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## 2.1 ACTION PLANS and IDENTIFICATION CARDS

**APRIL/OCELOT Run-In Action Plan Card**
**APRIL/OCELOT Action Plan Card and wallet-sized ID Card**
**APRIL/OCELOT Caregiver Action Plan Card**

There are several different Action Plan Cards used during APRIL/OCELOT. 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 starting APRIL therapy, when the study team should be contacted and when to seek immediate help. The wallet-sized ID card includes instructions for treatment of asthma attacks by physicians and ER personnel who may not be familiar with the study and should be given to the parent/guardian to be kept with them at all times. The Action Plan should be reviewed at all study visits. The Action Plan Card contains the same information as the wallet-sized ID card, but has a Respiratory Illness Daily Activities Guide on the reverse side. The reverse side should be referenced by the parent/guardian whenever the participant has started APRIL or OCELOT therapy.

**Visit 1**

**Dispense APRIL/OCELOT Run-in Action Plan Card**

- The APRIL/OCELOT Run-In Action Plan Card should be dispensed at Visit 1 and used during the Run-in.
- Complete the participant's name, date and the names and phone numbers of study contacts. During the Run-In, the 'After Hours Phone Number' should be the site's regular emergency contact. Do not use the FoneMed After-Hours phone number during the Run-In period.
- 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 or nebulizer, please try to contact one of the people listed on this card. Dr. Green is the Principal Investigator and Dr. Black is another physician working on this study. If you are unable to contact either of them, 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, including a record of any non-study medications taken. The back of the Diary Card can be used during the Run-In to keep track of illnesses, injuries and medications taken.

**Visit 2**

**Dispense APRIL/OCELOT action plan card, APRIL/OCELOT wallet-sized ID card and the APRIL/OCELOT caregiver action plan card (if needed)**

- Collect the APRIL/OCELOT Run-In Action Plan Card.
- The 'APRIL/OCELOT Action Plan Card' and the 'APRIL/OCELOT wallet-sized ID card' should be dispensed at Visit 2 and used for the remainder of the APRIL study and the OCELOT study (if needed). There is also an APRIL/OCELOT Caregiver Action Plan Card that can be dispensed at Visit 2 and given to Daycare providers, schools, etc.
- Write the participant's study ID number and the names and phone numbers of study contacts. The After Hours Phone Number should be the number provided to your site for FoneMed. Explain to the parent the purpose of the After Hours Phone Number.
- Review the contents of the card with the parent/guardian.

Due to the unique nature of the APRIL/OCELOT study, each action plan must be individualized. Coordinators need to use the parent's responses from the Symptoms of Breathing Illness Survey (P2_SURVEY) to complete the information on 'When to Start APRIL Illness Medication'. The P2_SURVEY form completed at Visit 2 should be used (not the P2_SURVEY form that was completed at Visit 1).

Coordinators will fill in the appropriate lines in the "When to Start APRIL Illness Medication" box. On the first line, fill in the answer to question 1010 on the Symptoms of Breathing Illness Survey (P2_SURVEY). The second line (most important symptom) should be the response to question 1040. The last line should be completed using the response from question 1070. If question 1020 is answered "no" and questions 1040 and 1070 are left blank, the second and third lines on the APRIL/OCELOT Action Plan and ID Card will be blank.

The back of the APRIL/OCELOT Action Plan contains a 'Respiratory Illness Daily Activities Guide'. The guide contains a simple summary of the study activities that must be carried out each day while taking APRIL or OCELOT medications, including instructions for study medications. This handout serves as a checklist for the parents to help them remember the study activities. Parents do not need to actually fill out the checklist and it will not be collected at the site. The guide also reminds the parents to contact the clinic within 72 hours of starting the study medications or if they have any questions.

Coordinators will review with the parents the section on 'When to Contact the Study Team' and 'Get Medical Help!'

