time AVICA study medication is dispensed at a visit. The form will be entered as a packet form at Visits 2-7 and can be entered as a single form at Visits 2 – 7 as needed

The AVICA Medication dose must be calculated and entered at each study visit.

At Visits 3, 5, and 7 if the AVICA Medication dose has not changed and the participant has not used AVICA Medication since the last study visit a new bottle of AVICA does not need to be dispensed. The entire form (Q1000-Q1030) should be completed, the bottle number of the previously dispensed AVICA bottle should be recorded in Q1010.

A new bottle of AVICA *must* be dispensed at Visits 2, 4, and 6 and the entire form (Q1000-Q1030) should be completed
If AVICA medication is distributed between scheduled visits, record the last completed visit in the **Visit Number** field and the current date in the **Visit Date** field. If the last completed visit was a phone visit, enter the form with the visit number of the last in clinic visit (i.e. if the participant terminates at Visit 5b, enter the form at visit 5).

Question 1. Enter the participant's current weight that was recorded in Q1130 on the SEXAM_PED form on the day of the visit. This value will not be entered into the database, it is a reference to determine the participant's AVICA medication dose. If the medication is being dispensed at an unscheduled visit and the participant is not present, use the weight recorded in Q1130 on the SEXAM_PED form at the last completed visit.

Question 1000. Record the participant's AVICA medication dose using the table on the form and the participant's weight recorded in Question 1.

Question 1010. Copy the drug label number onto the space provided in Question 1010.

Questions 1020 and 1030. It is important that the ID of the participant receiving the AVICA medications matches the information provided by the randomization module and that this information is recorded on the AVICA Participant Drug Log: Post-Randomization Study Medications (P4_AVICA_PART). The drug dispensation should also be recorded on the AVICA Drug Accountability Log: AVICA Medication (P4_AVICA_LOG). To verify that the information collected on this form is correct and

that it is documented correctly, the Clinic Coordinator should sign and date the source documentation box (Q1020 and Q1030).

4.2.3 AVICA Medication Diary (P4_AVICA_DIARY)

Purpose: To record the date, number of doses, and reason for AVICA study medication use.

Who: An AsthmaNet Coordinator completes the form.

When: Packet form at Visits 3 – 8, and single form at Visits 2 – 7.

Form Instructions:

The coordinator should use the Parental AVICA Study Medication Diary (P4_PARENT_DIARY) to complete this form. The Parental AVICA Study Medication Diary (P4_PARENT_DIARY) is completed by the parent/guardian at home each time AVICA medication is used. If the participant has not used AVICA medication since the last study visit or if the parent/guardian forgets to return the Parental AVICA Study Medication Diary (P4_PARENT_DIARY), this form can be set to missing during data entry.

If completed between scheduled visits, record the last completed visit in the **Visit Number** field and the current date in the **Visit Date** field. If the last completed visit was a phone visit, enter the form with the visit number of the last in clinic visit (i.e. if the participant terminates at Visit 7a, enter the form at visit 7).

Question 1000. Number each record with a unique and chronological number with the first recorded numbered as 1. During entry, users will be stopped on saving a record if a duplicate record number is entered on a form. Across visits (i.e., form entries), the first record should begin with 1.

Questions 1010-1030. When entering these dates during data entry, the month, day, and year are each represented by a separate entry field. The first box represents the month. Only enter the month into this box. The leading zeros can be left out. The second box represents the day. Only enter the day of the month into this box. The leading zeros can be left out. The third box represents the year. Only enter the year into this box. The year must be entered as four digits. For example, when entering 01/10/2010, enter 01 or 1 into the first box, enter 10 into the second box, and enter 2010 into the third box.

Partial dates can also be entered during data entry for these fields by leaving the box for the unknown information blank. If the day is missing, the month and year can be entered. If the parent does not know at least the month and year, the data should not be entered, and the row should be deleted.

If a complete date is entered, all doses given must be recorded in one record (i.e., Q1010 – Q1030 must be unique)

Question 1040. Record the number of doses of AVICA study medication the participant took on the specified date.

Question 1050. Record the primary reason for AVICA study medication use on the specified day. Record 1 to indicate fever, 2 to indicate discomfort, fussiness, irritability and/or pain, and 3 to indicate any other reason not captured by 1 or 2.

Question 1060. Indicate whether the participant was experiencing cold or flu symptoms on the specified day.

4.2.4 AVICA Study Failure (P4_AVICA_FAIL)

Purpose: To record the date and the events that occurred when a participant is deemed an AVICA study failure.

Who: An AsthmaNet Coordinator completes the form.

When: This form is completed when a participant has met the AVICA study failure criteria at Visits 2 – 8.

Form Instructions:

For more details on Study Failures, see the Study Failure discussion in Section 2 of the INFANT/AVICA MOP.

Complete the AVICA Study Failure (P4_AVICA_FAIL) form ***only*** if the participant has met AVICA study failure criteria. If the form is completed between visits, specify the ***Last Visit Number completed*** and ***Current Date*** in the upper right-hand corner. The AVICA Study Failure (P4_AVICA_FAIL) form must be entered into the database as a single form.

If the participant is deemed an AVICA study failure at a study visit complete the current visit number and current date on the AVICA Study Failure (P4_AVICA_FAIL) form.

Questions 1000 – 1030. If the answer to any of these questions is 'Yes' the participant is an AVICA study failure.

Question 1040. If any of the shaded boxes are selected (Q1000 - Q1030), the participant is an AVICA study failure.

Question 1050. Indicate the date AVICA study failure status occurred.

Questions 1060-1080. To verify that the information collected on this form is correct the Attending Physician must sign, date, and indicate the time in the source documentation box provided at the bottom of the form. Record the time based on a 24-hour clock (military time).

When an AVICA study failure occurs complete the Termination of AVICA (P4_AVICA_TERM) and the AVICA Study Treatment Questionnaire (P4_AVICA_TRTQX), collect any remaining AVICA medications and complete the P4_AVICA_COMPLY and P4_AVICA_DIARY forms as single forms.

4.2.5 AVICA Study Treatment Questionnaire (P4_AVICA_TRTQX)

Purpose: To assess how well controlled the child's fever/pain was throughout the study. This form also questions which treatment the parent/guardian and Clinic Coordinator thinks the child was receiving during the study.

Who: Parent/Guardian completes page 1 and an AsthmaNet Coordinator completes page 2.

When: Packet form at Visit 8, and single form at Visits 2 – 7.

Form Instructions:

This form can be entered as a packet form at Visit 8. This form can also be entered as a single form at Visits 2 – 7.

If completed between scheduled visits, record the last completed visit in the **Visit Number** field and the current date in the **Visit Date** field. If the last completed visit was a phone visit, enter the form with the visit number of the last in clinic visit (i.e. if the participant terminates at Visit 7b, enter the form at visit 7).

Page 2 should be completed by the clinic coordinator. Q1060 is on the last page and should be completed prior to the parent/guardian completing Q1000 – Q1050 so that the Clinic Coordinator is not influenced by the parent/guardian responses.

After a randomized participant has completed the AVICA study, give the AVICA Study Questionnaire (P4_AVICA_TRTQX) to the participant's parent/guardian to complete. Do not give the parent/guardian page 2 of the form. If the parent does not complete the P4_AVICA_TRTQX the form can be set to missing.

Page 1 (Q1000 – Q1050) is completed by the parent/guardian. Please be sure that the parent/guardian cannot see the response to Q1060 (coordinator completed question) when completing Q1000 – Q1050.

4.2.6 INFANT Compliance Checklist (P4_INFANT_COMPLY)

Purpose: To determine participant's compliance to spirotel® session completion and INFANT study medications.

Who: An AsthmaNet Coordinator completes the form.

When: Packet form at Visits 2 – 8, and single form at Visits 2 – 7.

Form Instructions:

The information for Q1000-1060 is obtained from the participant's spirotel® Participant Compliance Report (P4_COMPLY_RPT) at Visits 3 – 8.

If completed between scheduled visits, record the last completed visit in the **Visit Number** field and the current date in the **Visit Date** field. If the last completed visit was a phone visit, enter the form with the visit number of the last in clinic visit (i.e. if the participant terminates at Visit 3a, enter the form at visit 3).

Questions 1100-1060. The values will be transcribed directly from the spirotel® Participant Compliance Report; the field annotations and text from the INFANT Compliance Checklist (P4_INFANT_COMPLY) are used to display the results.

4.2.7 INFANT Eligibility Checklist 1 (P4_ELIG1)

Purpose: This eligibility form is completed during Visit 1. The form consists of basic interview questions, which assist in the determination of a participant's eligibility to enter the study.

Who: An AsthmaNet Coordinator completes the form.

When: Visit 1

Form Instructions:

For further guidance refer to the Eligibility Criteria in Section 2 of the INFANT/AVICA MOP.

Questions 1000 – 1010. The child's parent or guardian must display willingness to provide informed consent for the INFANT study. If the study consent form was signed in advance of Visit 1, it should be reviewed by the parent/guardian at the time of enrollment. The parent/guardian should then update the consent date and initial the change.

Questions 1020-1030. The child's parent or guardian must display willingness to provide informed consent for the AVICA study. If the study consent form was signed in advance of Visit 1, it should be reviewed by the parent/guardian at the time of enrollment. The parent/guardian should then update the consent date and initial the change.

Questions 1040 – 1070. The participant must be able to take the study medications. If the participant has an intolerance or allergy to fluticasone, montelukast, ibuprophen, acetaminophen, oral corticosteroids (Decadron, Dexamethasone, Orapred, Prelone, Pediapred, prednisone) or albuterol he/she is not eligible for INFANT.

Question 1080. The participant must be 12 to 59 months old at time of enrollment. Persons who are less than 12 months old **OR** 59 months old or older at the time of *enrollment* are not eligible for INFANT.

Question 1090. If the participant was born earlier than 35 weeks gestation, he/she is not eligible for INFANT.

Questions 1100 – 1110. The participant must be up-to-date with immunizations to be eligible for INFANT. The parent/guardian's word is sufficient.

Chicken pox immunization must be acquired by the participant (unless the participant has already had chicken pox). If the participant needs the chicken pox vaccine, this will be arranged with the primary AsthmaNet physician and must be received prior to randomization.

Questions 1120 – 1130. If the participant is receiving allergy shots AND the dose has been changed in the past 3 months, he/she is ineligible to participate in INFANT.

Questions 1140 – 1200. If the participant has had any immunodeficiency disorders, uncontrolled gastroesophageal reflux, concurrent medical conditions other than asthma that are likely to require oral or injectable corticosteroids during the study, any chronic or active lung disease other than asthma, he/she is ineligible to participant in INFANT.

Question 1210. If the participant has significant developmental delay or failure to thrive, he/she is not eligible to participate in INFANT.

Question 1220. If the participant has other significant medical illnesses as listed on the P4_EXCLMED reference card, he/she is not eligible to participate in INFANT.

Questions 1230 – 1240. Record the number of oral or systemic corticosteroid courses the participant has had within the past 6 months. If the number of courses is greater than or equal to 5, he/she is not eligible to participate in INFANT.

Question 1246. If the participant has used an oral or systemic corticosteroid for any reason in the past 2 weeks, he/she is not eligible to participant in INFANT.

Question 1244. Record the number of oral or systemic corticosteroid courses the participant has had within the past 12 months.

Question 1246. If the participant has used oral or systemic corticosteroids for any reason in the past 2 weeks, he/she is not eligible to participant in INFANT.

Question 1250. If the participant does not have a primary medical caregiver, he/she is not eligible to participate in INFANT.

Questions 1260 – 1320. This section includes the collection of data on other criteria that might make the participant ineligible to participate in the study.

If the participant has been hospitalized for wheezing illnesses 3 or more times, has experienced an asthma exacerbation resulting in intubation or assisted ventilation, is currently or within the past month involved in an investigational drug trial, or the family has plans to move out of the area before the end of the study, he/she is ineligible to participate in INFANT.

Question 1320. If there is any other reason why the participant cannot be included in the study and the response to Q1320 is ‘Yes’, please provide a description of the reason in Q1320D.

Question 1330. If any of the shaded boxes are selected, the participant is ineligible. ***Stop*** completion of the form.

When a participant is ineligible at Visit 1, the packet is not entered into the database.

Questions 1340. Indicate if the participant has been treated with a controller therapy in the past 4 weeks. If the response to Q1340 is 'No' complete the **P4_ELIG3** form. Do not complete the P4_ELIG2 form and mark the P4_ELIG2 form missing during data entry. Otherwise, proceed to Q1350.

Questions 1350 – 1820. If the participant has been treated with a controller therapy during the past 4 weeks, complete the table checking all controller therapies that apply.

If any of the doses are greater than the limit per day defined in column 6 of the table for each medication OR if the participant is taking more than 1 controller therapy and the second controller therapy is not an LTRA, he/she is not eligible to participate in INFANT.

Question 1830. If Q1830 is answered 'Yes', ***stop*** completion of the form, the participant is not eligible to participant in INFANT. When a participant is ineligible at Visit 1, the packet is not entered into the database.

Question 1840. If Q1840 is answered 'No' proceed to the **P4_ELIG2** form. Do not complete the P4_ELIG3 form and mark the P4_ELIG3 form missing during data entry.
If Q1840 is answered 'Yes', ***stop*** completion of the form, the participant is not eligible to participant in INFANT. When a participant is ineligible at Visit 1, the packet is not entered into the database.

4.2.8 INFANT Eligibility Checklist 2 (P4_ELIG2)

Purpose: This eligibility form is completed during Visit 1 for participants who have been treated with a controller therapy in the past 4 weeks (P4_ELIG1 Q30 is answered Yes).

Who: An AsthmaNet Coordinator completes the form.

When: Visit 1

Form Instructions:

This form should only be completed for participants who have been treated with a controller therapy in the past 4 weeks (Question 30 (Q1340) on the P4_ELIG1 form should be answered 'Yes'). If the participant has not been treated with a controller therapy in the past 4 weeks this form should not be completed and this form should be marked missing during data entry.

Question 1000. Indicate whether the participant is currently taking both ICS and LTRA. If the answer to Q1000 is 'No' skip to Q1030. If Q1000 is answered 'Yes' complete Q1010.

Question 1010. Indicate if the participant takes LTRA for reasons other than asthma. If Q1010 is answered 'Yes' the study physician should be consulted to determine if the participant can discontinue use of the LTRA and Q1020 should be completed.
If Q1010 is answered 'No' the participant is ineligible for INFANT, skip to Q1180. When a participant is ineligible at Visit 1, the packet is not entered into the database.

Question 1020. Indicate if the LTRA can be discontinued per the study physician. If Q1020 is answered 'No' the participant is ineligible for INFANT, skip to Q1180. When a participant is ineligible at Visit 1, the packet is not entered into the database.

Questions 1030-1050. Record the number of months the participant has been treated with a daily controller therapy during the past 6 months. If the response to Q1030 is less than 3, Q1040 should be answered 'No' and skip to Q1060. If the response to Q1030 is greater than 3 complete Q1050.

Questions 1060-1070. Record the number of wheezing episodes the participant had in the past 12 months. A wheezing episode is defined as 24 hours or more of symptoms. Note that the response to Q1070 should be recorded in Q1160 on the P4_ELIG4 form prior to Visit 2.

Questions 1080-1090. Record the number of asthma exacerbations requiring systemic corticosteroids the participant had in the past 12 months. Note that the response to Q1090 should be recorded in Q1170 on the P4_ELIG4 form, prior to Visit 2.

Questions 1100-1110. Record the number of days the participant had daytime asthma symptoms in the past 4 weeks.

Questions 1120-1130. Record the number of nights the participant had nighttime awakenings due to asthma in the past 4 weeks.

Question 1140. If either Q1070 or Q1090 is answered 'Yes' (i.e. the participant had 4 or more wheezing episodes or 2 or more asthma exacerbations requiring corticosteroids in the past 12 months), Q1140 should be completed, otherwise skip to Q1150.

Question 1150. If either Q1110 or Q1130 is answered 'Yes' (i.e. the participant had more than 8 days of daytime symptoms or more than 1 nighttime awakening in the past 4 weeks), Q1150 should be completed, otherwise skip to Q1170.

Question 1160. If Q1150 is answered 'Yes' Q1160 should be completed, otherwise skip to Q1170.

Question 1170. If there is any other reason why the participant cannot be included in the study and the response to Q1170 is 'Yes', please provide a description of the reason in Q1170D.

Question 1180. If any of the shaded boxes are selected, the participant is ineligible.

When a participant is ineligible at Visit 1, the packet is not entered into the database.

Run-In Study Medications:
If any of the starred (*) responses are selected (see Q1050, Q1140, Q1150 and Q1160), the participant should be enrolled in the study with either active LTRA ***or*** active ICS Run-in medication.

- If the participant is currently taking ICS, the Run-In will be with **active ICS** and **placebo LTRA**.
- If the participant is currently taking LTRA, the Run-In will be with **active LTRA** and **placebo ICS.**

If none of the starred (*) responses are selected (see Q1050, Q1140, Q1150 and Q1160), the participant should be enrolled with placebo ICS and placebo LTRA.

Questions 1190-1200. Record the type of LTRA and ICS the participant will be using during the Run-in period.

4.2.9 INFANT Eligibility Checklist 3 (P4_ELIG3)

Purpose: This eligibility form is completed during Visit 1 for participants who have NOT been treated with a controller therapy in the past 4 weeks (P4_ELIG1 Q30 is answered No).

Who: An AsthmaNet Coordinator completes the form.

When: Visit 1.

Form Instructions:
This form should only be completed for participants who have NOT been treated with a controller therapy in the past 4 weeks (Question 30 (Q1340) on the P4_ELIG1 form should be answered 'No'). If the participant has been treated with a controller therapy in the past 4 weeks this form should not be completed and this form should be marked missing during data entry.

Questions 1000-1010. Record the number of days the participant had daytime asthma symptoms in the past 4 weeks.

Questions 1020-1030. Record the number of nights the participant had nighttime awakenings due to asthma in the past 4 weeks.

Questions 1040-1050. Record the number of wheezing episodes the participant had in the past 12 months. A wheezing episode is defined as 24 hours or more of symptoms. Note that the response to Q1050 should be recorded in Q1160 on the P4_ELIG4 form prior to Visit 2.

Questions 1060-1070. Record the number of asthma exacerbations requiring systemic corticosteroids the participant had in the past 6 months. Note that the response to Q1070 should be recorded in Q1170 on the P4_ELIG4 form, prior to Visit 2.

Question 1080. In order for the participant to be eligible for the study he/she must exhibit a minimum number of asthma symptoms. The symptom requirement is evaluated using questions Q1010, Q1030, Q1050, and Q1070. If any of the starred (*) responses to these questions are selected, Q1080 should be answered 'Yes'.

Question 1090. If there is any other reason why the participant cannot be included in the study and the response to Q1090 is 'Yes', please provide a description of the reason in Q1090D.

Question 1100. If the participant is eligible for the study he/she should be enrolled with **placebo** LTRA and **placebo** ICS medication during the Run-In.
If any of the shaded boxes are selected, the participant is ineligible. When a participant is ineligible at Visit 1, the packet is not entered into the database.

4.2.10 INFANT Eligibility Checklist 4 (P4_ELIG4)

Purpose: This eligibility form is completed during Visit 2 or participants who were on PLACEBO medication during the Run-in.

Who: An AsthmaNet Coordinator completes the form.

When: Visit 2.

Form Instructions:

For further guidance refer to the Eligibility Criteria in Section 2 of the INFANT/AVICA MOP.

This form should only be completed for participants who were on *placebo* LTRA and *placebo* ICS during the Run-in. If the participant was on active LTRA ***or*** active ICS during the Run-in this form should not be completed and this form should be marked missing during data entry.

Question 1000. If the participant had any exacerbations requiring systemic corticosteroids since Visit 1 he/she is not eligible to participant in the study. If the response to Q1000 is 'Yes' complete Q1010 and record the exacerbation on the AECLIN form, otherwise skip to Q1020.

Question 1010. If the participant was hospitalized due to an exacerbation, complete the SERIOUS form and skip to Q1200.

Question 1020. If the participant has used any asthma medication other than albuterol since Visit 1 ***stop*** completion of the form and repeat the 2 week Run-In. Note that the Run-In can only be repeated once (see Section 2 of the MOP for details). Any forms that were completed at this visit should be filed in the participant folder and should not be entered into the database. A new Visit 2 packet should be completed at the visit following the repeated 2 week Run-in.

Question 1030. If the participant has developed any new medical conditions the study physician should be consulted to determine if the participant is still eligible for the study.

Questions 1040-1090. These values are obtained from the spirotel® INFANT Eligibility Report (P4_ELIG_RPT)*. The format of the report will match the field annotations and question text of the INFANT Eligibility Checklist 4 (P4_ELIG4) form.

If the compliance for the Diary Completion, Brown Daily Inhaler, and/or Oral Study Medication is less than 75%, he/she is not eligible for the study.

Questions 1100-1120. The response to Q1100 should be recorded from the spirotel® INFANT Eligibility Report (P4_ELIG_RPT)*. If the participant had daily asthma symptoms 7 days per week, he/she is not eligible for the study.

*Note: If the Run-In period was less than 14 days the compliance calculations for Q1040, Q1060, Q1080, and Q1100 will be inaccurate and must be re-calculated by the Clinic Coordinator using the data in the bottom half of the spirotel® INFANT Eligibility Report (P4_ELIG_RPT). To determine the number of days in the Run-In period count the number of calendar days between Visit 1 and Visit 2, including the Visit 1 date and excluding the Visit 2 date. For example if Visit 1 occurred on 1/1/13 and Visit 2 occurred on 1/12/13 the Run-In period would be 11 days (1/1/13-1/11/13).

To calculate Q1040: Divide the number of days where the PM scheduled session is complete by the number of days in the Run-In period and multiply by 100. Round to the nearest tenth of a percent and record the value in Q1040. For example, if the Run-In period is 12 days and the number of days the PM session is complete was 10: (10/12) X 100 = 83.33333, so you would record 83.3 in Q1040.
To calculate Q1060: Divide the number of puffs that were used from the brown daily inhaler by the number of days in the Run-In period, multiplied by 4. Then multiply by 100. Round to the nearest tenth of a percent and record the value in Q1060. For example if the Run-In period is 12 days and the number of puffs used from the brown daily inhaler is 40: (40/(12x4)) X 100 = 83.33333, so you would record 83.3 in Q1060.

To calculate Q1080: Divide the number of days where oral study medication was taken by the number of days in the Run-In period and multiply by 100. Round to the nearest tenth of a percent and record the value in Q1080. For example if the Run-In period is 13 days and the number days where oral study medication was taken is 12: (12/13) X 100 = 92.307, so you would record 92.3 in Q1080.

To calculate Q1110: Multiply the number of days with at least one asthma symptom with a score of 1 or higher by 7 and then divide this number by the number of days in the Run-In period. Round to the nearest tenth and record the value in Q1110. For example if the Run-In period is 13 days and asthma symptoms occurred on 5 days: (5 x 7)/13 = 2.692, so you would record 2.7 in Q1100.

Q1130 Does not need to be recalculated if there are fewer than 14 days in the Run-In period.

Questions 1130-1150. The response to Q1130 should be recorded from the spirotel® INFANT Eligibility Report. If the participant had more than 1 nighttime awakening from asthma, he/she is not eligible for the study.

Question 1160. The response to Q1160 should be recorded from Q1070 on the P4_ELIG2 form *or* Q1040 on the P4_ELIG3 form (whichever form was completed at Visit 1).

Question 1170. The response to Q1170 should be recorded from Q1230 on the P4_ELIG1 form.

Question 1180. In order for the participant to be eligible for the study he/she must exhibit a minimum number of asthma symptoms. The symptom requirement is evaluated using questions Q1120, Q1150, Q1160, and Q1170. If any of the starred (*) responses to these questions are selected, Q1180 should be answered 'Yes'.