**Visit 3-8, 8b, 8c, 8d, 20**

**Review the ID Card and 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 for 'When to Start APRIL Illness Medication' and 'When to Contact the Study Team' with the parents. Update the 'When to Start APRIL Illness Medication' section as needed based on discussions with the parents.
- 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 APRIL/OCELOT protocol are involved in study activities throughout the trial, especially when the participant is sick. 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 APRIL/OCELOT trial:

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

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

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

*Counseling for Non-Adherence*

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

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

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

**Visit 2**

It is very important at this visit to get a good sense of the ability of the parent/guardian to comply with protocol procedures, before allowing the participant to proceed and be randomized. The participant is required to have at least 80% adherence during the Run-In period with regards to the Run-In Diary completion in order to be eligible for APRIL/OCELOT. Since there are no Run-In study medications, there is no assessment of the participant's adherence with study medications. If the coordinator feels that the participant will not be able to comply with the study medications, the participant should not be randomized into APRIL/OCELOT.

Adherence with the Run-In Diary Card completion is assessed on Eligibility Checklist 2, Questions #6-#8. The participant must have at least 80% to be eligible.

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

## 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 <u>any</u> 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 subject 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 2-9, 20, 21

### 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 APRIL illness is being recorded, 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.

**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 APRIL/OCELOT 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 APRIL/OCELOT 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 APRIL MEDICATIONS

### Visit 2

The randomization module should be accessed at Visit 2 to obtain bottle numbers for 2 APRIL therapies.

### Visit 3-9

Once a participant uses the first APRIL therapy, the randomization module should be used to obtain bottle number(s) for the 3rd and 4th APRIL therapies.

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 APRIL therapy is dosed based on the participant's weight. Participants who weigh <=20 kg will require 1 bottle of APRIL therapy per RTI. Participants who weigh >20 kg will require 2 APRIL bottles per RTI. Thus, participants who weigh <=20 kg will be given 2 bottles of APRIL therapy at Visit 2. Participants who weigh > 20 kg will be given 4 bottles of APRIL therapy at Visit 2. Please refer to the APRIL Azithromycin Dosing Reference Card for exact dose by weight. The participant should take one dose per day for 5 days. The dose should be based on the participant's weight at Visit 2 and should remain the same throughout the study.

Special Instructions for APRIL dosing for participants weighing 20.1 to 20.8 kg:
There is a slight discrepancy between the randomization application and the APRIL Dosing Reference Card for the number of APRIL bottles needed per illness. The randomization application will issue 2 bottles per illness while the Dosing Reference Card indicates that only 1 bottle is needed. The Dosing reference card is correct. The Dosing Reference Card was created after the randomization application was programmed. While developing the Dosing Reference Card, it became apparent that ranges would need to be used since the measuring device could only measure to the closest 1/2 ml. (For example, a participant who weighs 20.5 kg, using a dosing of 12 mg/kg per day, should get a dose of 6.15 ml per day, which can't be measured with the device.) Since we have almost 25% of the participants randomized and this has only occurred one time, we expect this to be a rare event.

For sites that do not use a pharmacy: 2 of the 4 bottles should be dispensed to the parent for APRIL illnesses #1 and #2. The 3rd and 4th bottle should be clearly labeled with the participant's ID number and stored separately from the rest of the APRIL bottles. They can be used for the 3rd and 4th APRIL illnesses or as back-up medication, if needed. It is not necessary to use the randomization application for the 3rd and 4th APRIL therapies.

For sites that use a pharmacy to distribute medications: please ask the pharmacy for only 2 of the 4 bottles to be dispensed for APRIL illnesses #1 and #2. For these cases, it is necessary to use the randomization application for the 3rd and 4th APRIL therapies. The application will provide 2 APRIL bottle numbers for each illness, but you will only need to give the pharmacy 1 APRIL bottle number.

Please make a note on the Drug Dispensation Log (P2_DRG_AO) and APRIL Scheduled Medications (P2_MED) form indicating which bottles were dispensed.

APRIL therapy should be started at onset of a RTI based upon the individualized plan developed by the parent and site at Visits 1 and 2. The plan will consider both the pattern of symptoms identified by the participant's parent in the Parental Respiratory Illness Questionnaire that typically leads to episodes of LRT symptoms, as well as the clinician's judgment to promote as much consistency as possible and to avoid treating at the development of trivial symptoms. The subject-specific starting point will be based on the participant's previous history of symptom progression irrespective of whether symptoms originate in the upper or lower respiratory tracts. See the Respiratory Tract Illness/Starting APRIL Medications section for more details.

It is important to remind the parent/guardian that albuterol should be used while taking APRIL medications. Albuterol use while using APRIL medications is: inhaler (2 puffs) with spacer or nebulizer (1 vial) taken 4 times per day (while awake) for 2 days, then 'as needed' to control symptoms.

For each APRIL medication usage, the parent/guardian should collect a nasal sample on Days 1 and 4 of the illness. The Preschool Asthma Diary and corresponding Albuterol Log (on reverse side) should also be completed daily until the participant is symptom-free for 2 days.

Since azithromycin can stay in the system for up to 9 days after the last dose is taken, two consecutive APRIL therapies should be at least 14 days apart (i.e. there should be at least 14 days between the start of each APRIL therapy).

Missed Doses (Please refer to the Tips for Taking APRIL and OCELOT medications handout): If the morning dose is missed, it should be taken later in the day. If an entire day is missed, the prescribed dose should be resumed the next day (i.e. Do not take a double dose the next day.)

If a participant has used his/her 4th APRIL medications, he/she should be termed from the study. Visit 9 should be scheduled for 14 days after the last dose of APRIL medication is taken.

The APRIL Tracking Form should be completed each time the participant uses APRIL therapy. This is an administrative form that should be kept in the participant's folder at the center. Its purpose is to track the number of times APRIL therapy is used and provide instructions if the participant uses 4 APRIL therapies.

## 2.6 APRIL TREATMENT FAILURE/STARTING OCELOT

**Visits 2-9**
**Complete the APRIL Treatment Failure Form (P2_APRIL_TRTFAIL)**

A participant will be deemed an APRIL Treatment Failure by a study physician if any of the following criteria are met:

- Having symptoms that are more than mild after 3 albuterol treatments* in 1 hour
- Requiring albuterol treatment more than once every 4 hours**
- Requiring more than 6 albuterol treatments over a 24 hour period
- Having moderate-severe cough or wheeze for 5 or more days during which APRIL therapy was used.
- Physician Discretion – rationale must be clearly stated.

*An albuterol treatment is a 2.5 mg albuterol by nebulization with facemask or 2 puffs of albuterol via MDI/spacer/mask.

**For the purpose of determining treatment frequency, on one occasion up to 3 albuterol treatments may be administered back-to-back and counted as a single treatment.

The parent/guardian should be advised to start OCELOT medication immediately and to give the participant albuterol treatments every 4 hours. They should also be advised to call the site if the respiratory symptoms worsen. The action plan will direct them to call the site or after-hours triage site if a specific frequency of albuterol is used or significant symptoms develop.