Question 1190. If there is any other reason why the participant cannot be included in the study and the response to Q1190 is 'Yes', please provide a description of the reason in Q1090D.

Question 1200. If any of the shaded boxes are selected, the participant is ineligible. If the participant is ineligible based on P4_ELIG4 form, do not continue the Visit 2 procedures and mark the rest of the packet forms missing during data entry. Complete the P4_TERMR form single form, and enter it as a Visit 2 single form.

4.2.11 INFANT Eligibility Checklist 5 (P4_ELIG5)

Purpose: This eligibility form is completed during Visit 2 for participants who were on ACTIVE medication during the Run-In.

Who: An AsthmaNet Coordinator completes the form.

When: Visit 2

Form Instructions:

For further guidance refer to the Eligibility Criteria in Section 2 of the INFANT/AVICA MOP.

This form should only be completed for participants who were on active LTRA ***or*** active ICS during the Run-in. If the participant was on placebo LTRA ***and*** placebo ICS during the Run-in this form should not be completed and during data entry this form should be marked missing.

Question 1000. If the participant had any exacerbations requiring systemic corticosteroids since Visit 1 he/she is not eligible to participant in the study. If the response to Q1000 is 'Yes' complete Q1010 and record the exacerbation on the AECLIN form, otherwise skip to Q1020.

Question 1010. If the participant was hospitalized due to an exacerbation complete the SERIOUS form and skip to Q1200.

Question 1020. Indicate if the participant has used any asthma medication other than albuterol since Visit 1.

Question 1030. If the participant has developed any new medical conditions the study physician should be consulted to determine if the participant is still eligible for the study.

Questions 1040-1090. These values are obtained from the spirotel® INFANT Eligibility Report (P4_ELIG_RPT)*. The format of the report will match the field annotations and question text of the INFANT Eligibility Checklist 5 (P4_ELIG5) form.

If the compliance for the Diary Completion, Brown Daily Inhaler, and/or Oral Study Medication is less than 75%, he/she is not eligible for the study.

Questions 1100. The response to Q1100 should be recorded from the spirotel® INFANT Eligibility Report (P4_ELIG_RPT)*.

Questions 1110-1120. If the participant had daily asthma symptoms 7 days per week, he/she is not eligible for the study, skip to Q1160. If the participant had daytime asthma symptoms 2 – 7 days per week, ***stop*** completion of the form and repeat the 2 week

Run-In. Any forms that were completed at this visit should be filed in the participant folder and should not be entered into the database. A new Visit 2 packet should be completed at the visit following the repeated 2 week Run-in.

*Note: If the Run-In period was less than 14 days the compliance calculations for Q1040, Q1060, Q1080, and Q1100 will be inaccurate and must be re-calculated by the Clinic Coordinator using the data in the bottom half of the spirotel® INFANT Eligibility Report (P4_ELIG_RPT). To determine the number of days in the Run-In period count the number of calendar days between Visit 1 and Visit 2, including the Visit 1 date and excluding the Visit 2 date. For example if Visit 1 occurred on 1/1/13 and Visit 2 occurred on 1/12/13 the Run-In period would be 11 days (1/1/13-1/11/13).

To calculate Q1040: Divide the number of days where the PM scheduled session is complete by the number of days in the Run-In period and multiply by 100. Round to the nearest tenth of a percent and record the value in Q1040. For example, if the Run-In period is 12 days and the number of days the PM session is complete is 10: (10/12) X 100 = 83.33333, so you would record 83.3 in Q1040.

To calculate Q1060: Divide the number of puffs that were used from the brown daily inhaler by the number of days in the Run-In period, multiplied by 4. Then multiply by 100. Round to the nearest tenth of a percent and record the value in Q1060. For example if the Run-In period is 12 days and the number of puffs used from the brown daily inhaler is 40: (40/(12x4)) X 100 = 83.33333, so you would record 83.3 in Q1060.

To calculate Q1080: Divide the number of days where oral study medication was taken by the number of days in the Run-In period and multiply by 100. Round to the nearest tenth of a percent and record the value in Q1080. For example if the Run-In period is 13 days and the number days where oral study medication was taken is 12: (12/13) X 100 = 92.307, so you would record 92.3 in Q1080.

To calculate Q1110: Multiply the number of days with at least one asthma symptom with a score of 1 or higher by 7 and then divide this number by the number of days in the Run-In period. Round to the nearest tenth and record the value in Q1110. For example if the Run-In period is 13 days and asthma symptoms occurred on 5 days: (5 x 7)/13 = 2.692, so you would record 2.7 in Q1110.

Q1130 Does not need to be recalculated if there are fewer than 14 days in the Run-In period.

Questions 1130-1140. The response to Q1130 should be recorded from the spirotel® INFANT Eligibility Report. If the participant had more than 1 nighttime awakening from asthma, ***stop*** completion of the form and repeat the 2 week Run-In. Any forms that were completed at this visit should be filed in the participant folder and should not be entered into the database. A new Visit 2 packet should be completed at the visit following the repeated 2 week Run-in.

Question 1150. If there is any other reason why the participant cannot be included in the study and the response to Q1150 is 'Yes', please provide a description of the reason in Q115D.

Question 1160. If any of the shaded boxes are selected, the participant is ineligible. If the participant is ineligible based on P4_ELIG5 form, do no continue the Visit 2 procedures and mark the rest of the packet forms missing during data entry. Complete the P4_TERMR form, and enter it as a Visit 2 single form.

4.2.12 INFANT Laboratory Results (P4_LAB)

Purpose: To record blood test results, and blood, urine and nasal sample collection information.

Who: An AsthmaNet Coordinator completes the form.

When: Packet form at Visit 2 and a single form at Visits 2 – 8.

Form Instructions:

The Laboratory Tests (P4_LAB) form is entered into the database as a packet form at Visit 2. If the coordinator is unable to collect blood and/or urine at Visit 2, samples can be collected at a later visit. Each sample should only be collected once. For example, if blood is collected at Visit 2, but urine could not be obtained, only attempt urine collection at later visits. Nasal Samples are collected by the parent/guardian at home between visits, the information is not collected on a form.

Question 1000. Indicate if a blood sample was collected. If Q1000 is answered 'No' skip to Q1070.

Question 1010. Record the White Blood Count (WBC) result. If the units are 'x10E9/L', 'TH/mm3' or 'THOU/UL', then multiply by 1000 and you would record the calculated value on the P2_LAB form. For example if your lab report indicates a value of 8.0 you should multiply that by 1000 and report the value on the P4_LAB form as 8000/cu.mm.

Submit the original local lab report with the participant's visit packet. The coordinator should record the participant's ID number in the upper right-hand corner of the report. All identifying information (name, medical record number, etc.) should be blackened-out prior to forwarding the report to the DCC with the packet. If the DCC receives a report for which the identifying information has not been blackened-out, a protocol violation may be assigned.

Question 1020. Record the Eosinophil result. If the eosinophil count is not reported as a percentage, it can be calculated. To convert the eosinophil to a percent, you should divide it by the WBC value and multiple it by 100. For example 0.23/8.0 X 100 = 2.9%.

Questions 1030 - 1060. Indicate if each blood sample type was collected. Record each sample collected on the appropriate log (P4_IGE_LOG, GEN_SAMP_LOG P4_META_LOG and/or P4_GLUT_LOG) and enter all biological samples into the BST and any genetic samples into the GST.

Question 1070. Indicate if a urine sample was collected. If a urine sample was collected record the sample on the P4_URINE_LOG and enter the sample into the BST.

Questions 1080-1090. Indicate if a nasal sample was collected. If Q1080 is answered 'Yes', Q1090 should be completed to indicate which technique was used. If a nasal sample was collected record the sample on the P4_NASAL_COL_LOG and enter the sample into the BST.

4.2.13 INFANT Medications (P4_INFANT_MED)

Purpose: To record the dispensation of INFANT study drugs.

Who: An AsthmaNet Coordinator completes the form.

When: Packet form at visits 2, 4 and 6, single form at visits 2 – 7.

Form Instructions:

The INFANT Medications form must be completed ***every*** time INFANT study medication is dispensed at scheduled or unscheduled visits. The form will be entered as a packet form at Visits 2, 4 and 6 and can be entered as a single form at Visits 2 – 7 as needed.

If INFANT medications are distributed between scheduled visits, record the last completed visit in the **Visit Number** field and the current date in the **Visit Date** field. If the last completed visit was a phone visit enter the form with the visit number of the last in clinic visit (i.e. if the participant terminates at Visit 3b enter the form at visit 3.

Questions 1000-1020. Copy the drug label numbers onto the spaces provided in Questions 1010-1020.

Questions 1030 and 1040. It is important that the ID of the participant receiving the INFANT medications matches the information provided by the randomization module and that this information is recorded on the INFANT Drug Dispensation Logs (P4_ICS_LOG, P4_LTRA_GRAN_LOG, P4_LTRA_TAB_LOG) and Participant Drug Logs (P4_ICS_KIT_PART, P4_LTRA_PART). To verify that the information collected on this form is correct and that it is documented correctly, the Clinic Coordinator should sign and date the source documentation box (Q1030 and Q1040) after affixing the INFANT medication labels to the form.

If partial replacement of the INFANT inhaler kit is dispensed (not an entirely new kit with all 9 inhalers), record the drug label number from the INFANT inhaler kit that was dispensed for the given Treatment Period and add a comment in Q6000 to record the type and number of inhalers dispensed. See Section 5 of the INFANT/AVICA MOP for more information regarding replacement medications.

4.2.14 INFANT Prednisolone Medication (P4_PRED)

Purpose: To record prednisolone medication use during study.

Who: An AsthmaNet Coordinator completes the form.

When: As a single form at Visits 2 – 7.

Form Instructions:

This form should be completed each time the participant is prescribed prednisolone. Instruct the parent/guardian to call if the participant's condition worsens while taking prednisolone. A follow-up phone call should be made to the parent/guardian 48-96 hours after the start of a prednisolone course to reassess the participant's symptoms.

If completed between scheduled visits, record the last completed visit in the **Visit Number** field and the current date in the **Visit Date** field. If the last completed visit was a phone visit, enter the form with the visit number of the last in clinic visit (i.e. if the last visit completed is Visit 5a, enter the form at visit 5).

Question 1000. Record the start date of the prednisolone course. Be sure to also record the prednisolone use on the CMED form and the INFANT Oral/Systemic Corticosteroid Tracking (P4_OCS) administrative form. The concentration of the prednisolone is 15mg/5ml so in order to record the dose of prednisolone take the number of ml that were prescribed and multiple by 3. For example, if the participant was prescribed 8 ml for Days 1 and 2 and 4 mls for Days 3 and 4 record 24 mg for Days 1 and 2 and 12 mg for Days 3 and 4.

Question 1010. Indicate the reason prednisolone was prescribed. If Q1010 is answered 'Physician discretion', please provide an explanation in Q6000.

Question 1020. Indicate if the start date of prednisolone use was on the same day that Visit 4 or Visit 6 occurred. If YES, the visit should be postponed for 4 to 7 days. Study medications from the current treatment period should be continued. Any forms that were completed at this visit should be filed in the participant folder and should not be entered into the database. A new Visit 4 or 6 packet should be completed at the visit following the 4-7 days. If the visit is rescheduled the return visit number on the spirotel device should remain 4 or 6.
If the prednisolone course started on the day of Visit 4 or 6, the form should be entered at Visit 3 or 5, respectively, to ensure that the prednisolone course is associated with the correct treatment period.

Question 1030. Indicate if this course of prednisolone is the second prednisolone course within a treatment sequence (i.e. within Visits 2-4, Visits 4-6, or Visits 6-8). Refer to the INFANT Oral/Systemic Corticosteroid Tracking (P4_OCS) administrative form to determine how many courses were given within a particular treatment sequence.

4.2.15 INFANT Study Failure (P4_INFANT_FAIL)

Purpose: To record the date and the events that occurred when a participant is deemed an INFANT study failure.

Who: An AsthmaNet Coordinator completes the form.

When: This form is completed when a participant has met the study failure criteria at Visits 2 – 8.

Form Instructions:

For more details on Study Failures, see the Study Failure discussion in Section 2 of the INFANT/AVICA MOP.

Complete the INFANT Study Failure (P4_INFANT_FAIL) form ***only*** if the participant has met the INFANT study failure criteria. If the form is completed between visits, specify the ***Last Visit Number completed*** and ***the date that the form is completed in its entirety*** (including the physician signature in the Source Documentation box at the bottom of the page) in the upper right-hand corner. The INFANT Study Failure (P4_INFANT_FAIL) form must be entered into the database as a single form.

If the participant is deemed an INFANT study failure at a study visit complete the current visit number and current date on the INFANT Study Failure (P4_INFANT_FAIL) form.

Questions 1000 – 1020. If the answer to any of these questions is 'Yes' the participant is an INFANT study failure.

Question 1030. If any of the shaded boxes are selected (Q1000 - Q1020), the participant is an INFANT study failure. If the participant is an INFANT study failure complete the P4_INFANT_TERM and P4_INFANT_TRTQX forms. If the participant is currently participating in the AVICA study, the AVICA medications should be collected and the P4_AVICA_TERM, P4_AVICA_TRTQX, P4_AVICA_COMPLY, and P4_AVICA_DIARY forms should also be completed.

Question 1040. Indicate the date INFANT study failure status occurred.

Questions 1050-1060. To verify that the information collected on this form is correct the Attending Physician must sign and date the source documentation box provided at the bottom of the form.

4.2.16 INFANT Study Treatment Questionnaire (P4_INFANT_TRTQX)

Purpose: To assess how well controlled the participant's wheezing was throughout the study and if he/she experienced any adverse side effects related to the medication. This form also questions which treatment the parent/guardian and clinic coordinator thinks the child was receiving during the study.

Who: Parent/Guardian completes pages 1 – 4 and an AsthmaNet Coordinator completes page 5.

When: Packet form at Visits 4, 6 and 8, and single form at Visits 2 – 7.

Form Instructions:

This form can be entered as a packet form at Visits 4, 6 and 8. This form can also be entered as a single form at Visits 2-7.

If completed between scheduled visits, record the last completed visit in the **Visit Number** field and the current date in the **Visit Date** field. If the last completed visit was a phone visit, enter the form with the visit number of the last in clinic visit (i.e. if the participant terminates at Visit 5b, enter the form at visit 5).

Page 5 should be completed by the clinic coordinator. Q1180-Q1200 are on the last page and should be completed prior to the parent/guardian completing Q1000 – Q1170 so that the Clinic Coordinator is not influenced by the parent/guardian responses.

After a randomized participant has completed each INFANT treatment period or if the participant terminates from the study, give the INFANT Study Questionnaire (P4_INFANT_TRTQX) to the participant's parent/guardian to complete. Do not give the parent/guardian page 5 of the form. If the parent does not complete the P4_INFANT_TRTQX the form can be set to missing.

Pages 1-4 (Q1000 – Q1170) are completed by the parent/guardian. Please be sure that the parent/guardian cannot see the responses to Q1180-1200 (coordinator completed question) when completing Q1000 – Q1170.

If the participant has not used the specified INFANT medication, leave the questions blank and put a comment in Q6000.

4.2.17 INFANT Treatment Arm Failure (P4_INFANT_TRTFAIL)

Purpose: To record the date and the events that occurred when a participant is deemed an INFANT treatment arm failure.

Who: An AsthmaNet Coordinator completes the form.

When: When a participant is deemed an INFANT treatment arm failure at Visits 2 – 7.

Form Instructions:

This form can be entered as a single form at Visits 2 – 7.
If completed between scheduled visits, record the last completed visit in the **Visit Number** field and the current date in the **Visit Date** field. If the last completed visit was a phone visit, enter the form with the visit number of the last in clinic visit (i.e. if the last visit completed is Visit 7a, enter the form at visit 7.

Question 1000: Record whether the participant has received his/her second course of oral/systemic corticosteroids for an asthma exacerbation within any of the three treatment periods (Treatment Period 1 is between visits 2-4, Treatment Period 2 is between visits 4-6 and Treatment Period 3 is between visits 6-8). Refer to the INFANT Oral/Systemic Corticosteroid Tracking (P4_OCS) administrative form to determine how many courses were given within a particular treatment period. If the answer to Q1000 is 'No' the participant is not an INFANT treatment arm failure and this form should not be entered into the database. If Q1000 is answered 'Yes' during Treatment Periods 1 or 2 the participant should be scheduled to begin the next treatment period. If Q1000 is answered 'Yes' during Treatment Period 3, the participant should be scheduled for Visit 8 to terminate from the study.

4.2.18 Phone/Visit Symptom Assessment (P4_PHONE_CONTACT)

Purpose: This form assesses the participant's status at visits and at scheduled phone calls during the study to assist in the early identification of the lack of asthma control or other medical problems.

Who: An AsthmaNet Coordinator completes the form

When: Completed at Visits 3 – 8 and at all scheduled phone calls, Visits 3a, 3b, 5a, 5b, 7a, and 7b.

Form Instructions:

Questions 1000 – 1010. Indicate if the participant has been to a doctor for breathing problems since the last in clinic study visit or phone contact and the answer to Q1000 is 'Yes' complete Q1010. Otherwise, skip to Q1020.

Question 1020. Indicate if the participant has been to an ER/urgent care facility for breathing problems since the last in clinic study visit or phone contact. If Q1020 is answered 'Yes' assess whether the participant is a study failure. Refer to Section 2 of the INFANT/AVICA MOP for further details.

Question 1030. Indicate if the participant has been hospitalized for breathing problems since the last in clinic study visit or phone contact. If Q1030 is answered 'Yes' assess whether the participant is a study failure. Refer to Section 2 of the INFANT/AVICA MOP for further details.

Questions 1040 – 1060. Indicate if the participant has had wheezing or cough during the past 2 weeks. If Q1040 is answered 'Yes' complete Q1050. If Q1050 is greater than 5, and the cough was moderate-severe the study physician should be consulted to determine if prednisolone therapy should be started. Otherwise, skip to Q1070.

Questions 1070 – 1090. Indicate if the participant has had night time awakenings due to asthma during the past 2 weeks. If Q1070 is answered 'Yes' complete Q1080. If Q1080 is greater than 1, and there were at least 2 consecutive nights, the study physician should be consulted. Otherwise, skip to Q1100.

Questions 1100 – 1110. Indicate if the participant has taken albuterol (excluding pre-exercise use) during the past 2 weeks. If Q1100 is answered 'Yes', complete Q1110. Otherwise, skip to Q1120.

Question 1120. Indicate if the participant has been using the white Rescue inhaler each time the red Albuterol inhaler is used. If the participant has not used the red Albuterol inhaler since the last study contact, the question should be answered 'N/A'. If the question is answered 'No' review study adherence with the parent/guardian.

Questions Q1130- Q1150 Indicate if the parent/guardian is completing the spirotel® Diary daily, if the participant is using the brown Daily inhaler every morning and evening and if the participant has been taking the oral study medication once daily. If any of the questions are answered 'No' review study adherence with the parent/guardian.

Question 1160. Indicate if the participant has used AVICA study medication since the last in clinic visit or phone contact. If the participant has used AVICA study medication, instruct the parent/guardian to record the AVICA use on the Parental AVICA Study Medication Diary (P4_PARENT_DIARY).

Questions 1170-1180. If the participant has used prednisolone since the last in clinic visit or phone contact, and the answer to Q1170 is 'Yes', complete Q1180. If Q1180 is greater than 1, the participant is an INFANT treatment arm failure. The INFANT Treatment Arm Failure (P4_INFANT_TRTFAIL) form should be completed and the participant should be scheduled to start the next treatment period, if applicable.
If Q1170 is answered 'No,' stop completion of the form.

4.2.19 Termination of AVICA (P4_AVICA_TERM)

Purpose: To record the date and the primary reason for the participant's termination of AVICA study participation.

Who: An AsthmaNet Coordinator completes the form.

When: May be completed at Visits 2 - 7 as a single form or at Visit 8 as a packet form. It would be completed at Visit 2 only if the participant had been randomized and withdraws prior to Visit 3.

Form Instructions:

A participant should be terminated from the study when parent/guardian wishes to withdraw the participant early or the participant completes the study. The study investigator can also determine using physician discretion that it is in the best interest of the participant to discontinue participation in the trial.

If completed between scheduled visits, record the last completed visit in the **Visit Number** field and the current date in the **Visit Date** field. If the last completed visit was a phone visit, enter the form with the visit number of the last in clinic visit (i.e. if the participant terminates at Visit 3a, enter the form at visit 3).

Question 1000. If Q1000 is answered 'Yes' and the participant has completed the AVICA study, skip to Q1020. Otherwise complete Q1010.

The participant has completed the AVICA study if.
She/he has started all 3 INFANT treatment periods (completed visits 2, 4, and 6) **AND** is not an AVICA **OR** INFANT study failure.

Question 1010. Indicate the primary reason the participant has withdrawn from the study. If Q1010 is answered 4, 5, 8, 12, 14, or 15 an additional explanation is required in Q1010D. If the participant experienced a serious adverse event, please complete a Serious Adverse Event Reporting (SERIOUS) form.

Questions 1020 – 1050. This form requires the signatures of the Clinic Coordinator and the Principal Investigator to verify that all data collected for this subject are correct to the best of their knowledge. Any AsthmaNet investigator (site director, Principal Investigator, or other) may sign field Q1040 to verify that all data collected for this participant are correct to the best of their knowledge.

4.2.20 Termination of INFANT (P4_INFANT_TERM)

Purpose: To record the date and the primary reason for the participant's termination of INFANT study participation.

Who: An AsthmaNet Coordinator completes the form.

When: May be completed at or between Visits 2 - 7 as a single form or at Visit 8 as a packet form. It would be completed for Visit 2 only if the participant had been randomized and withdraws prior to Visit 3.

Form Instructions:

A participant should be terminated from the study when parent/guardian wishes to withdraw the participant early or the participant completes the study. The study investigator can also determine using physician discretion that it is in the best interest of the participant to discontinue participation in the trial.

If completed between scheduled visits, record the last completed visit in the **Visit Number** field and the current date in the **Visit Date** field. If the last completed visit was a phone visit, enter the form with the visit number of the last in clinic visit (i.e. if the participant terminates at Visit 3b, enter the form at visit 3).

Question 1000. If Q1000 is answered 'Yes' and the participant has completed the INFANT study, skip to Q1020. Otherwise complete Q1010.

The participant has completed the INFANT study if she/he:

a. has started all 3 INFANT treatment periods (completed visits 2, 4, and 6)
   AND
b. is not an INFANT study failure
   AND
c. has not withdrawn early from the study for any reason other than INFANT treatment arm failure

Question 1010. Indicate the primary reason the participant has withdrawn from the INFANT study. If Q1010 is answered 3, 4, 7, 12, 14, or 15 an additional explanation is required in Q1010D. If the participant experienced a serious adverse event, please complete a Serious Adverse Event Reporting (SERIOUS) form.

Questions 1020 – 1050. This form requires the signatures of the Clinic Coordinator and the Principal Investigator to verify that all data collected for this subject are correct to the best of their knowledge. Any AsthmaNet investigator (site director, Principal Investigator, or other) may sign field Q1040 to verify that all data collected for this participant are correct to the best of their knowledge.

4.2.21 Termination of INFANT Run-In (P4_TERMR)

Purpose: To record the date and the primary reason for the participant's termination of study participation during the run-in.

Who: An AsthmaNet Coordinator completes the form.

When: The P4_TERMR form may be completed between Visits 1 - 2 as a single form when a participant is deemed ineligible, has withdrawn consent, or has withdrawn assent prior to randomization.