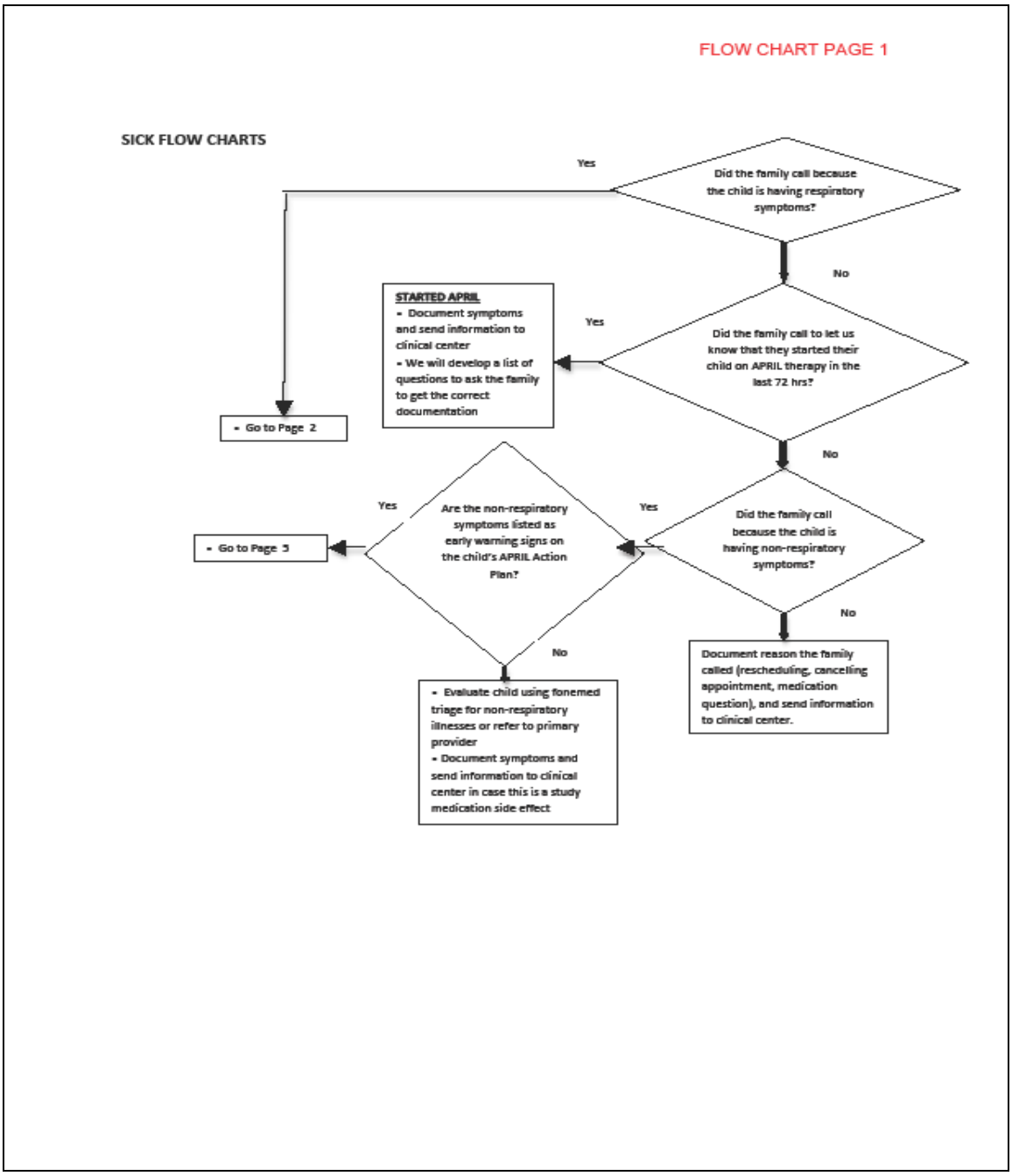
A follow-up phone call should be made to the parent/guardian 1-24 hours after telling the parent/guardian to start OCELOT medications. During that follow-up call, the OCELOT Scheduling Form (P2_OCELOT_SCHED) should be completed and a follow-up appointment (Visit 20) should be scheduled for 36-72 hours after starting OCELOT therapy.