Form Instructions:

A participant should be terminated from the study if the participant withdraws assent, the parent/legal guardian withdraws consent to participate, or the participant is found to be ineligible.

If completed between scheduled visits, record the last completed visit in the **Visit Number** field and the current date in the **Visit Date** field in the key variable information.

Question 1000. Indicate the primary reason the participant has withdrawn from the study. If Q1010 is answered 10 or 11 an additional explanation is required in Q1000D. If the participant experienced a serious adverse event, please complete a Serious Adverse Event Reporting (SERIOUS) form.

Questions 1010 – 1040. This form requires the signatures of the Clinic Coordinator and the Principal Investigator to verify that all data collected for this subject are correct to the best of their knowledge. Any AsthmaNet investigator (site director, Principal Investigator, or other) may sign field Q1030 to verify that all data collected for this participant are correct to the best of their knowledge.

If the 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 and this form would not need to be completed.

If the participant is deemed ineligible between Visit 1 and Visit 2 (Visit 1 packet was entered into the database) OR at Visit 2 **prior** to randomization, the P4_TERMR form should be completed and entered into the database as a single form and submitted to the DCC along with any study data that has been collected.

4.3 Administrative Forms

Administrative forms facilitate processing of the participant and visit flow by the clinical centers and the DCC, but they are not entered into the study database and they are not submitted to the DCC in most cases. The following is a list of all INFANT study administrative forms, the corresponding form code and related instructions.

Administrative Form Name	Form Code
INFANT Drug Accountability Log: Run-In Medication Logs	P4_ICS_ACT_ICS P4_ICS_PL_LOG P4_LTRA_ACT_GRAN_LOG P4_LTRA_ACT_TAB_LOG P4_LTRA_PL_GRAN_LOG P4_LTRA_PL_TAB_LOG
INFANT/AVICA Drug Accountability Log: Pre and Post-Randomization Medication Logs	P4_ALB_LOG P4_PRED_LOG
INFANT/AVICA Drug Accountability Log: Post-Randomization Medication Logs	P4_ACET_LOG P4_AVICA_LOG P4_IBUP_LOG P4_ICS_LOG P4_LTRA_GRAN_LOG P4_LTRA_TAB_LOG
INFANT/AVICA Participant Drug Log: Post-Randomization Study Medications	P4_AVICA_PART P4_ICS_KIT_PART P4_LTRA_PART
INFANT Nasal Mucus Collection Log	P4_NASAL_COL_LOG
INFANT Nasal Sample Kit Distribution Log	P4_NASAL_DISP_LOG
INFANT Oral/Systemic Corticosteroid Tracking Form	P4_OCS
INFANT Sample Collection Logs	P4_GLUT_LOG P4_IGE_LOG P4_META_LOG P4_URINE_LOG
INFANT Visit Procedure Checklists	P4_VISIT1 P4_VISIT2 P4_VISIT3_5_7 P4_VISIT4_6 P4_VISIT_PC P4_VISIT8
INFANT/AVICA Participant Assignment Log	P4_LOG
spirotel® Perfomance Checklist	P4_SPIROTEL_PERF

4.3.1 INFANT Brown Daily Inhaler Dates-of-Use Worksheet (P4_ICS_DOU)

Purpose: To calculate the dates necessary to complete the 'use from/to' fields on each Brown Daily Inhaler

Who: An AsthmaNet Coordinator completes the worksheet

When: At each visit where Brown Daily Inhalers are dispensed

Form Instructions:

Complete today's visit date and the next scheduled INFANT Kit Distribution Date (which will most likely be the next Start of a Treatment Period visit). The maximum duration for each inhaler is 28 days.

This worksheet should be stored in the participant's folder.

For use only at the Clinical Center, these forms are not data entered.

For example:

Today's Visit Date	Next Scheduled INFANT Kit Distribution Date	Daily Dose (puffs)	Maximum Duration (# days)	Inhaler Number	Dates of Use
3/01/2013	6/21/2013	4	28	1	3/1/2013 to 3/28/2013
				2	3/29/2013 to 4/25/2013
				3	4/26/2013 to 5/23/2013
				4	5/24/2013 to 6/20/2013
				5	6/21/2013 to 7/18/2013

4.3.2 INFANT/AVICA Drug Accountability Logs: Run-In Medication Logs (P4_ICS_ACT_ICS, P4_ICS_PL_LOG, P4_LTRA_ACT_GRAN_LOG, P4_LTRA_ACT_TAB_LOG, P4_LTRA_PL_GRAN_LOG, P4_LTRA_PL_TAB_LOG)

Purpose: To record information about the dispensation and collection of Run-In Study Medications.

Who: An AsthmaNet Coordinator completes the form.

When: When Study Medications are dispensed, returned, or lost.

Form Instructions:

See Section 5 of the MOP for more detailed instructions.

For use only at the Clinical Center, these forms are not data entered.

For use only at the Clinical Center, these forms are not data entered.

4.3.3 INFANT/AVICA Drug Accountability Logs: Pre and Post-Randomization Medication Logs (P4_ALB_LOG, P4_PRED_LOG)

Purpose: To record information about the dispensation and collection of Study Medications.

Who: An AsthmaNet Coordinator completes the log

When: When Albuterol or Prednisolone is dispensed, returned, or lost between visits.

Form Instructions:

See Section 5 of the MOP for more detailed instructions.

For use only at the Clinical Center, these forms are not data entered.

4.3.4 INFANT/AVICA Drug Accountability Logs: Post-Randomization Medications Logs (P4_ACET_LOG, P4_AVICA_LOG, P4_IBUP_LOG, P4_ICS_LOG, P4_LTRA_GRAN_LOG, P4_LTRA_TAB_LOG)

Purpose: To record information about the dispensation and collection of Post-Randomization Study Medications.

Who: An AsthmaNet Coordinator completes the logs, EXCEPT for P4_ACET_LOG and P4_IBUP_LOG which are completed by the pharmacy staff at the site

When: When Study Medications are dispensed, returned, or lost.

Form Instructions:

See Section 5 of the MOP for more detailed instructions.

For use only at the Clinical Center, these forms are not data entered.

4.3.5 INFANT/AVICA Participant Drug Logs: Post-Randomization Medications (P4_AVICA_PART, P4_ICS_KIT_PART, P4_LTRA_PART)

Purpose: To record the date the study medication is dispensed and returned, the dispenser's and the collector's initials, and the medication bottle or kit number(s).

Who: An AsthmaNet Coordinator completes the log

When: When Study Medications are dispensed, returned, or lost

Form Instructions:

When study medications are dispensed, returned, or lost, complete the appropriate part of this log.

The participant ID should be placed on the log when the initial medications are dispensed at Visit 2. Record the date dispensed, the dispenser's initials, and the medication bottle or kit number(s).

This log will be reviewed during AsthmaNet site visits.

For use only at the Clinical Center, this form is not data entered.

DO NOT forward to the DCC.

4.3.6 INFANT Nasal Mucus Collection Log (P4_NASAL_COL_LOG)

Purpose: To record a participant's nasal mucus collection.

Who: An Asthmanet Coordinator completes the log.

When: This log is completed every time a nasal mucus sample is collected.

Form Instructions:

When a sample is collected, the Coordinator must complete a row on the P4_NASAL_COL_LOG for the participant ID. All samples collected during the study must be recorded on this log, whether collected in clinic or at home.

A P4_LAB form should be completed and entered into the database for the visit during which a clinic sample has been collected, typically Visit 2. The samples collected at home visits will not be recorded on a data collection form.

Note: For the Visit Number column, use the Visit Number of the current visit.

This log will be reviewed during AsthmaNet site visits.

For use only at the Clinical Center, this form is not data entered.

DO NOT forward to the DCC when completed.

4.3.7 INFANT Nasal Sample Kit Distribution Log (P4_NASAL_DISP_LOG)

Purpose: To record dispensation of nasal sample kits.

Who: An Asthmanet Coordinator completes the log.

When: This log is completed every time a nasal sample kit is dispensed.

Form Instructions:

When a nasal sample kit is dispensed to a parent/guardian for home nasal mucus collection, the Coordinator must complete a row on the P4_NASAL_DISP_LOG. Sample kits used in the clinic do not need to be recorded on this log. An individual log should be kept for each participant and should be stored in the participant's binder.

Note: For the Visit Number column, use the Visit Number of the current visit.

This log will be reviewed during AsthmaNet site visits.

For use only at the Clinical Center, this form is not data entered.

DO NOT forward to the DCC when completed.

4.3.8 INFANT Oral/Systemic Corticosteroid Tracking Form (P4_OCS)

Purpose: To track prednisolone courses taken by the participant during the INFANT Treatment Phase.

Who: An AsthmaNet Coordinator completes the form.

When: Whenever the participant is prescribed a prednisolone course.

Form Instructions:

Record the date the prednisolone course started and was completed. Also indicate in which Treatment Period the course was taken. Treatment Period 1 is considered any time between visits 2-4, Treatment Period 2 is considered any time between visits 4-6, Treatment Period 3 is considered any time between visits 6-8. If the participant is prescribed 2 prednisolone courses during a Treatment Period, the participant is a treatment failure. The INFANT Treatment Failure (P4_TRTFAIL) form should be completed, and the participant should be scheduled to begin the next Treatment Period. If the Treatment Failure occurs during Treatment Periods 1 or 2 the participant should be scheduled to begin the next Treatment Period (either visit 4 or 6). If the Treatment Failure occurs during Treatment Period 3, the participant should be scheduled for Visit 8 to terminate from the study.

4.3.9 INFANT Sample Collection Logs (P4_GLUT_LOG, P4_IGE_LOG, P4_META_LOG, P4_URINE_LOG)

Purpose: To record a participant's biological specimen collection for glutathione and metabolites, Immunocap/IgE/ECP, Metabolomics and Proteomics and/or Urine analysis.

Who: An AsthmaNet Coordinator completes the log.

When: This log is completed every time a biological specimen sample is collected.

Form Instructions:

When a sample is collected, the Coordinator must complete a row on the appropriate log for the participant ID. All biological samples collected during the study must be recorded on a log.

A P4_LAB form should be completed and entered into the database for the visit during which a clinic sample has been collected, typically Visit 2.

Note: For the Visit Number column, use the Visit Number of the current visit.

If multiple aliquots are produced for one sample type, multiple barcodes can be recorded in the Cryovial Barcode # column.

This log will be reviewed during AsthmaNet site visits.

For use only at the Clinical Center, this form is not data entered.

DO NOT forward to the DCC when completed.

4.3.10 INFANT Visit Procedure Checklists (P4_VISIT1, P4_VISIT2, P4_VISIT3_5_7, P4_VISIT4_6, P2_VISIT_PC, P2_VISIT8)

Purpose: To provide the coordinator with a checklist of all procedures and forms that must be completed during a visit

Who: An AsthmaNet Coordinator completes the form.

When: At the specified visit and when a participant misses a visit.

Form Instructions:

These checklists serve as a guide for the coordinator and should be sent to the DCC, in front of the visit packet, with the other forms in the packet.

For all procedures and forms, indicate whether or not the procedure or form was completed. If it was not completed, indicate the reason in the comment field.

Procedures should be followed in the order they are presented on the visit checklist for applicable visits.

These forms are not entered during data entry, but should be sent to the DCC with the rest of the packet forms.

4.3.11 INFANT/AVICA Participant Assignment Log (P4_LOG)

Purpose: To track all participants enrolled in the INFANT and AVICA studies by their study-specific Participant ID numbers.

Who: An AsthmaNet Coordinator completes the form.

When: Visits 1 and 2.

Form Instructions:

A Participant Assignment Log (P4_LOG) has been developed for Clinical Sites to record the assignment of Participant ID numbers. It includes columns for unique participant ID numbers, participant initials, participant's name, and a box to check to indicate if the participant has been randomized (to be completed at Visit 2).

The first digit is the number of the AsthmaNet protocol. For INFANT/AVICA this digit is 4.

The second set of numbers (3 digits) is the AsthmaNet Clinical Site identifier which will pre-fill with the Site ID when printed from the website.

The last three digits constitute the participant identification number, which is unique within the Clinical Site. The first participant is assigned 001, the second 002, and so on.

The Participant Assignment Log (P4_LOG) **must** be used every time a **new** Participant ID number is assigned. The Participant Assignment Log (P4_LOG) is pre-numbered, so a new Participant ID number is assigned by selecting the next available blank entry on the log. This number will be the primary participant identifier used during the study; it should be used in all communications with the DCC. The participant ID number should also be labeled on the participant's study folder at the Clinical Site.

Once assigned, an ID number cannot be assigned to any other participant.

If a participant has withdrawn during the assessment/characterization period and later re-enrolls in the study, he or she should be assigned a new participant ID number; that is, the next available blank entry on the Participant Assignment Log.

A participant's three-letter initials will be used as a secondary identifier. All participants ***must*** have three initials for use during this study. Use the letter "X" if there is no middle initial and select three letters if there are 4 or more letters in the initials. These initials must remain constant throughout the study and throughout any future studies the participant is involved in.

Visit 1: Complete the Participant initials and Participant name columns for the new participants.

Visit 2: If the participant is randomized, check the box in the Randomized column.

Since the participant's name is recorded on this log, DO NOT forward this log to the DCC during the study. After the study, mail a copy to the DCC in a sealed envelope. The DCC will retain this sealed log for historical and safety purposes. The site needs to retain the original log in a secure and confidential location.

This log will be reviewed during Asthmanet site visits.

For use only at the Clinical Site, this form is not data entered.

DO NOT forward to the DCC.

4.3.12 spirotel® Performance Checklist (P4_SPIROTEL_PERF)

Purpose: To assess the parent/guardian's ability to correctly use the spirotel® device.

Who: An AsthmaNet Coordinator completes the form.

When: Visit 1

Form Instructions:

The parent/guardian must demonstrate the ability to coordinate use of the spirotel® device for entering diary information before leaving the performance site. These skills are assessed using the spirotel® Performance Checklist (P4_SPIROTEL_PERF). Complete Spirotel® Performance Checklist (P4_SPIROTEL_PERF) using the site demo device.

After the parent/guardian has had a chance to experiment with the INFANT demo device, he/she should undergo a formal spirotel® performance assessment using the steps on the spirotel® Performance Checklist (P4_SPIROTEL_PERF). He/she must pass the performance check with a score of 4 to remain eligible for the study. Results of the performance check are recorded in Q1290 on INFANT Eligibility Checklist 1 (P4_ELIG1) form.

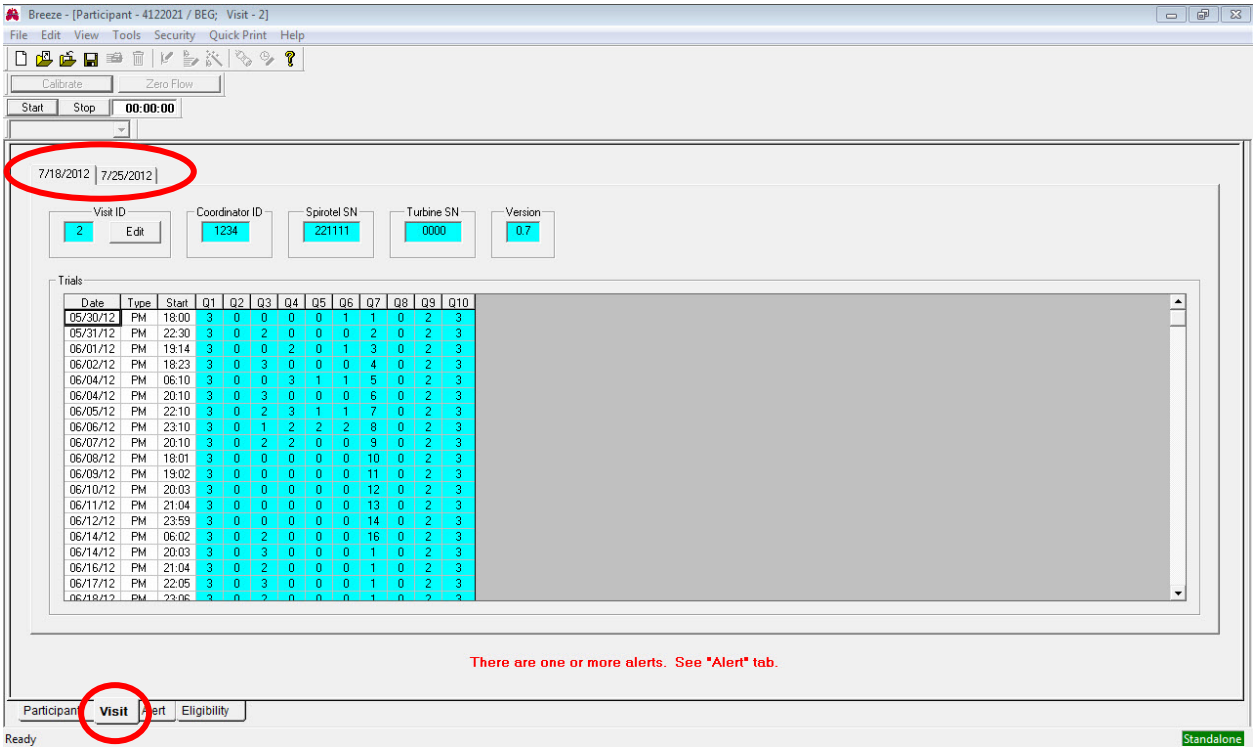
If a parent/guardian fails to perform all the steps on the performance checklist correctly, he/she may be retrained and undergo another assessment. There is no limit on the number of times the participant may attempt to pass the checklist. Store all completed P4_SPIROTEL_PERF forms in the participant's INFANT study folder at the performance site; they should not be forwarded to the DCC.

4.4 INFANT Specific spirotel® Tabs in Breeze Suite

The INFANT Visit Report, Eligibility Report, and Compliance Reports are generated and printed using the Breeze Suite software on the MedGraphics' PC. For each visit various tabs will appear in the Breeze Suite window. The information necessary to complete the data collection forms is contained in the printed reports that are generated in the Breeze Suite software. The information found in the tabs is only used for reference purposes.

4.4.1 Visit Tab

The Visit Tab will be available at Visits 2-8. This report is a data dump of all the information saved in the spirotel® for one visit. The top of the report shows the device configuration data. The body of the report shows all the entered data by trial date (the date an entry was made), trial type, time the session started, and all the diary responses identified by question number. If the spirotel® was downloaded more than once for a visit, there will be a tab for each download date at the top of the screen.



4.4.2 Alert Tab

The Alert Tab will be available at Visits 2-8. This report is a data dump of all the information saved in the spirotel® for one visit. The top of the report contains a legend of the criteria for alerts and the possible alerts that are displayed by the spirotel® device. The body of the report shows all the entered data by trial date (the date an entry was made), the trial type, the, time the session started, all the diary responses identified by question number, and several columns related to the alerts.

Columns C1-C4: If alert criteria was met, an * is displayed in the appropriate column.

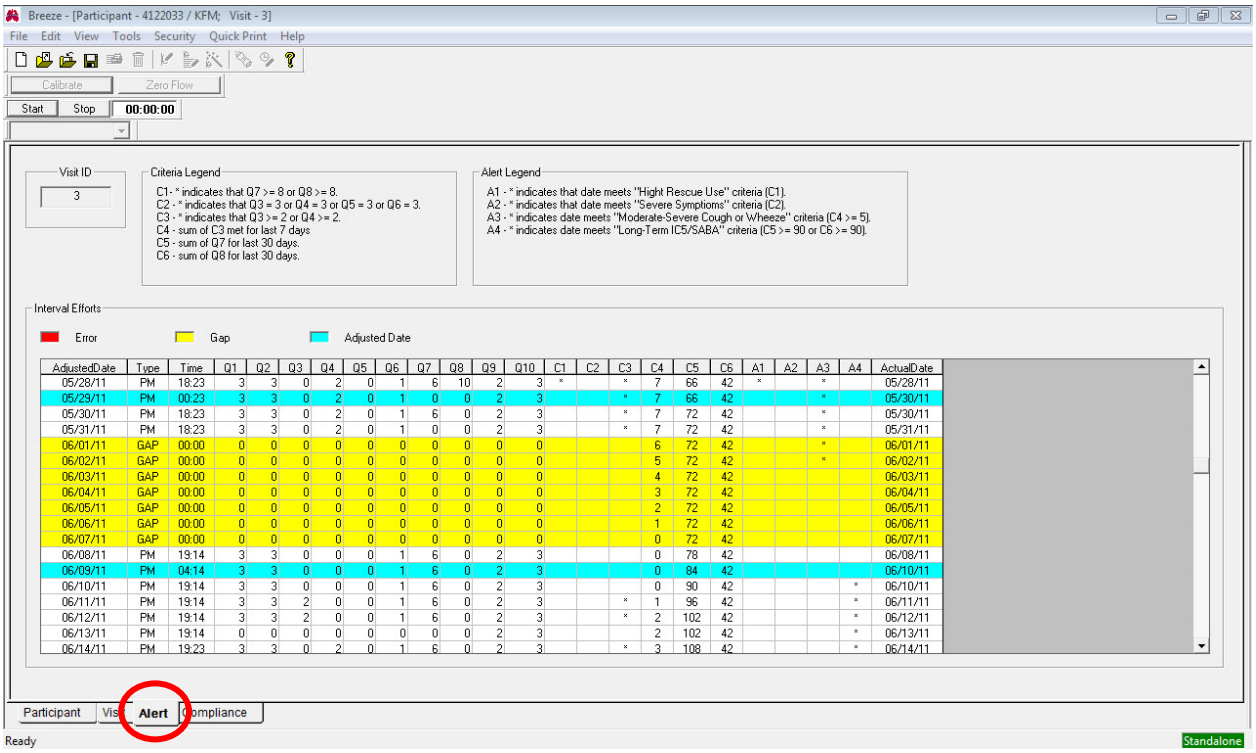
Columns C5-C6: Displays the sum of the number of puffs taken from the White rescue and Red Albuterol inhalers over the last 30 days.

Columns A1-A4: If an alert was displayed by the spirotel® device on a given day, an * is displayed in the appropriate column.

Yellow highlighted rows: These rows indicate gaps in diary days. If a session was not completed during the session window for a given day it will be shown as a Gap and all of the diary responses will be displayed as '0'. The gap rows are only used to assist in alert calculations.

Blue highlighted rows: These rows indicate Adjusted Dates. If the session was completed between midnight and noon, the session date will be adjusted to indicate the session was completed for the previous day.

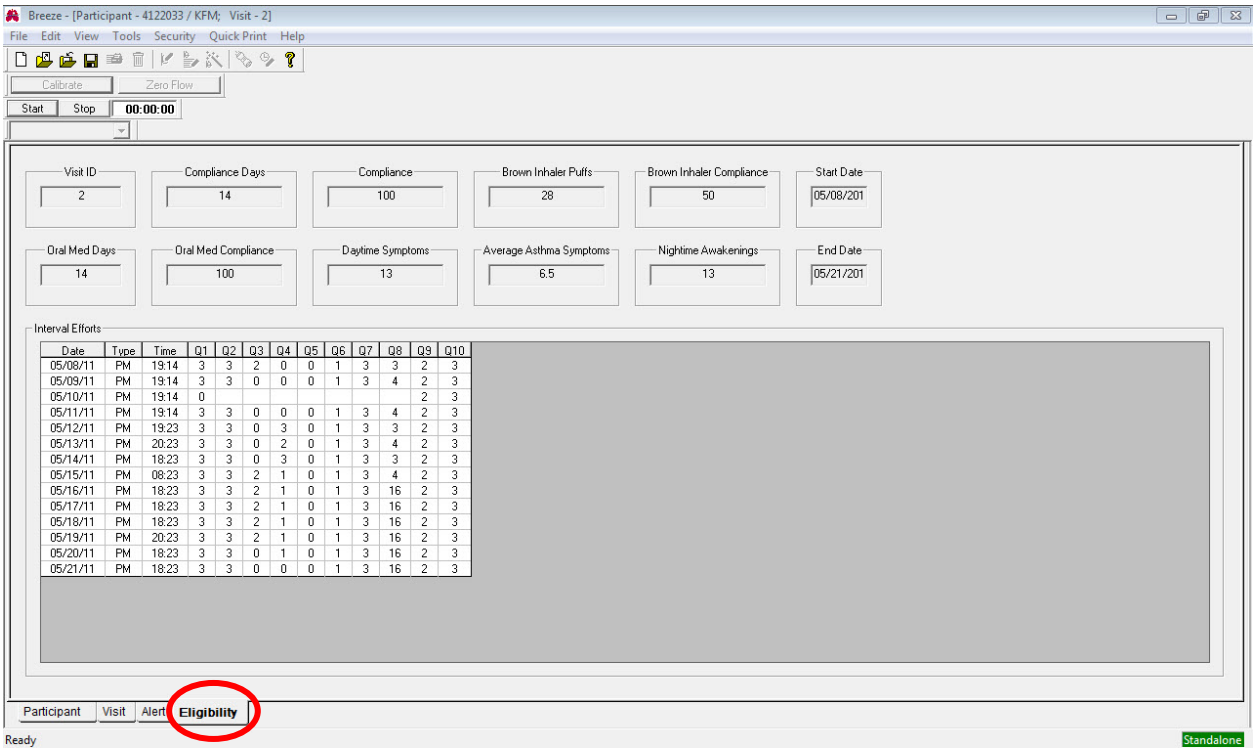
If the spirotel® was downloaded more than once for a visit, there will only be one alert tab for the entire visit. All of the downloaded data for a visit is combined to generate the alerts.



AdjustedDate	Type	Time	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	C1	C2	C3	C4	C5	C6	A1	A2	A3	A4	ActualDate
05/28/11	PM	18:23	3	3	0	2	0	1	6	10	2	3	*		*	7	66	42	*		*		05/28/11
05/29/11	PM	00:23	3	3	0	2	0	1	0	0	2	3			*	7	66	42			*		05/30/11
05/30/11	PM	18:23	3	3	0	2	0	1	6	0	2	3			*	7	72	42			*		05/30/11
05/31/11	PM	18:23	3	3	0	2	0	1	0	0	2	3			*	7	72	42			*		05/31/11
06/01/11	GAP	00:00	0	0	0	0	0	0	0	0	0	0				6	72	42			*		06/01/11
06/02/11	GAP	00:00	0	0	0	0	0	0	0	0	0	0				5	72	42			*		06/02/11
06/03/11	GAP	00:00	0	0	0	0	0	0	0	0	0	0				4	72	42					06/03/11
06/04/11	GAP	00:00	0	0	0	0	0	0	0	0	0	0				3	72	42					06/04/11
06/05/11	GAP	00:00	0	0	0	0	0	0	0	0	0	0				2	72	42					06/05/11
06/06/11	GAP	00:00	0	0	0	0	0	0	0	0	0	0				1	72	42					06/06/11
06/07/11	GAP	00:00	0	0	0	0	0	0	0	0	0	0				0	72	42					06/07/11
06/08/11	PM	19:14	3	3	0	0	0	1	6	0	2	3				0	78	42					06/08/11
06/09/11	PM	04:14	3	3	0	0	0	1	6	0	2	3				0	84	42					06/10/11
06/10/11	PM	19:14	3	3	0	0	0	1	6	0	2	3				0	90	42				*	06/10/11
06/11/11	PM	19:14	3	3	2	0	0	1	6	0	2	3			*	1	96	42				*	06/11/11
06/12/11	PM	19:14	3	3	2	0	0	1	6	0	2	3			*	2	102	42				*	06/12/11
06/13/11	PM	19:14	0	0	0	0	0	0	0	0	2	3				2	102	42				*	06/13/11
06/14/11	PM	19:23	3	3	0	2	0	1	6	0	2	3			*	3	108	42				*	06/14/11

4.4.3 Eligibility Tab

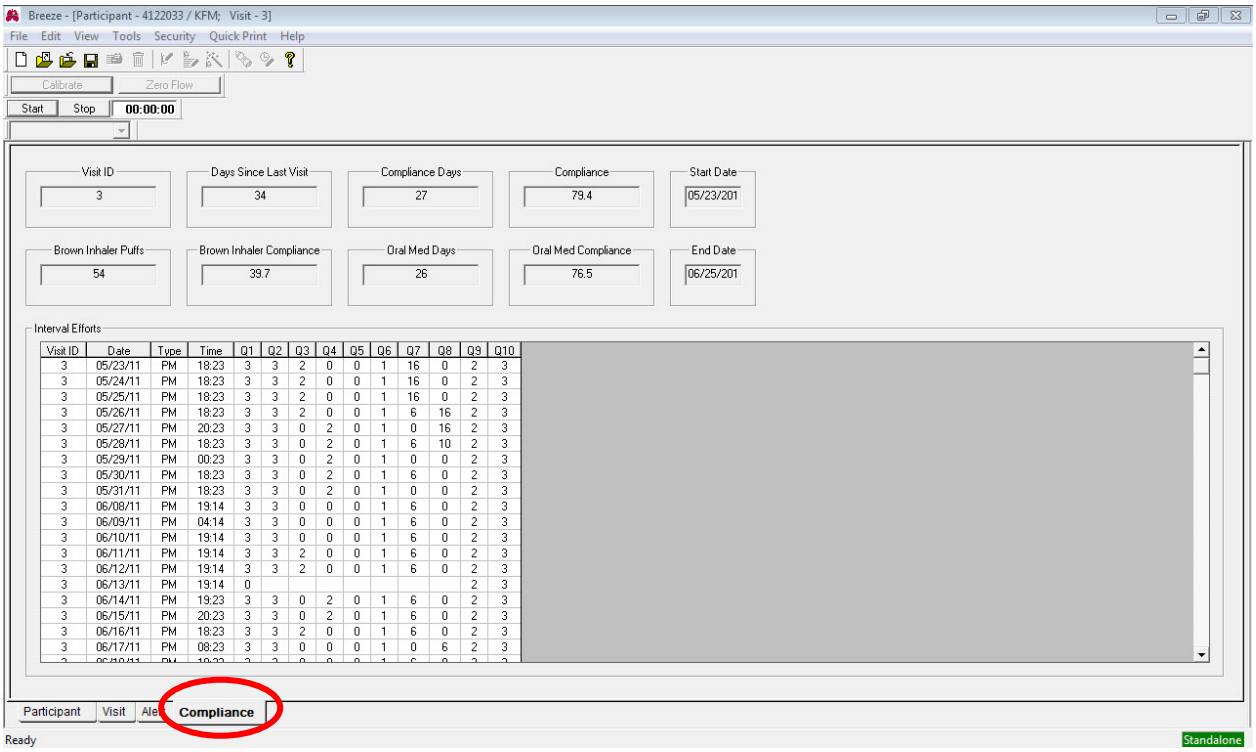
The Eligibility Tab is only displayed at Visit 2. This report is a data dump of all the information saved in the spirotel® during the Run-In period. The top of the report shows the compliance data for the last 14 calendar days of the Run-In period. If the Run-In period was less than 14 days, all of the available data is shown. The body of the report shows the last 14 calendar days of data entered data by trial date (the date an entry was made), trial type, time the session started, and all the diary responses identified by question number. If the spirotel® was downloaded more than once for Visit 2 there will only be one eligibility tab.



Date	Type	Time	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
05/08/11	PM	19:14	3	3	2	0	0	1	3	3	2	3
05/09/11	PM	19:14	3	3	0	0	0	1	3	4	2	3
05/10/11	PM	19:14	0								2	3
05/11/11	PM	19:14	3	3	0	0	0	1	3	4	2	3
05/12/11	PM	19:23	3	3	0	3	0	1	3	3	2	3
05/13/11	PM	20:23	3	3	0	2	0	1	3	4	2	3
05/14/11	PM	18:23	3	3	0	3	0	1	3	3	2	3
05/15/11	PM	08:23	3	3	2	1	0	1	3	4	2	3
05/16/11	PM	18:23	3	3	2	1	0	1	3	16	2	3
05/17/11	PM	18:23	3	3	2	1	0	1	3	16	2	3
05/18/11	PM	18:23	3	3	2	1	0	1	3	16	2	3
05/19/11	PM	20:23	3	3	2	1	0	1	3	16	2	3
05/20/11	PM	18:23	3	3	0	1	0	1	3	16	2	3
05/21/11	PM	18:23	3	3	0	0	0	1	3	16	2	3

4.4.4 Compliance Tab

The Compliance Tab is displayed at Visits 3-8. This report is a data dump of all the information saved in the spirotel® for one visit. The top of the report shows the compliance data for the visit. The body of the report shows all the entered data by trial date (the date an entry was made), trial type, time the session started, and all the diary responses identified by question number. If the spirotel® was downloaded more than once for a visit, there will only be one compliance tab. All of the downloaded data for a visit is combined to generate the compliance data.



2.1 ACTION PLANS and IDENTIFICATION CARDS

INFANT/AVICA Run-In Action Plan Card
INFANT/AVICA Action Plan Card and tri-fold ID Card
INFANT/AVICA Caregiver Action Plan Card

There are several different Action Plan Cards used during the INFANT/AVICA 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, using AVICA medicine for pain/fevers, 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 INFANT and AVICA studies. 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, and the AVICA medication dose will need to be updated at each study visit.

Visit 1

Dispense INFANT/AVICA Run-in Action Plan Card

- The INFANT/AVICA 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 INFANT/AVICA 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 INFANT/AVICA Action Plan Card, INFANT/AVICA tri-fold ID Card and the INFANT/AVICA Caregiver Action Plan Card (if needed)

- Collect the INFANT/AVICA Run-In Action Plan Card.
- Write the participant's study ID number and the phone numbers of study contacts. Explain to the parent 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, the Yellow Zone, and 'Get Medical Help!'
- Record the participant's AVICA medication dose on the back-side of the Action Plan. This will need to be updated at each visit as the participant's weight changes. The dose is calculated on the P4_AVICA_MED form.
- The 'INFANT/AVICA Action Plan Card' and the 'INFANT/AVICA tri-fold ID card' should be dispensed at Visit 2 and used for the remainder of the INFANT/AVICA study.
- There is also an INFANT/AVICA Caregiver Action Plan Card that can be dispensed at Visit 2 and given to Daycare providers, schools, baby-sitters, grandparents, etc. if needed.

The back of the INFANT/AVICA 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 taking AVICA medicine and what to bring to the next study visit.

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, the Yellow Zone, and 'Get Medical Help!'
- Update the participant's AVICA medication dose on the back-side of the Action Plan. This will need to be updated at each visit as the participant's weight changes. The dose is calculated on the P4_AVICA_MED form.
- 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 INFANT/AVICA 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 INFANT and AVICA trials:

- 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 INFANT/AVICA. 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 INFANT/AVICA.

Adherence with the spirotel® completion and study medications is assessed on Eligibility Checklist 4 or Eligibility Checklist 5. 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 and study medications is assessed via reports once the spirotel® data is downloaded. The study medication adherence gets recorded on the P4_INFANT_COMPLY form. See the Spirotel® Section for further details.

Adherence with the AVICA medications gets recorded on the P4_AVICA_COMPLY form. Parents will keep track of AVICA use between visits using the Parental AVICA Study Medication Diary. At each visit, the Diary should be reviewed and the coordinator should record any AVICA use by the participant on the AVICA Medication Diary (P4_AVICA_DIARY).

The reverse side of the Parental AVICA Study Medication Diary is an Illness and non-Study medication Diary. Parents should be encouraged to record any illnesses and non-study medication uses on the diary between visits. At each visit, the Illness and non-study medication Diary should be reviewed. The coordinator should record any adverse events on the AECLIN form and any non-study medications on the CMED form, if applicable.

In addition, for the INFANT/AVICA studies, the coordinator should record any non-study use of ibuprofen and acetaminophen on the CMED form. The Illness and non-study diary should be reviewed for ibuprofen and acetaminophen products. The parents will be given a handout at Visit 2 that instructs them how to read product labels and identify medications that contain ibuprofen and acetaminophen.

If a parent is non-compliant with the AVICA medications (i.e. gives the participant over-the-counter ibuprofen or acetaminophen products instead), the parent should be consulted as to the reason why the AVICA medications are not being used. The parent should be encouraged to use the AVICA medications. However, if the parent refuses to ever use the AVICA medication (i.e. maybe the participant dislikes the flavor of the medication and will never take it), the participant can be termed from the AVICA 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 or parenteral 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.

If an illness is being recorded where AVICA medication was used, please answer Q1110 as 2=medication. Since we do not record study medications on the CMED form, you will get an error that should be marked unresolvable. The AVICA medication use should be recorded on the AVICA Medication Diary (P4_AVICA_DIARY).

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 INFANT/AVICA 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 INFANT/AVICA 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.

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

2.5 AVICA Handouts

Visit 2

AVICA Reading Medication Labels Handout – The purpose of this handout is to:

- Teach parents to read medication labels and identify medications that contain acetaminophen and ibuprofen.
- Parents should be discouraged from giving medications other than AVICA medication that contain ibuprofen or acetaminophen.
- Parents should be instructed to inform medical providers of their child's participation in the study.

AVICA Letter to PCP – The purpose of this letter is to explain the AVICA study and guide medical care providers with the treatment of fevers and pain.

Pamphlet on Fevers –

- Written by American Academy of Pediatrics
- Pamphlets are to be given to parents.
- Provides parents information on treatment of fevers.
- Will be supplied by DCC.

2.6 AVICA MEDICATIONS

The use and purpose of the AVICA medication should be explained to the parent/guardian. AVICA therapy should be started when a parent would normally give the child ibuprofen or acetaminophen for pain or fever.

Parents should be reminded to give the dose specified on the bottle and not to give the AVICA medications to the participant more often than every 6 hours.

Parents should record AVICA medication use on the Parental AVICA Study Medication Diary between visits. The Diaries should be brought to all study visits. The site will need to record any AVICA medication use on the P4_AVICA_DIARY.

Visit 2

The randomization module will assign the participant to receive either ibuprofen or acetaminophen. It will provide the bottle number that should be dispensed to the parent/guardian at Visit 2.

The AVICA therapy is dosed based on the participant's weight at each visit. The P4_AVICA_MED form gets completed at each visit, and the child's dose is updated as the child's weight changes.

Visit 3-8

The P4_AVICA_MED form should be completed at each visit. The participant's dose is updated at each visit based on the child's weight. If necessary, a new bottle of AVICA medication can be obtained from the randomization module.

The P4_AVICA_COMPLY form should be completed at each visit. If the participant has used AVICA meds since the last visit, adherence will be assessed based on the weight of the bottle.

If the participant's weight exceeds the highest weight listed on the P4_AVICA_MED form (i.e. 34.0 kg), then the largest dose listed should be used (i.e. 15.5 mL) for the remainder of the study. Please contact the DCC so that a protocol exception can be assigned (since the participant's dose is no longer being adjusted by the participant's weight as specified in the protocol).

Replacement/Lost Drugs

The randomization module can also be used to obtain lost/replacement AVICA medications in the event that a parent would lose or spill the medication.

Additional Dose of AVICA Medication/Unblinding AVICA Medication

The following scenarios provide guidance when an additional dose of AVICA Medication or unblinding of the AVICA medication might be required:

If the treating provider is absolutely demanding that the AVICA medication be unblinded, follow the unblinding procedures as soon as possible.
If the treating provider is concerned about inadequate control (0-6 hours), but not demanding unblinding, an extra dose of over-the-counter acetaminophen can be given (see below for script).

If the treating provider is requesting unblinding, but unblinding is not immediately possible, an extra dose of over-the-counter acetaminophen can be given while awaiting unblinding (see below for script).

If parents are requesting unblinding due to concern of lack of efficacy of AVICA medication, they should follow-up with their study doctor or PCP for evaluation. If the participant has an uncontrolled fever/pain, the participant should be evaluated.

Script for Encouragement of Giving an extra dose of acetaminophen when PCP requests it:

'I understand that you want to give an additional unblinded dose of medication to your patient. The American Academy of Pediatrics has a Clinical Practice Guideline that specifies maximum daily doses for both acetaminophen and ibuprofen. While the AVICA study doses ibuprofen at the maximum daily dose of 40 mg/kg/day, the dose of acetaminophen in the study when given as directed is 60 mg/kg/day, which is below the maximum daily allowance of 90 mg/kg/day. Therefore, please consider giving an additional dose of 15 mg/kg of over-the-counter acetaminophen.'

Suspected Overdose of AVICA medications

If an overdose of the AVICA medication is suspected, poison control should be contacted immediately at 1-800-222-1222.

2.7 AVICA MEDICATION COMPLIANCE

Visits 3-8

Complete the AVICA Compliance Checklist (P4_AVICA_COMPLY)

Adherence with the AVICA medications is assessed on the AVICA Compliance Checklist (P4_AVICA_COMPLY).

Adherence will be measured by weighing the contents remaining in the bottles. Therefore, it is vital that the parent/guardian does not throw away the used study medication bottles and brings them to the next study visit.

The calculated adherence will not be exact and should be used to counsel the parent/guardian if it seems that he/she is not giving the participant the correct dose of medication.

If you know that the calculated adherence is not correct for reasons such as the parent spilled the medication, etc., please provide a comment in the comment field.

2.8 AVICA STUDY FAILURE

Visit 3-8

The participant will be deemed an AVICA Study Failure if he/she experiences any of the following:

- Febrile Seizure
- New onset hepatic, renal or biliary disease
- Jaundice
- Clinical signs/findings consistent with hepatitis or liver disease

If the participant has any of the above symptoms, he/she should be deemed an AVICA Study Failure. He/she should be termed from AVICA, but can continue with INFANT visits.

2.9 BLOOD SAMPLING PROCEDURES

Visit 2

A. Materials required:

- **1 gold-top serum separation tube (5 mL draw capacity)**
  - BD Vacutainer #367986, Fisher catalog #02-683-97
- **2 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
- **1 Becton Dickinson (BD) P700 tube (purple top, 3 mL draw capacity)**
  - BD catalog #366473
  - Note: When ordering tubes, the price quote is $280 for '1 Each'. '1 Each' is '1 Kit' which contains 20 tubes. The tubes have an expiration date of 1 year after manufacture, so do not order all tubes up front. Sites with consortiums may choose to order 1 Kit and divide them up to minimize the cost.
  - Note: The tubes will need to be refrigerated upon arrival at your site.
- **Sample tubes/vials (need two sizes)**
  - Fisherbrand 0.5 mL microcentrifuge tubes, Fisher catalog #02-681-370
  - Fisherbrand 5.0 mL cryogenic vials, Fisher catalog #10-500-27
- **Glutathione preservation vials (Oakland will supply)**
- **Pipetter for 200 µL, 250 µL, and 500 µL aliquots (DCC will supply)**
  - Gilson Pipetman P1000 pipetter, Fisher catalog #F123602
  - Gilson D1000 racked pipet tips, Fisher catalog #F171500G
- **Cryovial storage boxes for freezing of sample vials**
- **Venipuncture supplies**
  - Butterfly needles, tourniquet, alcohol wipes, gauze, Band-Aids

B. Tests to be performed:

The following blood tests will be performed in INFANT/AVICA 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
- Eosinophil cationic protein
- CBC with differential (total WBC and Eosinophils)

- Genetic Analysis (optional)
- Metabolomics and proteomics
- Glutathione and related metabolites

C. 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 10-15 mL** of blood will be drawn into **5 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 (no exceptions*)***:

- **Tube #1:**
  - 5 mL in one gold-top tube for Immunocap and eosinophil cationic protein
- **Tube #2:**
  - 1 mL in one small purple-top EDTA tube for CBC with differential
- **Tube #3:**
  - 4 mL in one plastic purple-top EDTA tube for genetics
  - * Genetics is optional based on consent to participate, this may be skipped if consent isn't obtained
- **Tube #4:**
  - Up to 3 mL in one BD P700 (purple top) tube for metabolomics/proteomics
- **Tube #5:**
  - 1-2 mL in one small purple-top EDTA tube for glutathione and related metabolites

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, Total IgE and Eosinophil Cationic Protein 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 **500 µL of serum to one small microcentrifuge tube (0.5 mL capacity)** for eosinophil cationic protein measurement.
5. Add **remaining serum to one large microcentrifuge tube (5 mL capacity, cat #10-500-27)** for ImmunoCap and IgE testing.
6. Discard the gold top blood collection tube.
7. Store the eosinophil cationic protein vial and the ImmunoCap/IgE vials in separate boxes and freeze immediately at -20° to -80° C.
8. 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 first 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 (P4_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.**

Metabolomics and Proteomics Procedures

***These instructions refer to the BD P700 (purple-top) 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. Centrifuge the tube at 1100-1300 RCF (*g*) for 10 minutes to separate the plasma.
3. Add **250 µL of plasma to one threaded vial (0.5 mL capacity, cat #02-681-370).** Continue adding 250 µL serum to other threaded vials until there is no plasma remaining (all plasma will be used). Be careful not to touch the red blood cell pellet.
4. Discard the BD P700 (purple-top) blood collection tube.
5. Immediately freeze the plasma vials at -20° to -80° C.
6. Metabolomic and proteinomic vials should be shipped monthly **on dry ice** on the first Monday of each month (if Monday is a holiday, then ship on Tuesday) (see shipping below).

Glutathione and Related Metabolites Procedures

***These instructions refer to the second small, 2 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. Centrifuge the tube at 1100-1300 RCF (*g*) for 10 minutes to separate the plasma and the red blood cell pellet.
3. Add **500 µL of plasma to one glutathione preservation vial***.
4. Add **100 µL of the red blood cell pellet to one glutathione preservation vial***.
5. Immediately freeze the vials at -80° C.
6. Glutathione vials should 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).

***** When the **glutathione preservation tubes** are needed, thaw the appropriate number of tubes on ice (will take about 1.5-2 hours). Make sure that the IAM solution collects on the bottom of the tube (you can do a quick spin if needed). If the participant is not eligible for randomization, the thawed tubes cannot be refrozen. Unused thawed tubes should be discarded.

D. Specimen Tracking – Collection Day

Enter the participant's 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 1.5" x.75"
http://divbio.com/lasercryotags150x0751200pk
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.

E. 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.

F. 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.

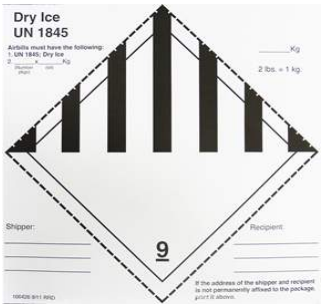
6. Fill bottom of shipping box with dry ice. **NOTE: There should be sufficient dry ice to keep the samples frozen until they reach the laboratories.**
   Suggestions:
    - Plastic bubble wrap can be used at the bottom and top of the shipping container.
    - Plastic bubble wrap can be reused if there 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. There should be both a FedEx shipping label and a secondary Avery address label (with both the 'to' and 'return' addresses listed).

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

G. 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 (P4_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 INFANT 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

Eosinophil Cationic Protein and Immunocap samples

- Enter participant's blood draw information into Sample Tracking module.
- The eosinophil cationic protein and immunocap samples can be sent together in one shipment. 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: leroys@njhealth.org

Metabolomics and Proteomics samples

- Enter participant's blood draw information into Sample Tracking module.
- The metabolomics/proteinomics and urine samples can be sent together in one shipment. Samples must be shipped **monthly** via FedEx priority overnight.
- Samples should be shipped to the following address:

National Jewish Health – Reisdorph Lab
1400 Jackson St
Room K924b
Denver, CO 80206
ATTN: Roger Powell
Tel: (303) 398-1853
Email: powellr@njhealth.org

Glutathione and related metabolites samples

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

Children's Hospital Oakland Research Institute
5700 Martin Luther King Jr. Way
Oakland, CA 94609
ATTN: Jung Suh
Tel: (415) 860-5941
Email: jsuh@chori.org

2.10 CERTIFICATION

Individuals who carry out INFANT/AVICA study visits must be certified to do so. That is, personnel who complete any of the protocol-specific INFANT/AVICA forms (designated by a P4 prefix in the form name) must possess INFANT/AVICA study certification.