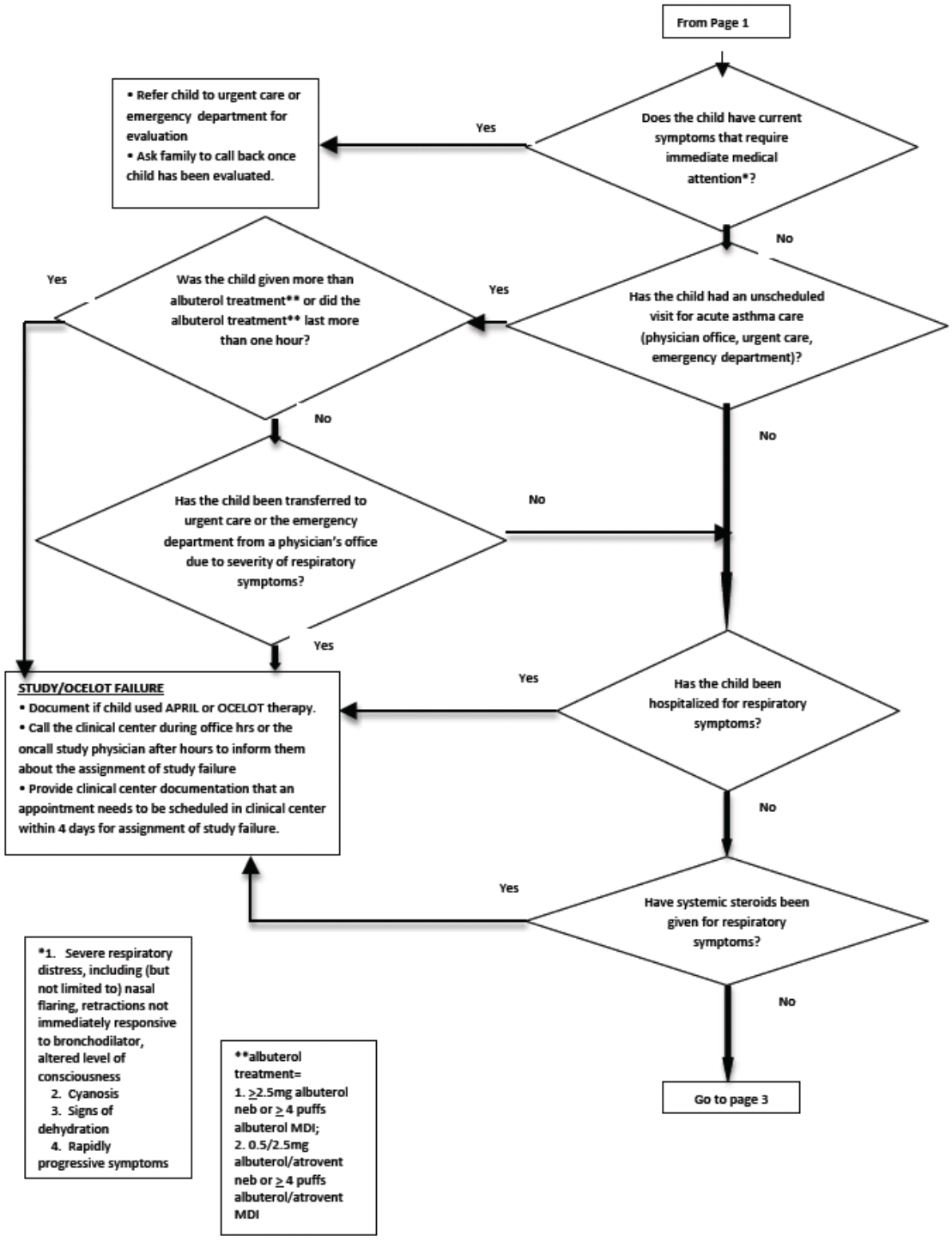
While on OCELOT medications, the Pre-School Asthma Diary (P2_PAD) and corresponding Albuterol Log (on reverse side) should be completed.