To obtain INFANT/AVICA certification, clinical personnel must complete the following steps:

- Thoroughly read the INFANT and AVICA protocols and this Manual of Operations.
- Pass the INFANT/AVICA certification exam. This exam can be found on the AsthmaNet secure website in the Certification folder. Exams should be completed and emailed to the AsthmaNet-Certification alias.
- Pass the Spirotel® Certification Exam.

Protocol Exceptions will be assigned when an uncertified individual performs protocol-related tasks or carries out procedures for which he or she is uncertified. Protocol violations will be assigned if this persists at a given site over a period of time.

The quality of AsthmaNet data is tracked and reported on a regular basis to the individual sites, the AsthmaNet Quality Control Committee (QCC), and to the Data and Safety Monitoring Board (DSMB).

2.11 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 INFANT/AVICA 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 <u>not taken</u> 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 INFANT and AVICA 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 (P4_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.

Be sure to capture any ibuprofen or acetaminophen use on the CMED form.

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 INFANT/AVICA studies, the record should be marked ‘ongoing at final visit.’

Collecting non-study use of ibuprofen and acetaminophen

Since the purpose of the AVICA study is to compare ibuprofen to acetaminophen, it is important to collect any non-study (i.e. non-AVICA) use of ibuprofen and acetaminophen. Parents will be given an instructional handout which explains how to read medication labels to find medications that contain ibuprofen or acetaminophen. They will be instructed to record any illness and non-study medication on an Illness/Non-study medication Diary. The Diary will be reviewed at each visit. The coordinator should record any non-study use of ibuprofen or acetaminophen on the CMED form.

2.12 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 INFANT/AVICA studies.

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.

2.13 ELIGIBILITY CRITERIA

Visit 1

Inclusion/Exclusion Criteria (P4_ELIG1)

INCLUSION CRITERIA

The following inclusion criteria pertain to both INFANT and AVICA. Participants may be reassessed if not initially eligible.

1. Willingness to provide informed consent by the participant's parent or guardian for both the INFANT study and AVICA study. If the study consent form was signed in advance of Visit 1, the parent/guardian should sign a new consent with the current date.

2. 12-59 months of age. Note: Participants who are 60 months old or older at the time of *enrollment* are not eligible for INFANT/AVICA. A participant who is between 59 and 60 months old should be considered 59 months old until he/she reaches 60 months.

3. 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.

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 INFANT/AVICA study.
2. Clinically relevant gastroesophageal reflux. Note: If a child takes medication daily to treat gastroesophageal reflux, it should be considered clinically relevant.

3. Concurrent medical conditions other than asthma that are likely to require oral or injectable corticosteroids during the study.
   >4 courses of systemic corticosteroids in past 6 months.
4. More than 2 hospitalizations for wheezing or respiratory illnesses within the preceding 12 months.
5. Participation presently or in the past month in another investigational drug trial.
6. Evidence that the family may be unreliable or nonadherent, or may move from the site area before trial completion.
7. Participant does not have a primary medical caregiver (nurse practitioner, physician assistant, physician or group medical practice).
8. Parent is unable to use the spirotel® e-diary correctly.
9. Use of any systemic corticosteroids in the 2 weeks prior to enrollment.

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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. History of significant adverse reaction to any study medication ingredient (fluticasone, montelukast, ibuprofen, acetaminophen, oral corticosteroids and albuterol).
2. Gestation less than late preterm as defined as birth before 35 weeks gestational age. Note: The APRIL criterion is 34 weeks.
3. Immunodeficiency disorders.
4. Chronic or active lung disease other than asthma, such as cystic fibrosis and BPD. Evaluation during the screening process will assure that an adequate evaluation of other lung diseases has been performed.
5. Co-morbid disorders associated with wheezing (aspiration, tracheomalacia, congenital airway anomalies or bronchiectasis).
6. Chronic medical disorder that could interfere with drug metabolism/excretion (chronic hepatic, biliary, renal disease or seizure disorder treated wth anticonvulsants).
7. Chronic medical disorder that may increase the risk of drug-related injury (Osteogenesis imperfect, Crohn's disease, ulcerative colitis, juvenile rheumatoid arthritis, clotting disorders, factor deficiency, G6PD deficiency, phenylketonuria).
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.
9. History of respiratory failure requiring mechanical ventilation.
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 < 5th percentile for age and gender, a growth chart from the previous year should be obtained from the participant's

primary care provider. If he/she crosses (downward) two major percentile lines during the previous year, he/she has significant developmental delay/failure to thrive and is ineligible.

If it is necessary to obtain a growth chart from the previous year, Q1210 should be left missing until the growth charts are obtained. It would also be helpful to add a comment in the comments section for the P4_ELIG1 form. A data correction for Q1210 should be submitted once the growth charts are obtained.

NOTE: The protocol writing committee recommends that children living in the same household should not be enrolled in the INFANT/AVICA study at the same time to prevent a mix-up of study drugs and other materials.

INCLUSION CRITERIA – MEDICATIONS

Participants who are ICS- and LTRA-naïve, as well as children on current step 2 therapy who are treated with daily ICS, daily LTRA, or intermittent ICS or LTRA are eligible.

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

1. On more than 1 controller therapy, unless the second controller therapy is a LTRA. If the second controller therapy is LTRA and can be discontinued per the study physician at Visit 1, the participant is eligible.
2. Controller Therapy Doses cannot be higher than the following

Medication		No more than this number puffs/day (limit)
Advair (fluticasone-salmeterol)	DPI: 100/50 mcg/inh DPI: 250/50 mcg/inh DPI: 500/50 mcg/inh HFA: 45/21 mcg/inh HFA: 115/21 mcg/inh HFA: 230/21 mcg/inh	Any child on this medication does not qualify
Symbicort (budesonide-fomoterol)	80/4.5 mcg/inhalation 160/4.5 mcg/inhalation	Any child on this medication does not qualify
Dulera (mometasone-formoterol)	100/5 mcg/inhalation 200/5 mcg/inhalation	Any child on this medication does not qualify

Medication		No more than this number puffs/day (limit)
Beclomethasone	HFA: 40 mcg/puff	6 puffs
Beclomethasone	HFA: 80 mcg/puff	3 puffs
Budesonide	Nebulizer 0.25mg suspension	4 nebs
Budesonide	Nebulizer 0.5mg suspension	2 nebs
Budesonide	Nebulizer 1mg suspension	1 neb
Budesonide	Flexhaler: 90 mcg/inh	4 inhalations
Budesonide	Flexhaler: 180 mcg/inh	2 inhalations
Ciclesonide	HFA: 80 mcg/puff	3 puffs
Ciclesonide	HFA: 160 mcg/puff	2 puffs
Flunisolide	HFA: 80 mcg/puff	3 puffs
Fluticasone	HFA: 44 mcg/puff	6 puffs
Fluticasone	HFA: 110 mcg/puff	2 puffs
Fluticasone	HFA: 220 mcg/puff	1 puff
Fluticasone	DPI: 50 mcg/inh	4 inhalations

Medication		No more than this number puffs/day (limit)
Fluticasone	DPI: 100 mcg/inh	2 inhalations
Fluticasone	DPI: 250 mcg/inh	1 puff
Mometasone	DPI: 110 mcg/inh	2 inhalations
Mometasone	DPI: 220 mcg/inh	1 inhalation
Singulair	4 or 5 mg/tablet	1 tablet
Singulair	4 mg/packet	1 packet
Triamcinolone	MDI: 75 mcg/puff	6 puffs

INCLUSION CRITERIA – SYMPTOMS

1. Participants who are currently taking long-term asthma controller therapy must have at least one of the following criteria:

    - Taking ICS or LTRA for more than 3 months out of the previous 6 months
    - Daytime asthma symptoms more than 2 days per week (average over the past 4 weeks)
    - At least 1 nighttime awakening from asthma (over the past 4 weeks)
    - 2 or more asthma exacerbations requiring systemic corticosteroids (**in past 12 months**)
    - 4 or more wheezing episodes (in past 12 months) (Note: 1 wheezing episode = 24 hours or more of symptoms)

Participants who have been treated with a controller therapy during the 4 weeks prior to enrollment will complete the INFANT Eligibility Checklist 2 (P4_ELIG2). Based on the responses to P4_ELIG2, these participants will be put on active or placebo Run-In medications. If the participant requires active Run-In medications, he/she should be put on either active ICS or active LTRA, not both. The decision of which one should be active should be based on whether the participant was using active ICS or active LTRA prior to enrollment.

<u>Completing the P4_ELIG2 Form:</u>

Q1000-Q1020: If the participant is taking LTRA for reasons other than asthma (in addition to ICS), the study physician should be consulted. If the LTRA can be discontinued per study physician, then the participant is eligible and can continue. If the LTRA can't be discontinued, then the participant is ineligible since he/she would be on 2 controllers. If the participant is taking LTRA for asthma (in addition to ICS), he/she is ineligible since 2 controllers would be considered greater than Step 2 therapy.

2. Participants who are not currently taking long-term 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)
    - At least 1 nighttime awakening from asthma (over the past 4 weeks)
    - 2 or more asthma exacerbations requiring systemic corticosteroids (**in past 6 months**)
    - 4 or more wheezing episodes (in past 12 months) (Note: 1 wheezing episode = 24 hours or more of symptoms)

Participants who haven't been treated with a controller therapy during the 4 weeks prior to enrollment will complete the INFANT Eligibility Checklist 3 (P4_ELIG3). If eligible, these participants will be put on placebo Run-In medications (placebo ICS and placebo LTRA).

VISIT 2

1. Participants who are using placebo Run-In medications during the Run-In should complete the INFANT Eligibility Checklist 4 (P4_ELIG4).

<u>Completing the P4_ELIG4 Form:</u>

Q1000-Q1010: If the participant has had an asthma exacerbation requiring systemic corticosteroids since Visit 1, he/she is ineligible and should be termed from the study. In addition, if the participant was hospitalized, the event should be reported as a SERIOUS Adverse Event. Documentation should be completed and sent to the DCC. If the participant wasn't hospitalized and the number of corticosteroid bursts in the past 6 months is less than 5, the participant can be re-enrolled in 2 months. Otherwise, if the number of corticosteroid bursts in the past 6 months is 5 or more, the study physician should be consulted and step-up therapy should be considered. The participant can potentially be re-enrolled at a later date once the number of steroid bursts in the past 6 months is fewer than 5.

Q1020: If the participant used any asthma medications other than albuterol since Visit 1, he/she is ineligible. The Run-In should be repeated. The partially-completed Visit 2 packet should be filed in the participant folder, re-run the Visit Scheduler to

determine a new Visit 2 date, re-issue all study medications and supplies and do not update the Visit number in the Spirotel® device. The Run-In period can only be repeated once for participants who have used asthma medications other than albuterol. If the participant does not meet the eligibility requirements at the repeated Visit 2, he/she is ineligible and should be termed.

Q1030: If the participant has developed any new medical conditions since Visit 1, the study physician should be consulted. If the new medical condition was not related to study participant, the participant may be randomized if all other eligibility criteria are met.

Q1040-Q1090: If the percent compliance with either the Diary Completion, the Brown Daily Inhaler or the Oral Study Medication is less than 75%, the participant is ineligible. If there are justifiable reasons for the low compliance that can be over-come, the participant can be given a second chance. The Run-In should be repeated. The Run-In period can only be repeated once for participants who have compliance less than 75%. The participant should be termed and can be re-enrolled at any time. If there is an unusual circumstance that led to the low adherence (family crisis, etc.), the DCC can be contacted for a protocol exception to allow the Run-In to be extended instead of re-enrollment.

Q1110: If the participant had daily daytime asthma symptoms during the Run-In (i.e. 7 days per week), he/she is ineligible and should be termed. The study physician should be consulted and step-up therapy should be considered. The participant can potentially be re-enrolled at a later date if/when eligibility criteria are met.

Q1140: If the participant had more than 1 nighttime awakening from asthma during the Run-In, he/she is ineligible and should be termed. The study physician should be consulted and step-up therapy should be considered. The participant can potentially be re-enrolled at a later date if/when eligibility criteria are met.

Q1180: If the participant has not marked any starred boxes (Q1120, Q1150, Q1160, Q1170) and also has not marked any shaded boxes, he/she is not eligible for randomization at this time. The Run-In should be extended for another 2 weeks. The partially-completed Visit 2 packet should be filed in the participant folder, re-run the Visit Scheduler to determine a new Visit 2 date, re-issue all study medications and supplies and do not update the Visit number in the Spirotel® device. The Run-In period can be extended up to 8 total weeks. The participant needs to demonstrate some asthma symptoms during the Run-In to be randomized (or meet the wheezing or asthma exacerbation requirement prior to enrollment – Q1160, Q1170).

2. Participants who are using active Run-In medications during the Run-In should complete the INFANT Eligibility Checklist 5 (P4_ELIG5).

<u>Completing the P4_ELIG5 Form:</u>

Q1000-Q1010: If the participant has had an asthma exacerbation requiring systemic corticosteroids since Visit 1, he/she is ineligible and should be termed from the study. In addition, if the participant was hospitalized, the event should be reported as a SERIOUS Adverse Event. Documentation should be completed and sent to the DCC. If the participant wasn't hospitalized, he/she can be re-enrolled in 2 months.

Q1020: If the participant used any asthma medications other than the study medications since Visit 1 (including an increase in medication dose or frequency), he/she is ineligible and should be termed. The study physician should be consulted and step-up therapy should be considered. The participant can be re-enrolled at a later date if/when eligibility criteria are met.

Q1030: If the participant developed any new medical conditions since Visit 1, the study physician should be consulted. If the new medical condition was not related to study participant, the participant may be randomized if all other eligibility criteria are met.

Q1040-Q1090: If the percent compliance with either the Diary Completion, the Brown Daily Inhaler or the Oral Study Medication is less than 75%, the participant is ineligible. If there are justifiable reasons for the low compliance that can be over-come, the participant can be given a second chance. The Run-In should be repeated. The Run-In period can only be repeated once for participants who have compliance less than 75%. The participant should be termed and can be re-enrolled at any time. If there is an unusual circumstance that led to the low adherence (family crisis, etc.), the DCC can be contacted for a protocol exception to allow the Run-In to be extended instead of re-enrollment.

Q1120: If the participant had daily daytime asthma symptoms during the Run-In (i.e. 7 days per week), he/she is ineligible and should be termed. The study physician should be consulted and step-up therapy should be considered. The participant can potentially be re-enrolled at a later date if/when eligibility criteria are met.

If the participant had daytime asthma symptoms between 2-7 days per week on average, the Run-In should be repeated. The participant has too many daytime asthma symptoms to be randomized at this time. The partially-completed Visit 2 packet should be filed in the participant folder, re-run the Visit Scheduler to determine a new Visit 2 date, re-issue all study medications and supplies and do not update the Visit number in the Spirotel® device. The Run-In period can only be repeated once for participants who are too symptomatic. If the participant does not meet the eligibility requirements at the repeated Visit 2, he/she is ineligible and should be termed.

If the participant had <2 days per week of asthma symptoms, he/she is potentially eligible.

Q1140: If the participant has more than 1 nighttime awakening due to asthma during the Run-In, the Run-In should be repeated. The participant has too many nighttime asthma symptoms to be randomized at this time. The partially-completed Visit 2 packet should be filed in the participant folder, re-run the Visit Scheduler to determine a new Visit 2 date, re-issue all study medications and supplies and do not update the Visit number in the Spirotel® device. The Run-In period can only be repeated once for participants who are too symptomatic. If the participant does not meet the eligibility requirements at the repeated Visit 2, he/she is ineligible and should be termed.

Problems with the Spirotel® device

It is important that the parents clearly understand how to use the Spirotel® device at Visit 1. The data in the device cannot be updated or changed at Visit 2 if it was not entered correctly.

If something happens and the Spirotel® data is not accurate and the participant meets all other eligibility requirements, please use the following process:

1. Call the DCC for a protocol exception.
2. Complete the ELIG4/ELIG5 forms by recording the data as it appears on the Spirotel Eligibility report. (i.e. If Brown Daily Inhaler adherence is 50%, record 50%. Is the brown daily adherence >= 75%? Answer 'No'. Please provide a comment about the situation and that a DCC gave a protocol exception. The comment will get entered and stored in the database.)

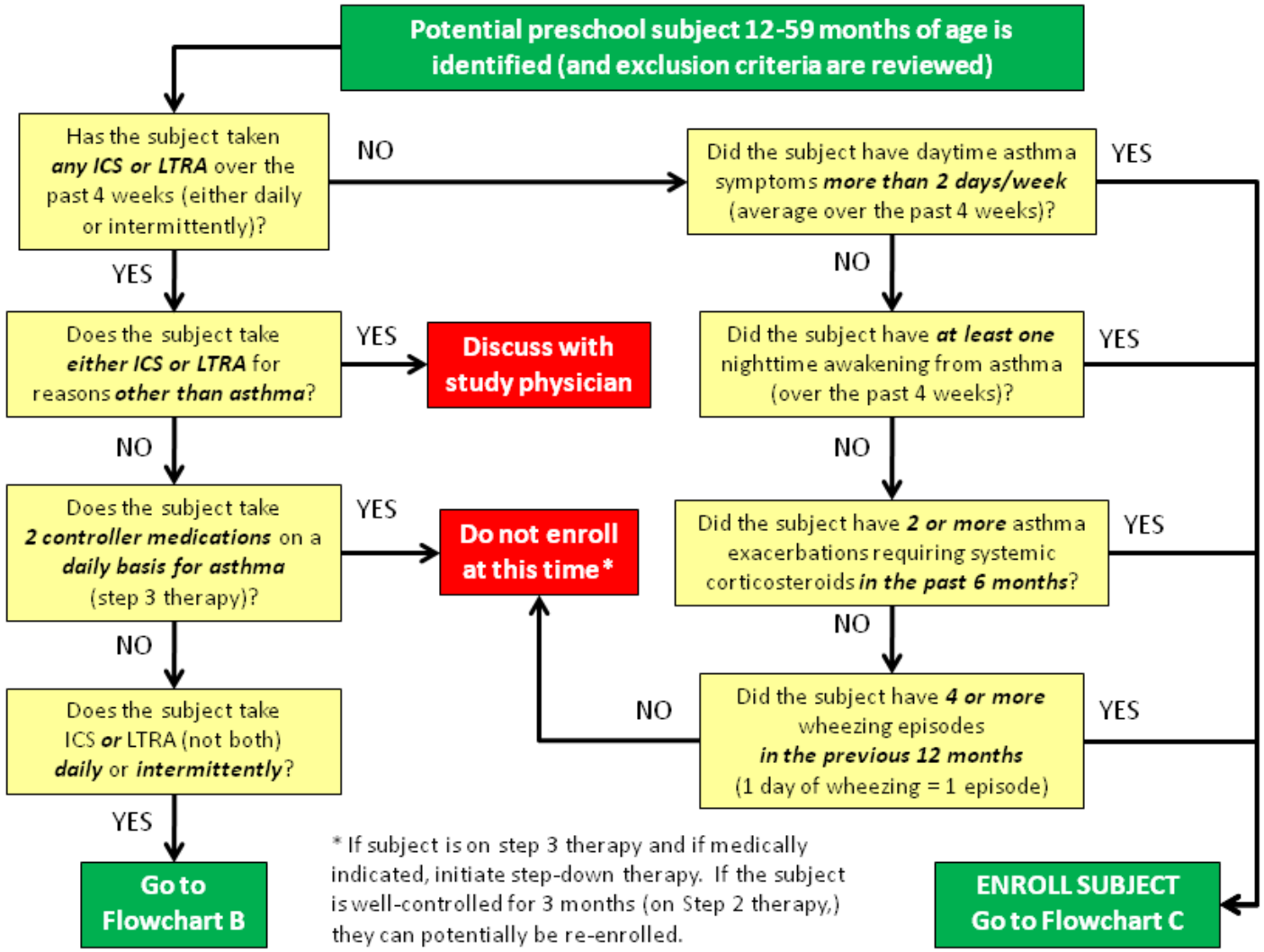
Common Mistakes that Parents make when using the Spirotel Device – There are several questions that parents are answering incorrectly during the Run-In period. Please try to spend a little extra time when reviewing the Spirotel Device at Visit 1. There is a lot of information for the parent to absorb at Visit 1, but spending a few extra minutes at Visit 1 may prevent problems down the road. The questions that the parents are answering incorrectly are:

Question #2: Woke Diff Breath: Did your child awaken at night with difficulty breathing from asthma? We have had a number of parents recording nighttime awakenings but when the coordinator inquires about them, it turns out they weren't really nighttime awakenings. It might be helpful to review with the parent examples of what would not be a nighttime awakening (i.e. child awakens at his/her normal time in the morning coughing, child is coughing before bed but does not wake up during the night, etc.)

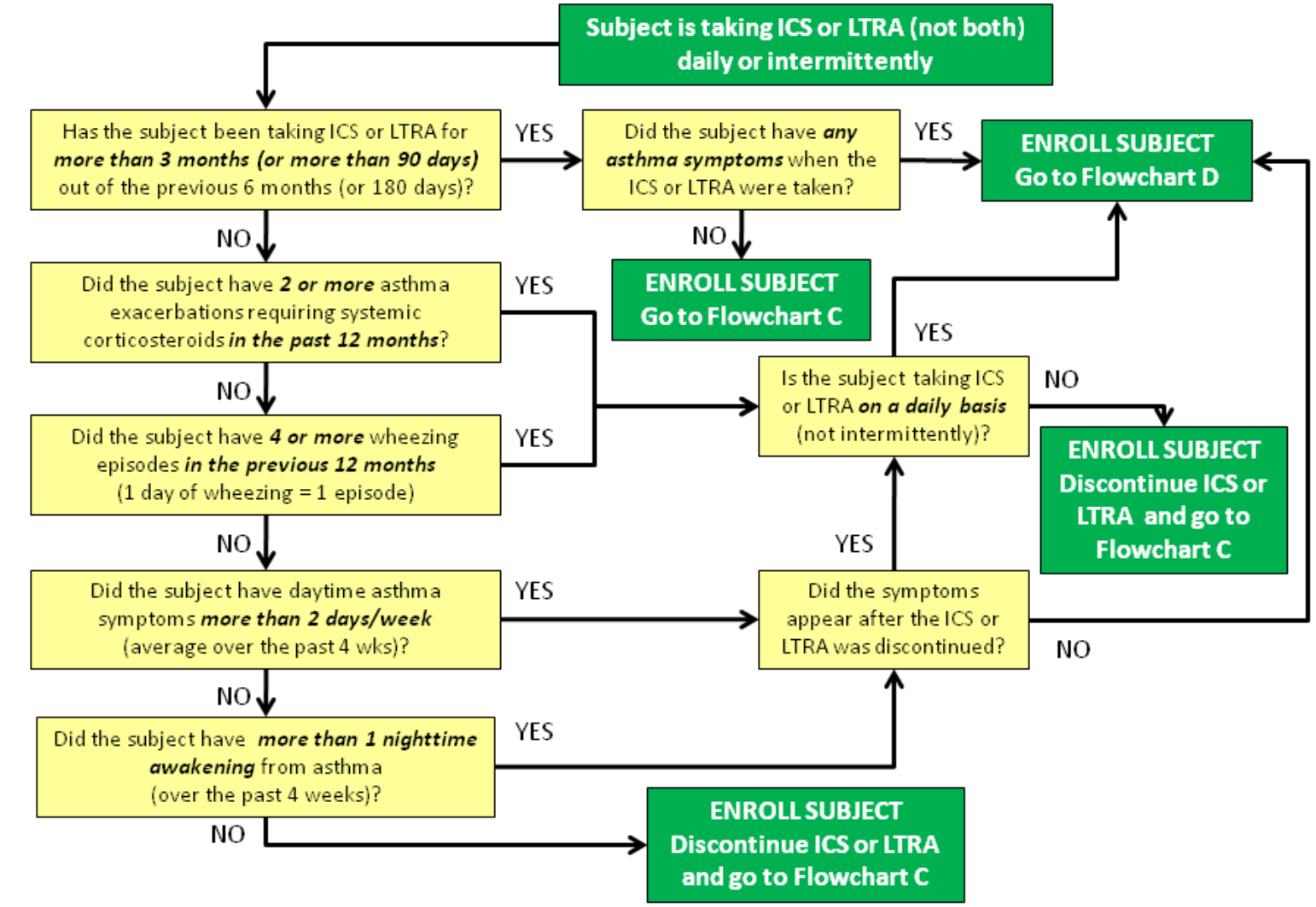
Question #9: # Puffs Brown: The number of puffs your child took from the brown daily inhaler during the past 24 hours. A common problem is the parent records the number of times (i.e. 2) instead of the number of puffs (i.e. 4).

Question #10: Oral Med Taken: Was the oral study medication taken before bedtime? Several parents have interpreted this to be prednisolone instead of LTRA. They consistently answer 'no' to that question.

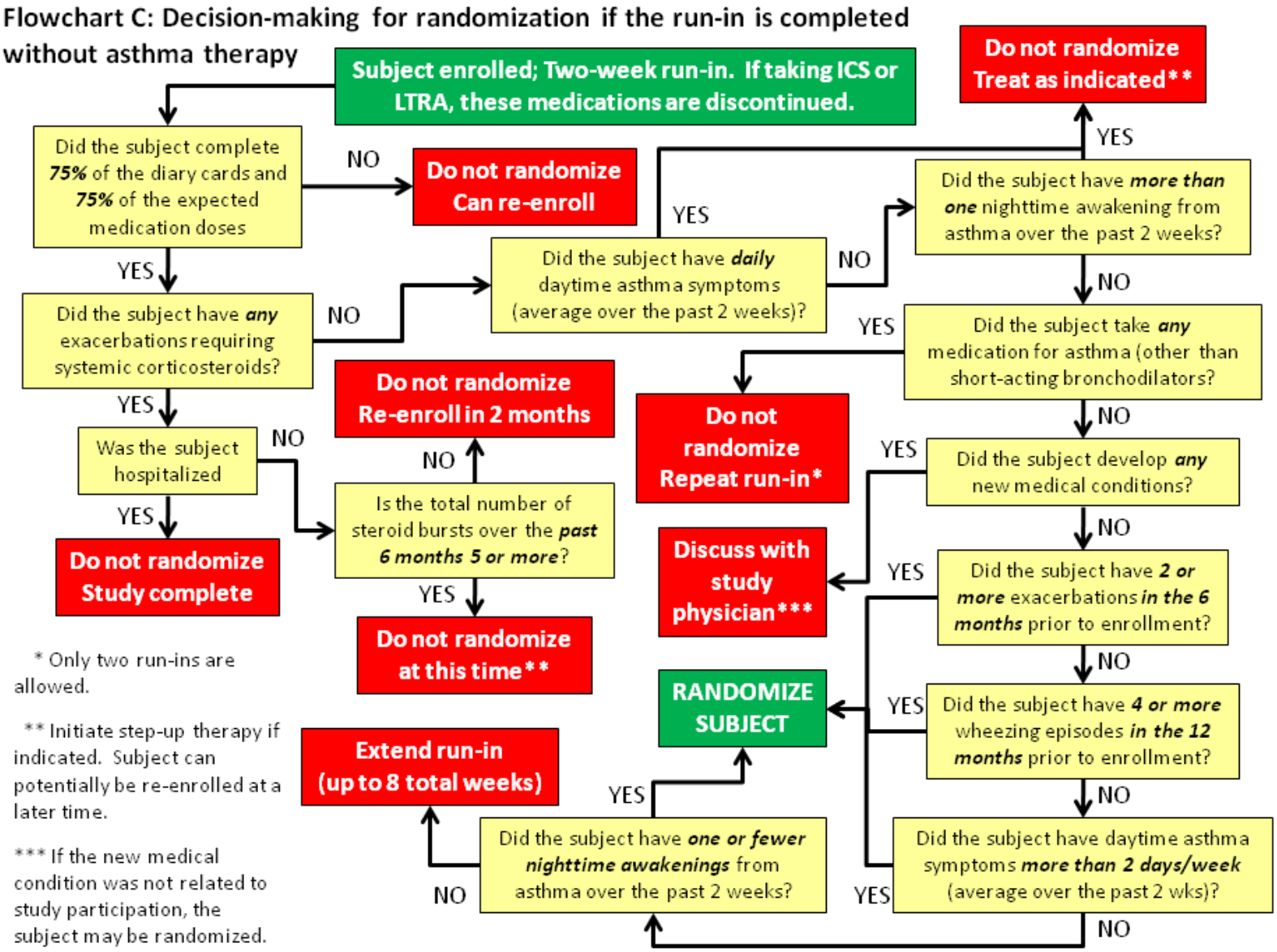
Flowchart A: Decision-making for enrollment once a subject is identified



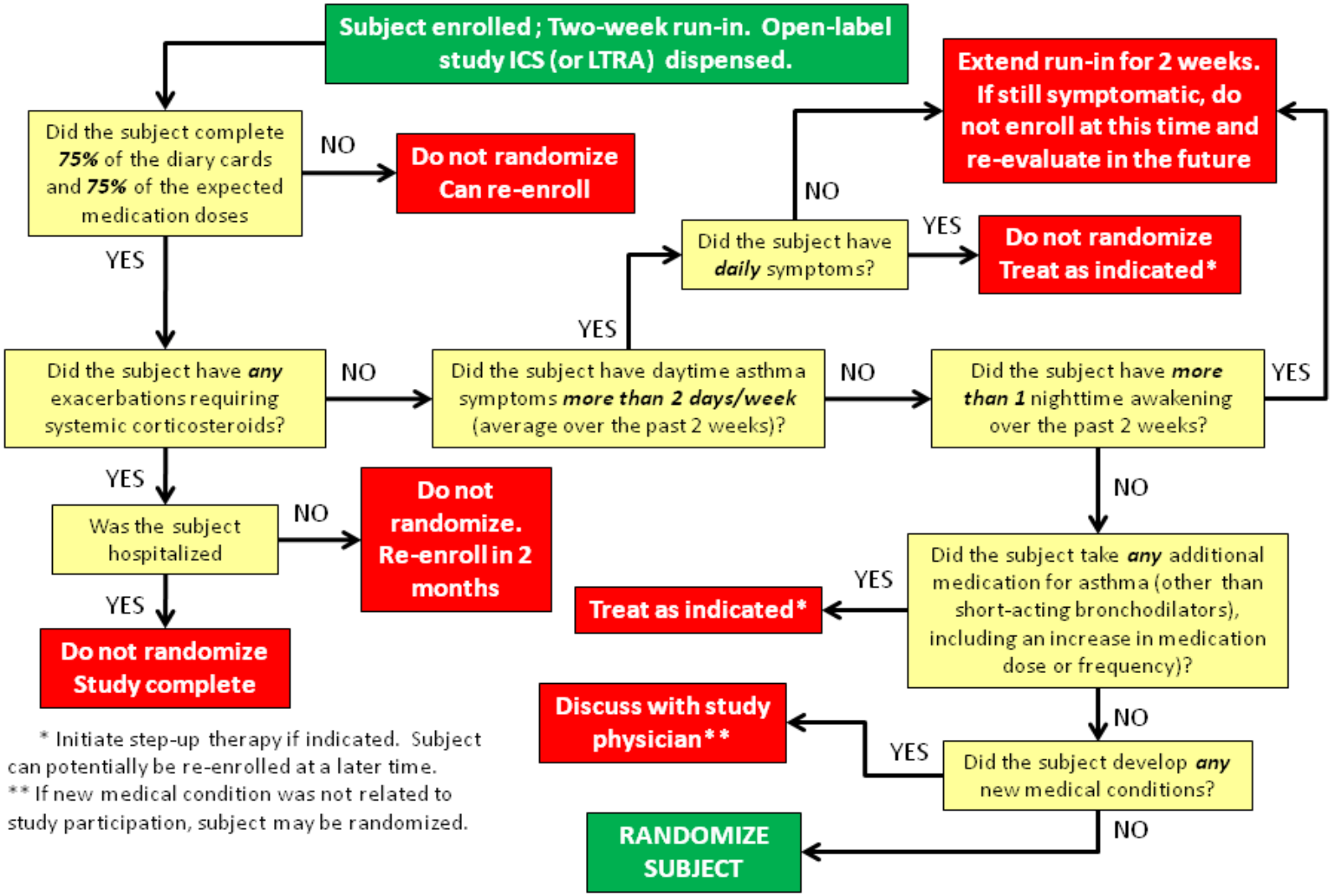
Flowchart B: Decision-making for enrollment if the subject is currently taking long-term asthma controller therapy



Flowchart C: Decision-making for randomization if the run-in is completed without asthma therapy



Flowchart D: Decision-making for randomization if the run-in is completed with long-term asthma controller therapy



* Initiate step-up therapy if indicated. Subject can potentially be re-enrolled at a later time.
** If new medical condition was not related to study participation, subject may be randomized.

Exclusionary Medical Conditions during INFANT/AVICA

Addison's disease
Cardiac arrhythmias (clinically significant)
Cardiac disorder (except hemodynamically
insignificant ASD, VSD, or heart murmur)
Cataract's
Chest surgery (call for exception)
Clotting disorders
Congenital anomalies of the lung and chest,
including growth abnormalities that affect predictability of expected lung function parameter
Crohn's disease
Cushing's disease
Diabetes mellitus (poorly controlled)
Dyspnea by any cause other than asthma
Eating disorder (e.g. anorexia or bulimia)
Eczema, severe (if likely to require oral/systemic corticosteroid treatment)
Factor deficiency
Failure to Thrive
Gastroesophageal reflux (not controlled by
standard medical therapy)
G6PD deficiency
Glaucoma
Hematologic disease
Hepatic disease
HIV/AIDS
Hypertension (poorly controlled)
Inflammatory bowel disease (if likely to require oral/systemic corticosteroid treatment)
Immunologic compromise
Lung disease other than asthma (COPD,
emphysema, chronic bronchitis, pulmonary
embolism, malignancy, cystic fibrosis,
bronchiectasis, bronchopulmonary dysplasia,
among others)
Lupus
Malignancy
Mental illness (bipolar disorder, schizophrenia, oppositional defiance disorder, conduct disorder, uncontrolled panic disorders)

Mental retardation
Myasthenia gravis
Neurologic disease including any seizure disorder (including febrile seizure in infancy)
Osteogenesis imperfecta
Peptic ulcer disease (active)
Phenylketonuria
Premature birth (before 35 weeks gestation)
Renal disease (active)
Rheumatoid arthritis (if likely to require oral/systemic corticosteroid treatment)
Thyrotoxicosis
Tracheomalacia (unresolved)
Tuberculosis (active)
Ulcerative colitis
Vocal cord dysfunction (active)

Allowed medications during INFANT/AVICA

Allowed During Run-In and Treatment Phase:

- acyclovir (e.g., Zovirax) for herpes
- antibiotics (e.g. tetracycline, penicillin, cephalosporin, quinolones, monobactam, macrolides)
- all antihistamines
- anti-fungal therapy
- calcium-based antacids (e.g. TUMS®)
- calcium supplements
- CNS stimulants (e.g. Ritalin, Dexedrine)
- eye preparations for allergic eye symptoms (topical)
- laxatives
- nasal cromolyn
- all nasal decongestants (e.g., Afrin)
- nasal steroids (beclomethasone, budesonide, flunisolide, fluticasone, mometasone, triamcinolone)
- nasal saline spray
- all oral decongestants (e.g., Sudafed)
- oxymetazoline (e.g., Afrin)
- Selective Serotonin Reuptake Inhibitor (SSRI) class antidepressants (e.g., Paxil, Prozax, Zoloft, Effexor)
- study medications
- tacrolimus and pimecrolimus (e.g., Elidel) – avoid daily use
- thyroid replacement medication (e.g. Levothroid, Levoxyl, Synthroid)
- Topical corticosteroids - low potency (aciometasone dipropionate, desonide, dexamethasone, dexamethasone sodium phosphate, fluocinolone acetonide, hydrocortisone, hydrocortisone acetate)
- Topical corticosteroids - medium potency (betamethasone benzoate, betamethasone dipropionate, betamethasone valerate, clocortolone pivalate, desoximetasone, fluocinolone acetonide, flurandrenolide, fluticasone propionate, hydrocortisone butyrate, hydrocortisone valerate, mometasone furoate, triamcinolone acetonide)
- Vitamins, minerals

Allowed During <u>Run-In</u> Only:

- Acetaminophen
- Ibuprofen

2.14 FOLLOW-UP MEDICATION PRESCRIPTION

Visit 8

Prescribe Medication based on Physician Discretion

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, 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.

2.15 FORGOTTEN STUDY MATERIALS

The table below details what to do regarding forgotten study materials at an INFANT/AVICA 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
Forgotten Item	spirotel®	**Visit must be rescheduled.**	**Visit must be rescheduled.**
	Run-In MEDS	**Visit must be rescheduled.**	**NA**
	INFANT MEDS	NA	Bring to next visit
	AVICA MEDS	NA	Bring to next visit
	Albuterol/ Prednisolone	Bring to next visit	Bring to next visit
	Nasal Samples	NA	Bring to next visit
	Parental AVICA Study Med Diary and Illness/Non-study Diary	Bring to next visit	Bring to next visit

2.16 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 INFANT/AVICA 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 INFANT/AVICA study. The genetic analysis participation rate for each clinical center partnership and performance site will be summarized on the INFANT/AVICA 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 4 ml (age 12-60 months). 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.

2.17 GROWTH CHARTS

Height/Length

Visit 1-8

Plot Height or Length 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

NOTE: The same procedure (Height or Length) should be used for the duration of the study. The participant should not change procedures throughout the study.

For Visits 1-8, plot the participant's height or length on the age-specific and gender-specific growth charts provided. The participant's height or length should be plotted at all visits to identify potential growth failures. The Growth Charts are located on the secure AsthmaNet website.

See Growth Failure Protocol in this section for more information on growth failure.

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

Weight

Visit 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 Visits 1-8, plot the participant's weight on the age-specific and gender-specific growth charts provided. The participant's weight should be plotted at all visits to identify potential growth failures. The Growth Charts are located on the secure AsthmaNet website.

See Growth Failure Protocol in this section for more information on growth failure.

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

2.18 GROWTH FAILURE PROTOCOL

Visit 1

Height/Length and Weight

If the participant's height/length or weight plots less than the 5th percentile for age and gender, a growth chart for the previous year should be obtained from the participant's primary care provider. If the participant has crossed two major percentile lines during the previous year, he/she has significant developmental delay/failure to thrive and is ineligible.

Visits 2-8

Plot height/length 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.

A referral should be made to a pediatric endocrinologist for a GROWTH FAILURE evaluation if any of the following occur:

1. If the participant's height/length 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/length (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/length only).

The DCC will identify any potential growth failures from the database within two weeks of data entry. Events identified as potential growth failures may be the result of measurement error rather than actual growth failures. The following procedure will be followed when potential growth failures are identified:

- Email notification will be sent to the lead PI and CC at the site with the potential growth failure. The participant line of the email will state INFANT/AVICA: Potential Growth Failure'.
- The email will also be forwarded to the lead PIs for the INFANT/AVICA study.
- The email will contain all information related to the participant's growth while in the INFANT/AVICA 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 INFANT/AVICA study.

According to the INFANT/AVICA protocol, 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 INFANT/AVICA PIs will decide if the participant will continue in INFANT/AVICA or be termed from the study.

2.19 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.

The parent/guardian completes this questionnaire. 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'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.

2.20 HOSPITALIZATIONS

Participants who are hospitalized for an acute asthma exacerbation for >24 hours during INFANT/AVICA are assigned study failure status. Hospitalizations ≤ 24 hours are not study failures, and the participant can continue in the study. See the *Study 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 INFANT/AVICA MOP and Section 4 of the General MOP for more information.

2.21 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.

2.22 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.

2.23 INFANT MEDICATIONS

Visit 2, 4 and 6

The randomization module should be accessed at Visit 2, 4 and 6 to obtain INFANT medications for each of the 3 treatment periods.

For each of the three treatment periods, a participant will be assigned to an INFANT inhaler kit (which contains the daily inhalers, the intermittent inhalers and the albuterol rescue inhalers). In addition, the participant will be randomized to 2 cartons of LTRA medication (granules or chewable pills).

If the participant is < 2 years old, granules must be dispensed. Participants ≥ 2 years old will be able to choose between granules and chewable pills. Whatever type is chosen at Visit 2 must be used for the duration of the study.

Replacement/Lost Drugs

The randomization module can also be used to obtain lost/replacement drugs in the event that a parent would lose or spill the medication. The randomization module can be accessed to obtain replacement drugs for the LTRA medication. If the participant has lost part of his/her INFANT inhaler kit, please contact the DCC for replacements.

Pre-treatment before Exercise

Participants should be instructed to use 2 inhalations from the red albuterol inhaler and 0 inhalations from the white rescue inhaler. These preventative inhalations should not be recorded in the spirotel® Device.

Dates of Use

Daily Brown Inhaler: Please complete the 'Brown Daily Inhaler Dates-of-Use Worksheet' to determine what dates to complete the use from/to blanks on the label of each Brown Daily Inhaler.

Red Albuterol Inhaler – Instruct the parent to change inhalers when the counter reaches '080'.

White Rescue Inhaler – Instruct the parent to change inhalers whenever the Red Albuterol Inhaler is replaced (or its counter reaches '080').

Additional White Inhaler

If the participant requires an additional white inhaler to keep at a second location (i.e. daycare, school, etc.), the randomization module can be used to obtain the extra white inhaler. Unfortunately, since the white inhaler is part of the INFANT inhaler kit, an entire kit must be assigned to the participant, even if the only item needed is the white inhaler. The participant should only be given the medications from the INFANT inhaler kit that is needed. If only the white inhaler is required, then that should be the only item that is given to the participant from the extra kit.

Since you cannot obtain replacement medications on the same day as a regular visit dispensation (i.e. Visits 2, 4 or 6), you will need to go into the randomization module on a different day to obtain the replacement inhaler kit. Visit 2 is the only visit that cannot be randomized prior to the visit. For all other visits, medications can be obtained from the randomization module up to 3 days prior to the visit.

2.24 INFANT MEDICATION COMPLIANCE

Visits 3-8

Complete the INFANT Compliance Checklist (P4_INFANT_COMPLY)

Adherence with the INFANT medications is assessed on the INFANT Compliance Checklist (P4_INFANT_COMPLY).

The spirotel® Report should be downloaded and results should be transcribed on to the P4_INFANT_COMPLY form.

2.25 INFANT/AVICA TREATMENT QUESTIONNAIRES

Visits 4, 6 and 8 – or last visit
Complete the INFANT Treatment Questionnaire (INFANT_TRTQX)

Visit 8 – or last visit
Complete the AVICA Treatment Questionnaire (AVICA_TRTQX)

The study treatment questionnaires are 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 questionnaires, except for the last page. The last page should be completed by the coordinator.

If a participant withdraws from the INFANT and AVICA studies following randomization and prior to Visit 8, the INFANT and AVICA Treatment questionnaires should be completed at the time of the participant's final contact with the site. Participants who term early from AVICA, but remain in INFANT should complete the AVICA questionnaire at the time the participant terms from AVICA. The INFANT questionnaire should be completed at Visit 4, 6 and 8, or whenever the participant terms from INFANT.

2.26 INFANT TREATMENT ARM FAILURE

Visits 3-8
Complete the INFANT Treatment Arm Failure Form (P4_INFANT_TRTFAIL)

A participant will be deemed an INFANT Treatment Arm Failure if he/she receives two courses of oral/systemic corticosteroids for an asthma exacerbation within any of the three treatment periods (V2-V4, V4-V6, V6-V8). Two courses of prednisone should be separated by at least 1 week to be considered different courses. A course that is extended to 8 days should only be counted as 1 course.

The participant should be scheduled to begin the next treatment period 4-7 days after starting the prednisolone course (or once the prednisolone course is finished).

Prednisone courses given for reasons other than asthma should not count towards treatment arm failure.

2.27 INFORMED CONSENT

Visit 1
Acquire signed INFANT and AVICA informed consents

There are 2 separate Informed Consent forms for INFANT and AVICA. The parent must agree to enroll in both INFANT and AVICA. A participant may drop out of the AVICA study after randomization and remain in the INFANT study. However, a participant cannot drop out of INFANT and stay in the AVICA study.

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

The informed consent documents explain the procedures and time commitment necessary to participate in the INFANT and AVICA trials, 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 INFANT or AVICA consent documents 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 INFANT and AVICA 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 (P4_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 Document (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 INFANT/AVICA 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 INFANT/AVICA trial, he/she must be given the IRB-approved INFANT/AVICA 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 INFANT/AVICA 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.

2.28 MDI INHALATION TECHNIQUE ASSESSMENT

Visit 1

Instruct Use of Albuterol (Rescue) Inhaler (TECH_MDI_FACE, HTMDI_FACE)

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_FACE) has been implemented.

Visits 2-7

Instruct Use of Albuterol (Rescue) Inhaler (TECH_MDI_FACE)

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_FACE checklist. See Section 4 in this manual for details regarding the completion of the TECH_MDI_FACE 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_FACE form, then there should be a note in the clinic progress notes that the technique assessment was reviewed with the participant.

2.29 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.

2.30 MEDICATION ADHERENCE

Visits 3-8

INFANT

Medication adherence will be assessed at the next visit via parental report from the spirotel® device. See spirotel® Section for further information.

AVICA

Medication adherence will be assessed at the visit following use of AVICA medications. It is imperative that the parent/guardian does not throw away medication bottles. They should bring them to the next scheduled visit.

The contents remaining in the bottles should be weighed. The compliance form (P4_AVICA_COMPLY) should be completed. If more than one AVICA bottle was used since the previous visit, a P4_AVICA_COMPLY single form should be completed.

If the parent/guardian reports that the medication was spilled (more than a little), then the adherence estimate will not be accurate. Please provide a comment on the appropriate form noting the spillage and thus, inaccurate measurement of adherence.

2.31 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, 2, 4, 6, 8

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 INFANT Scientific Coordinator at the DCC if scheduling issues arise for these visits.

Visit 3, 5, 7

These visits occur 4 weeks after the start of each treatment period. While it is not ideal for these visits to be missed since AVICA drugs may need to be dispensed and this visit is the only in-clinic visit in the middle of each treatment period, these visits may be skipped if absolutely necessary. Contact the INFANT 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. Arrangements should be made to get a new bottle of AVICA medication if needed.

2.32 NASAL SAMPLING PROCEDURES

Visit 2 AND Day 1 of each illness

Nasal mucus samples will be taken by the coordinator during Visit 2 AND Day 1 of each respiratory illness (by parent at home). Please note: a nasal sample can be obtained up to a maximum of 7 days after the onset, if symptoms are still present. Ideally the samples should be collected on Day 1. However, if the parent forgets on that day, the samples can still be collected within a few days of the ideal date (up to 7 days as stated above). Nasal samples should be collected for all respiratory illnesses (includes both upper and lower respiratory illnesses).