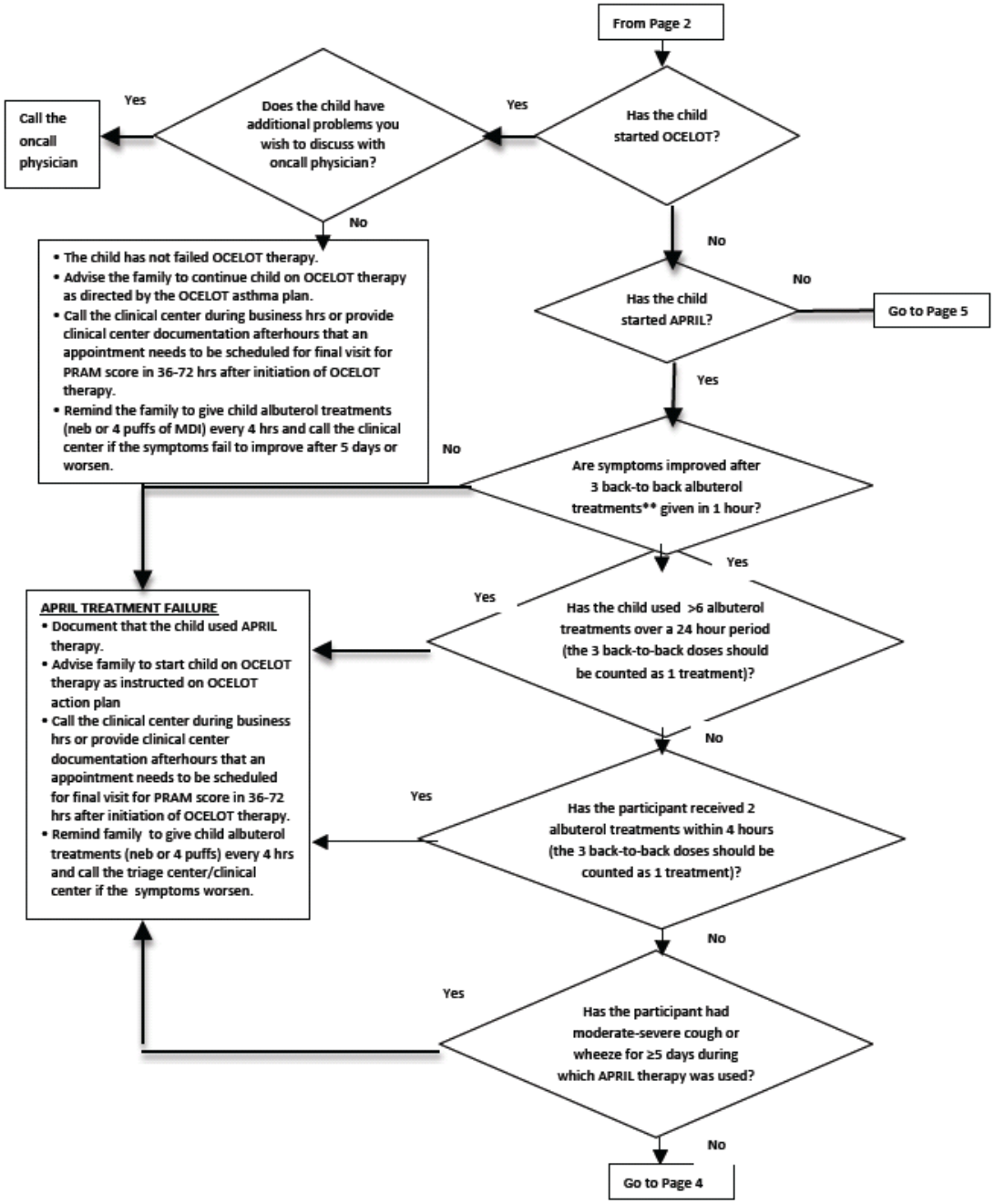
If the participant is still taking the APRIL medications at the time OCELOT is started, he/she should finish the five day course of APRIL medications even if it overlaps with