Parents should be given 2 nasal kits to take home. Additional kits can be distributed at visits or mailed to the parents, as needed throughout the study. (Since there are 12 week periods during the study where no visits take place, it might be necessary to mail additional kits.) Sites should inquire at all visits and phone contacts if any nasal samples have been collected and mail additional kits as needed.

There is no maximum number of nasal samples that can be collected during the study. Parents should be instructed that any 2 illnesses should be separated by at least 2 weeks to be considered 2 **different** illnesses (and thus, necessitating collecting 2 different nasal samples).

The 'Daily Activities' Guide on the back of the INFANT/AVICA Action Plan will serve as a reminder to collect nasal samples on Day1 of each illness. For the in-clinic samples that are obtained at Visit 2, the P4_LAB form is part of the visit packet and includes questions regarding whether the nasal sample was collected.

The nasal mucus sample can be obtained by nasal blow or nasal swab technique. The technique would be decided based on the participant's ability to blow their nose during the study visit. If a participant can blow his/her nose, then a nasal blow sample is obtained. If the participant is able to learn the blow technique during the course of the study, they may switch from swab to blow technique at any time. Written instruction should be provided to parents 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 vial or baggie prior to dispensing; assuring the appropriate ID is applied. Parents will write the date collected on the vial or baggie, whichever one they are able to perform.

Two nasal mucus sample kits should be sent home at Visit 2 and maintain two kits at the participant's home during the study.

Contents of Nasal Blow Kit:

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

Contents of Nasal Swab Kit:

- Saline Spray Bottle
- Transport solution
- Swab
- Biohazard Bag (orange)
- Koldtogo Bag
- Ice Pack

Receiving Nasal Samples from home:

- Parents 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

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

Label specifications: Avery 5160 labels

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) 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 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

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 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

    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:

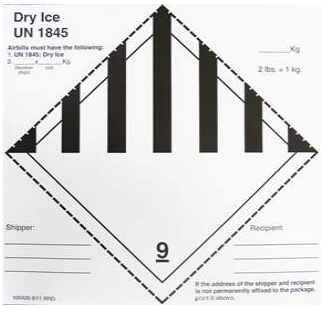
i. Plastic bubble wrap can be used at the bottom and top of the shipping container.
ii. Plastic bubble wrap can be reused if there is no leakage
iii. Cardboard can also be used to stabilize samples.

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. There should be both a FedEx shipping label and a secondary Avery label (with both the ‘to’ and ‘return’ addresses listed).

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 once per month, on the first day that each site ships genetic samples to Tucson. INFANT nasals can be shipped with APRIL nasal samples. As long as INFANT and APRIL samples are being shipped together, the DCC FedEx number can be used to cover the cost of shipping. Otherwise, the site is responsible for the cost.

- Ship to:

  University of WI - Madison
  600 Highland Avenue
  H4/469 CSC
  Attn: Tressa Pappas/Heather Floerke
  Madison, WI 53792-9988
  FAX: (608) 263-9833
  Phone: (608) 263-8539 (Tressa) or (608) 261-1377 (Heather)
  Email: tep@medicine.wisc.edu or hfloerke@medicine.wisc.edu

- 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).

2.33 PARTICIPANT ASSIGNMENT LOG/PROTOCOL ENROLLMENT

Visit 1

Assign participant ID number (P4_LOG)

A Participant Assignment Log (P4_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 P4_LOG and are comprised of 8 digits:

- The first two digits are the number of the AsthmaNet protocol. For the INFANT/AVICA protocol the first two digits are 04.

- The next 3 digits are the AsthmaNet performance site identifier (112=Boston Children's Hospital, 122=Children's Memorial - Chicago, 124=University of Chicago-Peds, 125=Stroger Hospital/Rush Univ., 132=National Jewish – Peds, 141=University of Wisconsin – Peds, 143=Milwaukee, 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, 192=University of Virginia-Peds, 194=Emory University)

- 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 INFANT/AVICA Participant Assignment Log. This number will be the primary participant identifier used during the INFANT/AVICA 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 (P4_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 (P4_LOG)

Following assignment of the participant's ID number on the INFANT/AVICA Participant Assignment Log (P4_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.

Visit 2

Complete the checkbox if the participant has been randomized.

2.34 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 INFANT/AVICA study:

Handouts Distributed at Visits

Visit 1	Run-In Action Plan Asthma Triggers (Asthma_Triggers) – optional How To Use the spirotel® Device (P4_HTSPIROTEL) SPIROTEL® Reference Card (P4_SPIROTEL_REF) How To Use Your albuterol RESCUE Inhaler (HTMDI_FACE)
Visit 2	I/A Action Plan Card / Daily Activities Guide I/A Action Plan wallet-size ID Card I/A Action Plan for Caregivers - optional INFANT Nasal Swab (P4_HTNASAL_SWAB)/ INFANT Nasal Blow (P4_HTNASAL_BLOW) Parental AVICA Study Medication Diary and Illnesses and Non-Study Medication Diary AVICA Reading Medication Labels Handout AVICA Letter to PCP Fever Pamphlet

Run-In Action Plan, I/A Action Plan Card, I/A Action Plan wallet-size ID Card, and I/A Action Plan for Caregivers

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 (P4_HTSPIROTEL)

These instructions can be used as a tool to introduce the spirotel® Device (P4_SPIROTEL) to the parent/guardian at Visit 1. See "spirotel® Device" for further details.

spirotel® Device Reference Card (P4_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.

INFANT Nasal Swab (P4_HTNASAL_SWAB)/ INFANT Nasal Blow (P4_HTNASAL_BLOW)

These handouts demonstrate the two techniques for obtaining a nasal sample.

AVICA Parental Diary/Non-Study Illness and Medication Diary

One side of the Diary should be used by the parent to record AVICA medication use. The reverse side of the Diary should be used by the parent to record any illnesses and non-study medications that are used between visits. At each visit, the coordinator should review both sides of the diary and record the following: adverse events on the AECLIN form, concomitant medications (including non-study use of ibuprofen and acetaminophen) on the CMED form, and AVICA medication use on the AVICA medication diary (P4_AVICA_DIARY).

AVICA Reading Medication Labels

This handout teaches parents how to read medication labels to identify medications that contain ibuprofen or acetaminophen.

AVICA Letter to PCP

This letter if for parents to give to PCP which explains the AVICA study and guides medical care providers with the treatment of fevers and pain.

Fever Pamphlet

This pamphlet provides parents with information on treatment of fevers.

2.35 PHONE CONTACTS

Every 4 and 8 weeks after Visits 3, 5 and 7

COMPLETE VISIT PROCEDURE CHECKLIST (P4_VISIT_PC)

Scheduled phone contacts during the INFANT/AVICA 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 respiratory illnesses, 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 INFANT/AVICA medications, the spirotel® device, collected nasal samples and completed Parental AVICA Study Medication Diary and Illnesses and Non-Study Medications Diary (P4_ILLNESSES_DIARY).

2.36 PHYSICAL EXAMS

Visit 1
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 INFANT/AVICA 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.

2.37 PREDNISOLONE

Visits 1-8

There are 4 scenarios for which prednisolone may be administered.

1. Symptoms:

    A. Symptoms do not improve after 3 ICS/SABA treatments administered every 15 minutes,

    -OR-

    B. >6 rescue treatments are needed for >24 hours (*Note: 1 rescue treatment equals 1 nebulized albuterol treatment or 2 inhalations of albuterol by a metered dose inhaler),

    -OR-

    C. Moderate-severe cough or wheeze occurs for at least 5 of the preceding 7 days,

    -OR-

    D. Specified thresholds of rescue ICS/SABA use are reached (see below):

        I. **Short-term use**: a 2-day average of 528 mcg or more of fluticasone per day. This is equivalent to 12 or more inhalations of fluticasone (44 mcg/inhalation) for symptom relief for 2 consecutive days (1056 mcg or more in total over those two days).

        II. **Medium-term use**: a 5-day average of 352 mcg or more of fluticasone per day. This is equivalent to 8 or more inhalations of fluticasone (44 mcg/inhalation) for symptom relief for 5 consecutive days (1760 mcg or more in total over those 5 days).

        III. **Long-term use:** a 30-day average of 132 mcg or more of fluticasone per day. This is equivalent to 3 or more inhalations of fluticasone (44 mcg/inhalation) for symptom relief for 30 consecutive days (3960 mcg or more in total over those 30 days).

Note: the evaluation period for assessing short-, medium-, and long-term excessive use of as-needed ICS will be reset at the beginning of each 16-week treatment period.

-OR-

2. There is an unscheduled visit for acute asthma care requiring repeated doses of SABA (physician office, urgent care, emergency department),

-OR-

3. Hospitalization is needed for asthma,

-OR-

4. Physician discretion.

If physician discretion is utilized, a specific reason for initiation of prednisolone will be recorded.

Prednisolone course. Parents 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 prednisolone is indicated for the treatment of their child's asthma symptoms. The prednisolone course will consist of a 4 day course of oral prednisolone: 2 mg/kg/day for 2 days (maximum 60 mg/day), followed by 1 mg/kg/day for 2 days (maximum 30 mg/day). All administered will be rounded down to the nearest 0.5 ml (see P4_PRED_DOSE reference card).

The participant's weight at Visit 1 should be used to determine the dose for the entire study. This original weight should be used for the entire study even if new bottles are dispensed.

If albuterol is used while taking prednisolone, the participant should continue to use both the red albuterol inhaler and white rescue inhaler in combination.

If prednisolone is recommended by AsthmaNet Clinical Center medical personnel, these personnel will telephone the parents within 48-96 hours after the initiation of the prednisolone. The purpose this telephone call is to reassess the child's condition and determine whether additional prednisolone 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 prednisolone 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 prednisolone is warranted, the prednisolone course will be repeated as described above.

If the child's symptoms worsen at any time after the initiation of prednisolone (during either the first or second prednisolone course), 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 study failures.

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 prednisolone during a single 16-week treatment arm (separated by at least 1 week) will be considered a treatment failure and will move forward to the next treatment arm. A course that gets extended to 8 days should only be counted as 1 course.

If a child requires a prednisolone course at Visits 4 or 6 (start of treatment periods #2 and #3), the visit should be postponed for 4 to 7 days. Study medications from the current treatment period to should be continued.

Complete the INFANT Prednisolone Medication Form (P4_PRED) and record the course on the INFANT Oral/Systemic Corticosteroids Tracking Form (P4_OCS). In addition, record the course on the Concomitant Medication form (CMED) by recording the dose for Days 1-2 as one record and Days 3-4 as a second record. The concentration of the prednisolone is 15mg/5ml so in order to record the dose of prednisolone take the number of ml that were prescribed and multiple by 3. For example, if the participant was prescribed 8 ml for Days 1 and 2 and 4 mls for Days 3 and 4 record 24 mg for Days 1 and 2 and 12 mg for Days 3 and 4.

Corticosteroids prescribed by non-AsthmaNet personnel

If a prednisolone course is prescribed by someone not at the AsthmaNet site (i.e. ER, PCP, etc.), please complete the P4_PRED form, mark '7. 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 prednisolone course. Please contact the DCC if you have any questions about a particular dose.

2.38 PROTOCOL VIOLATIONS and DEVIATIONS

The following is a list of **protocol violations** that may be assigned during the INFANT/AVICA protocol:

Eligibility

- Participant with an exclusionary medical condition was enrolled.
- Participant who demonstrated lack of asthma control exceeding protocol-limits during Run-In period was randomized.
- Participant without sufficient asthma symptoms during the Run-In period was randomized.
- Participant who used oral or systemic corticosteroids during the Run-In period was randomized.
- Participant with an exclusionary event (i.e. hospitalization for asthma) during the Run-In period was randomized.
- Participant was not 12 to 59 months old at the time of enrollment (Visit 1).
- Participant whose parent did not consent was enrolled at Visit 1.
- Participant who did not meet adherence criteria (brown daily inhaler, oral study medication and overall e-diary completion) was randomized at Visit 2. (Adherence based on electronic diary completion.)
- Participant who did not meet the eligibility criteria at visit 1 was enrolled.
- Participant who did not meet the eligibility criteria at visit 2 was randomized.
- Participants living in the same household were enrolled at the same time.

Drug Dispensation

- Participant given incorrect Run-In medications – was dispensed active, but should have been given placebo.
- Participant given incorrect Run-In medications – was dispensed placebo, but should have been given active.
- No scheduled medications dispensed (participant left without drug due to clinic negligence).
- Incorrect medications for participant dispensed (wrong bottle/kit number).
- Participant < 2 years old was dispensed chewable LTRA pills instead of LTRA granules.
- Incorrect Dose prescribed for AVICA medication (based on child's current weight.)

Serious Adverse Event

- Site failed to report a serious adverse event within the prescribed time limits (unless the site was unaware that the serious adverse event had occurred).

Blood Sampling

- Blood drawn after participant has been deemed ineligible.
- Blood drawn at a visit after Visit 2 without the permission documented on the Consent form.
- Blood drawn for genetics when consent was not obtained.

Miscellaneous

- Site failed to recognize and document an INFANT or AVICA treatment failure (unless details are unavailable due to participant being lost-to-follow-up, etc.).
- Site failed to recognize and document a study failure (unless details are unavailable due to participant being lost-to-follow-up, etc.).
- Site incorrectly identified an INFANT or AVICA treatment failure.
- Site incorrectly identified a study failure.
- Site performed a visit without spirotel® device (safety).

The following is a list of **protocol deviations** that may be assigned during the INFANT/AVICA protocol:

Certification

- Coordinator without INFANT/AVICA protocol certification completed INFANT/AVICA forms. Note: repeated occurrences of this may result in a protocol violation.
- Individual without spirotel® certification configured spirotel® device.
- Individual without Registry certification completed the Registry (REGISTRY) form.
- Individual without GCP certification, HIPAA certification or human subjects certification on file at DCC performed INFANT/AVICA procedures and/or data collection tasks.

Source Documentation

- Required complete physician or coordinator source documentation missing.

- Required complete parent/guardian source documentation not obtained.

Confidentiality

- Participant's contact information, Informed Consent, Registry Form or any other identifying information (i.e. unmasked lab reports) sent to DCC. (includes breaches of confidentiality resulting from lost or stolen study documents). Note: repeated occurrences of this may result in a protocol violation.

Blood Sampling

- Blood not drawn.
- Blood procedures not followed correctly (i.e. samples drawn in the wrong order, incorrect amounts drawn, blood samples not processed correctly, etc.)

Miscellaneous

- Site failed to notify DCC of use of a backup randomization.
- Physical exam not performed.
- Incorrect participant information entered into spirotel® device.

2.39 RANDOMIZATION

Visits 2, 4 and 6 (INFANT drugs) and Visits 2-8 (AVICA drugs, if needed)

The randomization module may be accessed for three reasons during the INFANT/AVICA study: Visit 2, 4 and 6 for the INFANT drug distribution, Visits 2-8 for the AVICA drug distribution (if needed) 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.

Visit 2, 4 and 6

At the start of each of the 3 treatment periods, the randomization module will provide an INFANT inhaler kit number, numbers for 2 LTRA bottles, and an AVICA bottle number. There will be room for the LTRA and AVICA medications to be added to the INFANT inhaler kit, as well as other items, such as the spirotel® Device and prednisolone.

Visits 2-8: AVICA therapy

The randomization module should be used to additional AVICA bottles at any visit after randomization, if needed. If the participant has not used AVICA since the previous visit, it is not necessary to get a new bottle, unless the current bottle will soon be expiring.

Visits 2-8: Lost/Replacement Drugs

If the participant loses/spills the INFANT or AVICA medications or drugs 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.

If the participant needs replacement LTRA or AVICA medications, the randomization module should be accessed. If the participant needs replacement inhalers from the inhaler kit (i.e. a second set of white rescue inhalers is needed to keep at school), the randomization application should be used. The participant should only be given what he/she needs from the kit (not the entire kit).

Visits 3-7

Since many sites are using a pharmacy which makes the process of getting study drugs more difficult and time consuming, 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.

2.40 RECRUITMENT

INFANT/AVICA visits will commence in November 2012. 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 INFANT/AVICA 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 INFANT protocol. Each of the 9 participating performance sites is expected to randomize approximately 33 participants for a Network total of 294 randomized participants in the INFANT protocol combined.

2.41 REGISTRATION

Visit 1 or Prior
Register participant in AsthmaNet Registry

Before a participant can be enrolled in the INFANT/AVICA 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 (P4_VISIT1) in the participant's Visit 1 packet.

2.42 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 may not be reenrolled for the following reasons:

1. Gestation less than late preterm as defined as birth before 35 weeks gestational age.
2. Presence of lung disease other than asthma, such as cystic fibrosis and BPD. Evaluation during the screening process will assure that an adequate evaluation of other lung diseases has been performed.
3. Presence of other significant medical illnesses (cardiac, liver, gastrointestinal, endocrine) that would place the study subject at increased risk of participating in the study.
4. Co-morbid disorders associated with wheezing (aspiration, tracheomalacia, congenital airway anomalies or bronchiectasis).
5. Chronic medical disorder that could interfere with drug metabolism/excretion (chronic hepatic, biliary, renal disease or seizure disorder treated wth anticonvulsants).
6. Chronic medical disorder that may increase the risk of drug-related injury (Osteogenesis imperfect, Crohn's disease, ulcerative colitis, juvenile rheumatoid arthritis, clotting disorders, factor deficiency, G6PD deficiency, phenylketonuria).
7. Immunodeficiency disorders.
8. History of respiratory failure requiring mechanical ventilation.
9. History of significant adverse reaction to any study medication ingredient.
10. The participant has significant developmental delay/failure to thrive, defined as crossing of two major percentile lines during the last year for age and gender. If a participant plots less than the 5^{th} percentile for age and gender, a growth chart for the previous year will be obtained from the participant's primary care provider.

If a participant re-enters the study, he/she must be given a new Participant ID number from the Participant Assignment Log (P4_LOG). However, specific data can be reused:

- A new copy of the INFANT and AVICA informed consents must be read and signed. The documents signed at the initial enrollment should reside in the folder created for the participant's original participant ID number. The new signed consents should reside in the participant's current study folder. The informed consents 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), 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 INFANT/AVICA.

2.43 RESPIRATORY TRACT ILLNESS

Parents 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.

Any two illnesses should be separated by at least 2 weeks to be considered 2 different illnesses (and necessitating collection of 2 nasal samples).

2.44 RUN-IN MEDICATIONS

Visit 1

The participant will receive either active Run-In medications (active ICS and active LTRA) or placebo Run-In medications (placebo ICS and placebo LTRA). See flowcharts in Eligibility Section for further details.

Participants who have been treated with a controller therapy during the 4 weeks prior to Visit 1 will receive active Run-In medications (ICS or LTRA, but not both) if one of the following is true:

- Been treated with a daily controller medication for at least 3 of the last 6 months and had asthma symptoms while on the controller medication.
- During the past 12 months had at least 2 asthma exacerbations requiring systemic corticosteroids or had at least 4 wheezing episodes while taking the controller medication.
- During the past 4 weeks had on average at least 2 days with daytime asthma symptoms or more than 1 nighttime awakenings due to asthma and the symptoms appeared after the ICS or LTRA was discontinued (ICS or LTRA was taken daily, not intermittently, prior to being discontinued.

Otherwise, participants will receive placebo Run-In medications.

At visit 1, the participant will receive the following medications:

- Daily Brown Inhaler (open-label active or placebo)
- LTRA granules or chewable pills (open-label active or placebo) *
- Red Albuterol MDI
- Prednisolone

No White Rescue Inhaler will be used (in conjunction with the red Albuterol Inhaler) during the Run-In.

*Participants < 2 years old should receive the granules. Participants ≥ 2 years old can choose between the granules and chewable pills. They must stay with same choice throughout the study.

2.45 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 INFANT/AVICA, it is present in the Visit 8 packet. In addition, the questionnaire is also posted appended to the single INFANT Termination of Study Participation (P4_INFANT_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 INFANT/AVICA 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 INFANT Termination of Study Participation (P4_INFANT_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 P4_INFANT_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.

2.46 SCREEN FAILURES

Visit 1

If an INFANT/AVICA 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 or 3.

2.47 SPIROTEL® DEVICE

The spirotel® is an electronic diary (e-diary). Parents will be given a device and trained in its use at the beginning of the run-in period. Parents will be expected to complete scheduled PM sessions daily for the duration of the study. A scheduled session includes answering a set of questions in the e-diary. 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.

This section covers INFANT-specific spirotel® information (also refer to Section 4.4 of the INFANT MOP). For additional information on the spirotel® device, refer to appendix 6 of the AsthmaNet General Manual of Operations.

Participant Instruction

Visit 1
Instruct parent in use of spirotel® (use demo device) (P4_HTSPIROTEL, P4_SPIROTEL_REF)

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

Demo devices that have been programmed with the INFANT e-diary questions may present alerts following the scheduled PM session. The “Rescue Use High” alert will be presented if # Puffs Red is >= 8 and/or # Puffs White is >= 8. The “Severe Symptom” alert will be presented if Cough Score, Wheezing Score, Breathing Score, or Activity Affect is answered Severe.

At Visit 1 when the spirotel® is first introduced to the parent, clinical personnel should review the information on the How to Use Your INFANT spirotel® Electronic Diary (P4_HTSPIROTEL) handout. The parent 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 has reviewed the P4_HTSPIROTEL handout, clinical personnel should introduce the parent to the demo device. Reinforce to the parent 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 P4_HTSPIROTEL handout that covers the spirotel® procedures in general, an INFANT-specific handout (INFANT spirotel® Reference Card (P4_SPIROTEL_REF)) has been created to fit into the spirotel®’s case for quick

reference by the parent at home during a session. This reference includes each question abbreviation (i.e., the up to 16 character representation the parent 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 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 INFANT spirotel® Performance Checklist (P4_SPIROTEL_PERF, P4_ELIG1) (use demo device)

After the parent has had a chance to experiment with the INFANT demo device, he/she should undergo a formal spirotel® performance assessment using the steps on the INFANT spirotel® Performance Checklist (P4_SPIROTEL_PERF). He/she must pass the performance check with a score of 4 to remain eligible for the study. Results of the performance check are recorded in Q1290 on INFANT Eligibility Checklist 1 (P4_ELIG1).

If a parent 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 may attempt to pass the checklist. Store all completed P4_SPIROTEL_PERF forms in the participant's INFANT study folder at the performance site; they should not be forwarded to the DCC.

Loading the INFANT Program and Preparing Device for Participant Use

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

Determine which spirotel® device will be assigned to the participant. Load the INFANT program into the device. The following setup screen will appear with the protocol name (INFANT), device serial number, software version number, first digit of the participant ID (4), and the choice between English language (default) or Spanish language.