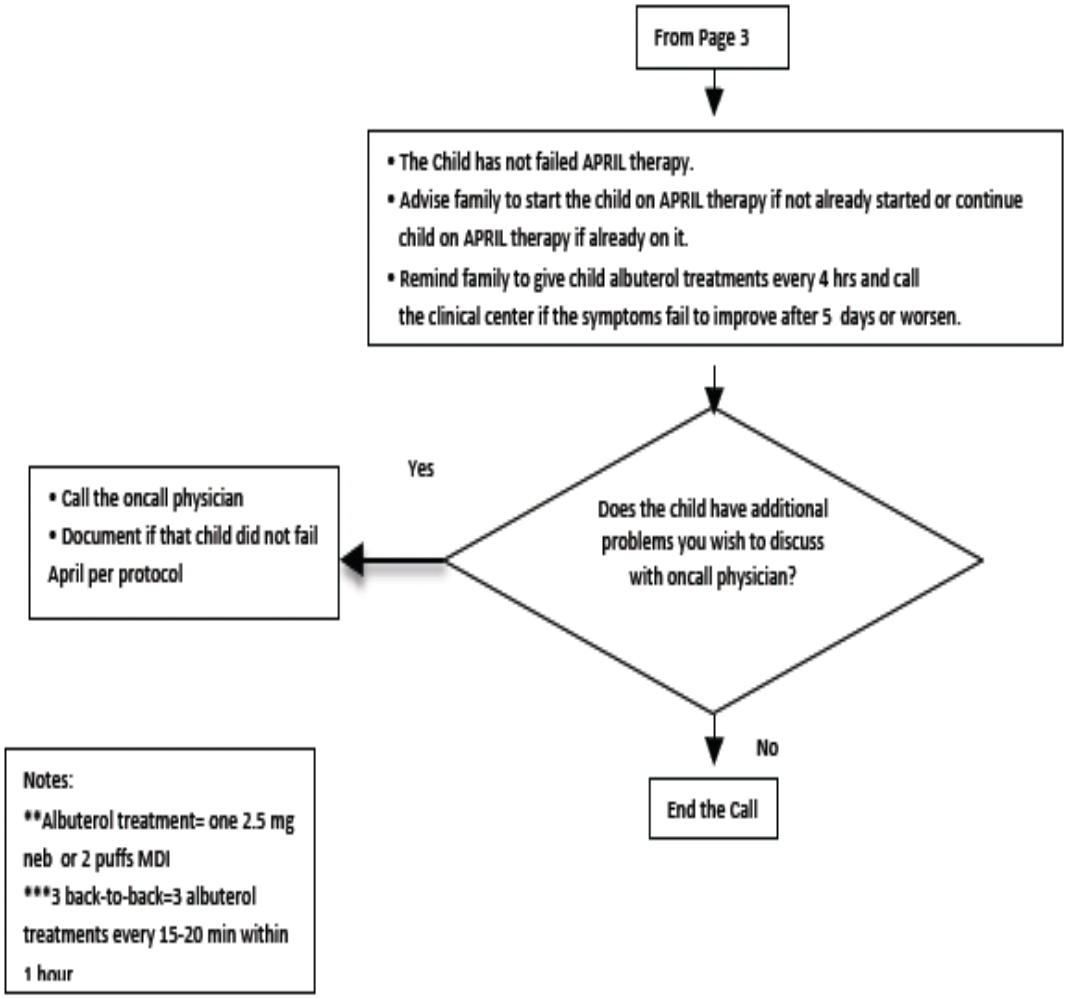
taking the OCELOT medications. APRIL medications and OCELOT medications can be taken at the same time.