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

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

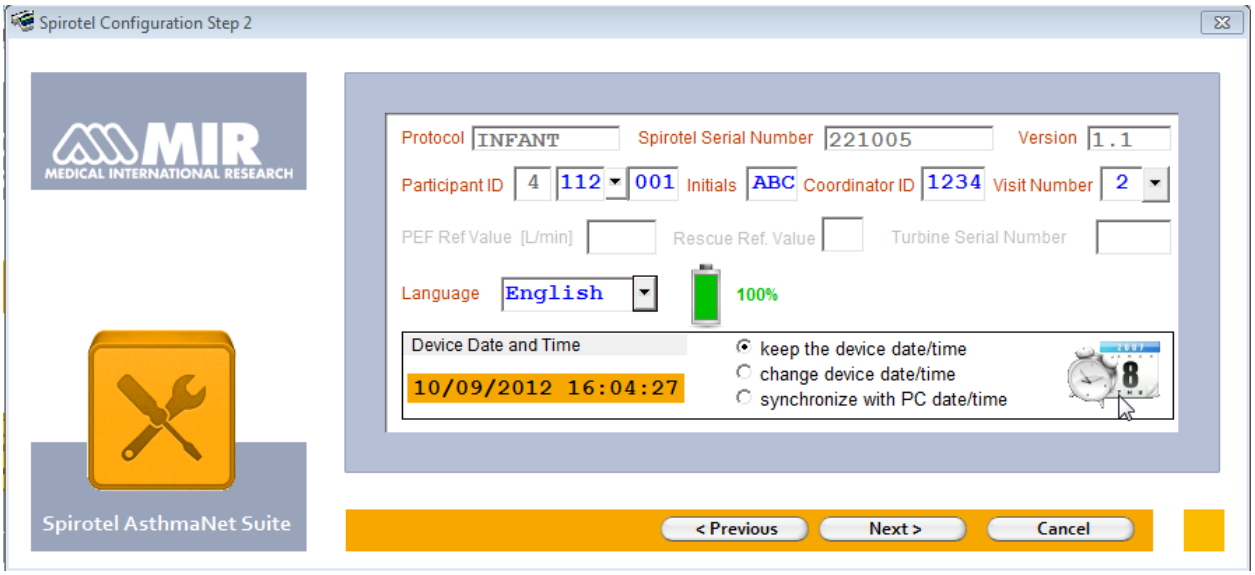
Participant ID: This is the participant's assigned INFANT ID number. The ID is broken into three sections: protocol number (4 pre-completed), performance site number, and ID number. Clinical personnel must complete the site number and ID number portions.

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, Rescue Ref Value, and Turbine Serial Number fields have been disabled for INFANT.

A sample completed setup screen with information for participant 4-112-001 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 INFANT 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 (P4_INFANT_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 INFANT 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 summarizes three values that will be recorded on the INFANT Compliance Checklist (P4_INFANT_COMPLY):

- Number of full days since the last visit: This value does not include the current visit date or the maximum download date from the previous visit. 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 P4_INFANT_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 were answered. This value is recorded in Q1010 on P4_INFANT_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 P4_INFANT_COMPLY.

- Number of puffs that were taken from the brown daily inhaler. This value is recorded in Q1030 on P4_INFANT_COMPLY.

- Percent compliance: This value is computed as the number puffs from the brown daily inhaler days divided by the number of expected puffs x 100. This value is recorded in Q1040 on P4_INFANT_COMPLY.

- Number of days where oral study medication was taken. This value is recorded in Q1050 on P4_INFANT_COMPLY.

- Percent compliance: This value is computed as the number days the oral study medication was taken divided by the number of full days x 100. This value is recorded in Q1060 on P4_INFANT_COMPLY.

INFANT spirotel® Reports

Visits 3-8
Print and review spirotel® Participant Visit Report (P4_SPIROTEL_RPT)
Print and review spirotel® Participant Compliance Report (P4_INFANT_COMPLY)

Visit 2
Print and review spirotel® Participant Visit Report (P4_SPIROTEL_RPT)
Print and review spirotel® INFANT Eligibility Report (P4_ELIG4 or P4_ELIG5)

Three spirotel® reports will be generated and consulted during the INFANT 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 INFANT spirotel Reports. 6) Three options are available for printing: All Reports, the Participant Visit Report, the Participant Compliance Report, or the INFANT Participant Eligibility Report (available only at Visit 2).

Descriptions of the INFANT 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, 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, trial type, time trial started (military time), INFANT diary questions Q1-Q10. INFANT diary questions correspond to the order in which the participant answers them in the device. Refer to the INFANT spirotel® Coordinator Reference Card (P1_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, 3=Yes)

Note: A 'No' response skips to Q9
Q2: Did your child awaken at night with difficulty breathing from asthma? (0=No, 3=Yes)
Q3: How severe was your child's cough in the past 24 hours? (0,1,2,3)
Q4: How severe was your child's wheezing in the past 24 hours? (0,1,2,3)
Q5: How severe was your child's trouble breathing in the past 24 hours? (0,1,2,3)
Q6: How much did your child's asthma interfere with your child's activities in the past 24 hours? (0,1,2,3)
Q7: Number of puffs your child took from the red albuterol inhaler for asthma symptoms in the past 24 hours (0-16)
Q8: Number of puffs your child took from the white rescue inhaler for asthma symptoms in the past 24 hours (0-16)
Q9: Number of puffs your child took from the brown daily inhaler for asthma symptoms in the past 24 hours (0-4)
Q10: Was the oral study medication taken before bedtime? (0=No, 3=Yes)

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.

- spirotel® INFANT Eligibility Report: This report is used only at Visit 2 to determine if his/her e-diary compliance and symptoms meet the INFANT eligibility criteria.

  The top of the report shows the participant's INFANT ID number and initials.

  The next two sections of the report determine whether or not the participant meets the e-diary compliance and symptom eligibility criteria. Data on the report provide answers to Q1040-Q1130 on INFANT Eligibility Checklist 4 or 5 (P4_ELIG4, P4_ELIG5).

  If the Run-In period was less than 14 days the compliance calculations will be inaccurate and must be re-calculated by the coordinator using the data in the bottom half of the report. For instructions see Section 4.2.10 of the INFANT MOP.

INFANT spirotel® Alerts

Several alert messages have been programmed into the INFANT 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.

- Timing Alert

  This alert appears when a parent turns on the spirotel® to complete a PM session after midnight. The parent is reminded that the session refers to yesterday.

- High Rescue Use Alert

  This alert appears after a completed scheduled PM session when the participant meets the high rescue alert. If the number of puffs entered for the red albuterol inhaler or the white rescue inhaler is equal to or greater than 8 for any daily session, the spirotel® will display the following message after all the diary questions have been answered – 'Rescue Use High/Call Clinic ASAP'.

- Severe Symptom Score Alert

  This alert appears after a completed scheduled PM session when the participant meets the severe symptom score criterion. If the parent records a 'Severe' symptom score for either the child's cough, wheezing, breathing, or activity effect, the spirotel® will display the following message after all the diary questions have been answered – 'Symptom Severe/Call Clinic ASAP'.

- 7 Consecutive Day Symptom Alert

  This alert appears after a completed scheduled PM session when the participant meets the 7 Consecutive Day Symptom criterion. If the parent records a 'Moderate' or 'Severe' symptom score for either the child's cough or wheezing for 5 diary sessions in any 7 calendar day period, the spirotel® will display the following message after all the diary questions have been answered – 'Day Symp High/Call Clinic ASAP'.

- High ICS Use over 30 Consecutive Days Alert

  This alert appears after a completed scheduled PM session when the participant meets the High ICS Use over 30 Consecutive Days criterion. If the parent records a total of 90 or more puffs from either the red or white rescue inhalers over any 30 calendar day period, the spirotel® will display the following message

after all the diary questions have been answered – '30DayRescueHigh/Call Clinic ASAP'.

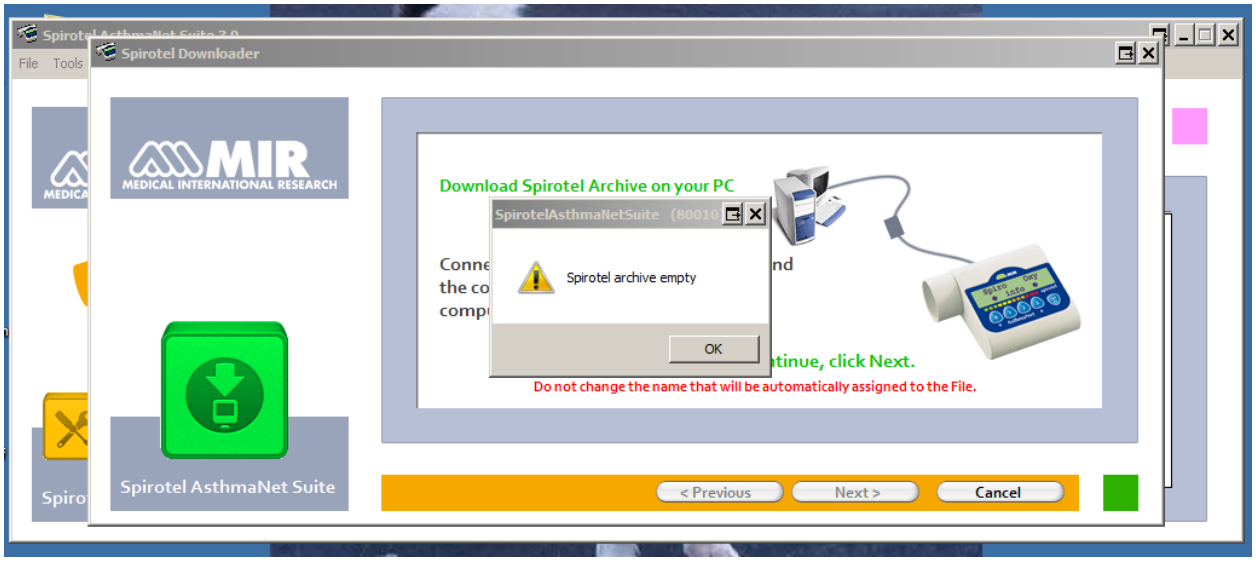
Handling participant travel

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 hasn't used the device at all, the following error will be displayed when the data is downloaded:



2.48 STUDY FAILURES

Visits 2-8
Complete the INFANT Study Failure Form (P4_INFANT_FAIL)

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

- Four courses of prednisolone are required after randomization.
- Hospitalization >24 hours is required for an acute asthma exacerbation.
- If a child moves forward to the next treatment arm due to recurrent exacerbations (protocol-defined) two times during the course of the study.

The Study Failure Form (P4_INFANT_FAIL) should be completed and the participant should be scheduled for Visit 8 as a final closeout visit.

2.49 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 INFANT/AVICA 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 INFANT/AVICA 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 INFANT/AVICA 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, an INFANT Termination of Study Participation Run-In (P4_TERMR) 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.

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 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 INFANT Study Treatment Questionnaire (P4_INFANT_TRTQX) and AVICA Study Treatment Questionnaire (P4_AVICA_TRTQX), please ask him/her to do so. Parents 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 INFANT and AVICA studies. An INFANT Termination of Study Participation form (P4_INFANT_TERM) and an AVICA Termination of Study Participation form (P4_AVICA_TERM) should also be submitted.

If the parent/guardian of a randomized participant withdraws consent between visits, the INFANT Termination of Study Participation form (P4_INFANT_TERM) and the AVICA Termination of Study Participation form (P4_AVICA_TERM) should be completed and submitted. The study coordinator who was primarily responsible for the participant's study visits should complete the last page of the INFANT Treatment Questionnaire (P4_INFANT_TRTQX) and the AVICA Treatment Questionnaire (P4_AVICA_TRTQX). No other data should be collected for this individual.

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

If a randomized participant's 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. An INFANT Termination of Study Participation form (P4_INFANT_TERM) and an AVICA Termination of Study Participation form (P4_AVICA_TERM) should also be submitted.

If the parent/guardian of a randomized participant withdraws consent between visits, the INFANT Termination of Study Participation (P4_INFANT_TERM) form and the AVICA Termination of Study Participation form (P4_AVICA_TERM) should be completed and submitted.

Upon withdrawal, the parent/guardian should also meet with the Principal Investigator/study physician to discuss treatment recommendations. See “Follow-up Medication Prescription” for more details earlier in this section.

2.50 URINE SAMPLING

Visit 2

A. PURPOSE

Asthma is a chronic inflammatory disorder of the large and small airways that is associated with a number of unique biochemical abnormalities, including increased or decreased expression of several different proteins and metabolites. These substances (such as leukotriene E4 **(LTE4)**) may be associated with the clinical and pathologic features of asthma in young children as well as clinical responsiveness to available asthma treatments. Recently, techniques have emerged that permit measurement of these substances non-invasively in the urine.

For the INFANT-AVICA study, we will collect urine from all participating children for analysis of LTE4 and other proteins and metabolites. The hope is that LTE4 and other proteins and metabolites will predict whether or not young children with asthma respond to selected asthma treatments. If this finding is observed, these substances will become important "biomarkers" that will allow physicians to better diagnose and treat asthma in young children in the future.

Urine will be collected at the randomization visit (visit 2) and sent to National Jewish Health using the following schedule and protocol. **Parents may also be given the option of collecting the urine at home prior to visit 2**. If urine is unable to be collected at Visit 2 or at home prior to visit 2, it can be collected at a later visit provided the site's Consent Form has an allowance for doing so. However, it is preferable that the urine collection takes place within 48 hours of Visit 2. Methods for both procedures are described below.

B. MATERIALS REQUIRED

Before collecting urine, be sure that the following supplies/equipment are available (catalog numbers correspond to those found at www.fisherscientific.com):

Processing supplies:

- Refrigerated centrifuge capable of centrifugation at 3000 x g at 4°C
- Pipetter and tips or Pasteur transfer pipet
- 15 mL conical tubes (for example, Fisher catalog #14-959-49D)
- Fisherbrand 5.0 mL cryogenic vials (4 per patient), Fisher catalog #10-500-27
- Sample storage boxes

Collection supplies (clean catch method with cup/toilet hat):

- Disposable toilet hats (for example, Henry Schein Medical #1033383)
- Specimen cup for urine collection (for example, Fisher catalog #16-320-730)
- Ice or cold packs

Collection supplies (cotton ball method)

- Jumbo size cotton balls or square/circular cotton pads
- Plastic cling wrap (for example, Saran Wrap)
- 20 mL needleless syringe (for example, Fisher catalog #03-377-24)
- Specimen cup for urine collection (for example, Fisher catalog #16-320-730)
- Ice or cold packs

Collection supplies (bag method)

- Infant wet wipes (do not need to be aseptic)
- Urine collection bags (for example, Fisher catalog #22-275-348)
- Syringe for transferring urine from bag to cup
- Specimen cup for urine collection (for example, Fisher catalog #16-320-730)
- Ice or cold packs

C. PROCEDURES FOR URINE COLLECTION IN THE CLINIC

Clean catch method

If the child is toilet trained, a clean-catch void is the preferred method for urine collection. The coordinator, nurse, or caregiver must assist the child if this method is used. The steps are as follows:

1. Wash your hands with soap and warm water.
2. Unscrew the lid of the urine cup. Do not touch the inside of the cup or the lid.
3. Use a wet wipe to clean the genital area. For girls, be sure to wipe from the front to the back.

4. Have the child urinate into the toilet. After the first few drops are voided hold the urine cup a few inches from the urethra and collect the urine until the cup is about half full. Alternatively, children may void into a urine collection hat that is placed in the toilet.

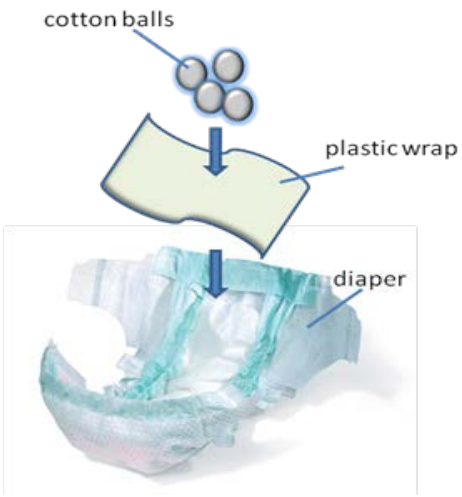
5. Screw the lid tightly on the cup. Place the sample on ice or cold packs for transport to the laboratory.

Cotton Ball/cotton pad urine collection (if unable to perform a clean-catch void)

If the participant is wearing a diaper, the urine can be collected by inserting cotton balls in the diaper. Procedures for collecting urine from cotton balls are outlined below:

1. Cut out a piece of plastic wrap (approximately 7 inches in length).

2. Remove the child's diaper. Place the plastic wrap on top of the diaper lining. Place 3 to 4 jumbo sized cotton balls in the center of the plastic wrap (the number of cotton balls to be used is dependent on the size of the patient; for infants use 3 cotton balls and for young children use 4 cotton balls). Ensure the alignment of the cotton balls to the area of urine collection in the diaper (i.e. centered for female patients and towards the front of the diaper for male patients).



3. Check the diaper regularly to avoid fecal contamination of the cotton balls.

4. To remove the cotton balls, simply re-wrap the cotton balls in the plastic wrap and place in the collection cup. If no urine is produced by the cotton ball method after 1 hour, consider applying a urine collection bag for sample collection (some participants will be able to void into the bag but not into the diaper, and vice versa).

5. To extract urine from the cotton ball, simply squeeze the cotton balls into the collection cup, either manually (always wear gloves) or by using a needleless 20 mL (or larger) syringe. To use the syringe, pull the plunger out, add the cotton balls, and then replace the plunger and push.

6. Screw the lid tightly on the urine collection cup. Place the sample on ice or cold packs for transport to the laboratory.

Bag urine collection (if unable to perform a clean catch void)

If the pediatric participant is not wearing a diaper but cannot provide a clean-catch void, then a urine collection bag may be used to obtain urine.

1. Gently wipe the vaginal area from front to back (girls) or the gently wipe the tip of the penis (boys). For boys, do not force retraction of the foreskin.

2. Gently wipe the area which will be covered by the urine collection bag with the moist cloth. If the area of the skin where the bag will be stuck is significantly irritated, either place a gauze pad on that area to avoid bag-skin contact (if very localized irritation) or abort use of the urine collection bag.

3. Gently pat-dry the area of skin where the urine collection bag will be taped.

4. Firmly apply the urine collection bag to the area, making sure that there is as good a seal as possible between the bag and the skin. For girls, the vulvar area should be completely covered and for boys, the lower portion of the bag should be stuck on just below the testes (avoid the anal region).

5. Once voiding has occurred, gently remove the bag. If no urine is produced by the urine collection bag method after 1 hour, consider putting on a diaper with cotton balls for sample collection (some participants will be able to void into the diaper but not the bag, and vice versa). **If fecal matter is present in the urine, the procedure should be repeated.**

6. Using a syringe, draw out the urine from the bag, avoiding contamination and transfer the urine to the designated urine collection cup.

7. Screw the lid tightly on the urine collection cup. Place the sample on ice or cold packs for transport to the laboratory.

D. COLLECTION OF URINE SAMPLES AT HOME

Parents may be given the option of collecting the urine sample at home prior to Visit 2. If this option is selected, **the urine should be collected within 48 hours of visit 2 and stored in the home refrigerator. Alternatively, if unable to collect a urine sample at Visit 2, it can be collected 2 days after Visit 2. That would require the parent bring the sample to the site within 48 hours of collection. Samples should be transported to the clinic on cold packs and then immediately processed and frozen as detailed below**.

Parents may choose which method they feel would be most appropriate for their child. **The appropriate supplies should be dispensed at Visit 1 if this option is to be used**. If Visit 2 gets rescheduled for any reason, it will be necessary to discard the original sample and collect a second sample with 48 hours of the rescheduled Visit 2.

For parents of infants and toddlers who wear diapers, the cotton ball method may be best. If parents elect to try this method at home, be sure to teach them how to use the syringe. Also, instruct them that we need to have a urine specimen that isn't contaminated with fecal matter.

E. URINE SAMPLE PROCESSING

The following protocol should be used for the aliquotting of urine samples:

1. Remove urine from the ice or cold packs. The sample can remain on ice or cold packs for up to one hour prior to processing, if necessary.

2. Add urine to a 15 mL conical tube. It is not necessary to add the entire urine sample to the conical tube.

3. Centrifuge the tube at 3000 x g for 10 minutes at 4° C. Be sure the centrifuge is at 4°C before use.
4. Place 2.0 mL (=2000 µL) of urine supernatant (the top part of the urine and not the solid part at the bottom) in four 5.0 mL cryogenic vials (Fisher catalog #10-500-27).

    a. If the volume of urine is not sufficient for 4 tubes, make as many tubes as you can.

    b. If less than 2.0 mL of urine is available in total, place as much urine as you can into the first tube.

5. Label the tubes with the bar code (see instructions below).

6. Store tubes at -80° C.

F. SPECIMEN LABELING

Enter the participant's 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 1.5" x.75"
http://divbio.com/lasercryotags150x0751200pk

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 (-80° C) until shipping.

G. SPECIMEN PACKAGING AND SHIPPING

The samples should be bar-code 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 urine collection 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

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.

5. Place tubes 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 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

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

6. 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 tubes use additional sheet. If shipping fewer than 12 tubes half sheets may be used.

7. Use bubble wrap or cardboard to keep the tubes stable should the dry ice dissipate.
NOTE: There should be sufficient dry ice to keep the samples frozen until they reach the National Jewish laboratory.
    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 tubes.

8. Fill bottom of shipping box with dry ice

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

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

h. 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)

i. 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)

j. The name, address, and telephone number of a person responsible for the shipment is required on the box. There should be both a FedEx shipping label and a secondary Avery label (with both the 'to' and 'return' addresses listed).

k. 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**. The box will hold materials for at least 10 tubes, using the following method. Put 1 inch of crushed dry ice in the bottom of the shipping box. Add a plastic transport bag containing urine 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 urine in the screw top transfer tubes. Make sure there is room for 2 inches of dry ice at the top. In this way, at least 10 tubes will fit in the shipping box. It may be more depending on the size of the particular box. (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.

1. All urine specimens should be sent FedEx Priority Overnight. No other form of shipping is acceptable. Samples should be shipped to National Jewish 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 National Jewish. They need to make sure the lab person is available to receive the shipment on the alternate day. Note: Urine samples can be shipped with the metabolomics/proteomics samples since they are going to the same lab.

Ship to:

National Jewish Health – Reisdorph Lab
1400 Jackson St
Room K924b

Denver, CO 80206
ATTN: Roger Powell

2.51 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 must be run 4 times during the study: Visit 1 (start of Run-In), Visit 2 (start of treatment period 1), Visit 4 (start of treatment period 2), and Visit 6 (start of treatment period 3).

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, 4, 6

At Visit 2, run the Visit Scheduler to determine the schedule for the first treatment period (Visits 2-4).

At Visit 4, run the Visit Scheduler to determine the schedule for the second treatment period (Visits 4-6).

At Visit 6, run the Visit Scheduler to determine the schedule for the third treatment period (Visits 6-8).

The table below describes the INFANT/AVICA 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.

Run-In Phase:

Visit at which the Visit Scheduler is run.	Visit Number	Ideal Date	Lower Window	Upper Window
Visit 1	2	14 days	0 days, +7 days	14-21 days

Note: The Run-In period may be repeated or extended, based on the participant's symptoms during the Run-In. See Eligibility Section in this MOP.

Treatment Phase:

There are three treatment periods: Visits 2-4, Visits 4-6 and Visits 6-8. The visit schedule will be reset at the start of each treatment period.

Visit at which the Visit Scheduler is run.	Visit Number	Ideal Date	Lower Window	Upper Window
Visit 2	3	28 days	- 3 days	+ 7 days
	PC	56 days	- 3 days	+ 5 days
	PC	84 days	- 3 days	+ 5 days
	4	112 days	- 3 days	+ 7 days

Visit at which the Visit Scheduler is run.	Visit Number	Ideal Date	Lower Window	Upper Window
Visit 4	5	28 days	- 3 days	+ 7 days
	PC	56 days	- 3 days	+ 5 days
	PC	84 days	- 3 days	+ 5 days
	6	112 days	- 3 days	+ 7 days

Visit at which the Visit Scheduler is run.	Visit Number	Ideal Date	Lower Window	Upper Window
Visit 6	7	28 days	- 3 days	+ 7 days
	PC	56 days	- 3 days	+ 5 days
	PC	84 days	- 3 days	+ 5 days
	8	112 days	- 3 days	+ 7 days
	PC	140 days	- 3 days	+ 5 days