## 2.7 APRIL/ TREATMENT FAILURE/STARTING OCELOT FLOWCHARTS

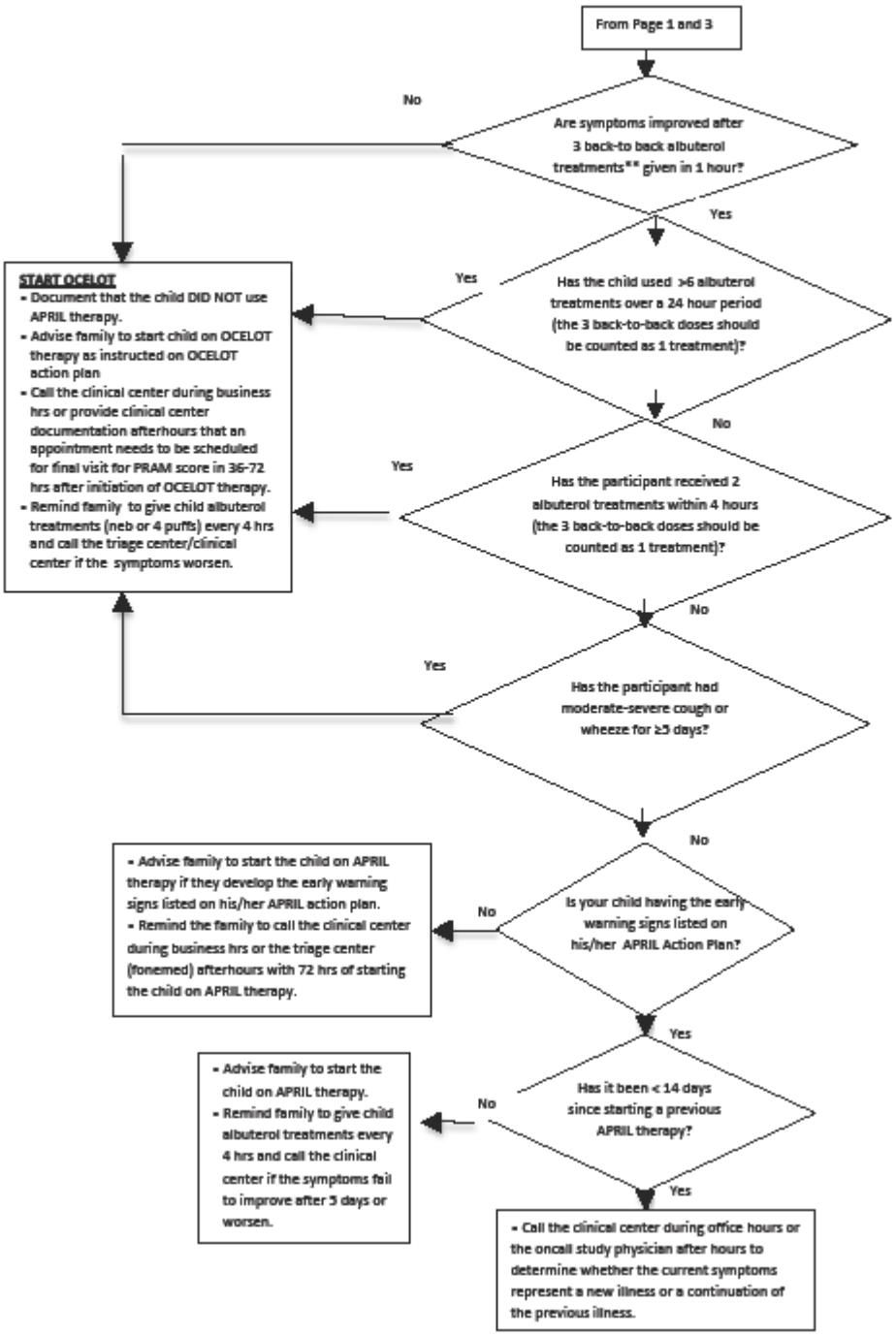



From Page 1
Does the child have current symptoms that require immediate medical attention*?
Yes
• Refer child to urgent care or emergency department for evaluation
• Ask family to call back once child has been evaluated.
No
Has the child had an unscheduled visit for acute asthma care (physician office, urgent care, emergency department)?
Yes
Was the child given more than albuterol treatment** or did the albuterol treatment** last more than one hour?
Yes
No
Has the child been transferred to urgent care or the emergency department from a physician's office due to severity of respiratory symptoms?
No
Yes
Has the child been hospitalized for respiratory symptoms?
Yes
No
STUDY/OCELOT FAILURE
• Document if child used APRIL or OCELOT therapy.
• Call the clinical center during office hrs or the oncall study physician after hours to inform them about the assignment of study failure
• Provide clinical center documentation that an appointment needs to be scheduled in clinical center within 4 days for assignment of study failure.
Have systemic steroids been given for respiratory symptoms?
Yes
No
Go to page 3
*1. Severe respiratory distress, including (but not limited to) nasal flaring, retractions not immediately responsive to bronchodilator, altered level of consciousness
2. Cyanosis
3. Signs of dehydration
4. Rapidly progressive symptoms
**albuterol treatment=
1. ≥2.5mg albuterol neb or ≥ 4 puffs albuterol MDI;
2. 0.5/2.5mg albuterol/atrovent neb or ≥ 4 puffs albuterol/atrovent MDI


From Page 2
Has the child started OCELOT?
Yes
Does the child have additional problems you wish to discuss with oncall physician?
Yes
Call the oncall physician
No
• The child has not failed OCELOT therapy.
• Advise the family to continue child on OCELOT therapy as directed by the OCELOT asthma plan.
• Call the clinical center during business hrs or provide clinical center documentation afterhours that an appointment needs to be scheduled for final visit for PRAM score in 36-72 hrs after initiation of OCELOT therapy.
• Remind the family to give child albuterol treatments (neb or 4 puffs of MDI) every 4 hrs and call the clinical center if the symptoms fail to improve after 5 days or worsen.
No
Has the child started APRIL?
No
Go to Page 5
Yes
Are symptoms improved after 3 back-to back albuterol treatments** given in 1 hour?
No
Yes
Has the child used >6 albuterol treatments over a 24 hour period (the 3 back-to-back doses should be counted as 1 treatment)?
Yes
No
Has the participant received 2 albuterol treatments within 4 hours (the 3 back-to-back doses should be counted as 1 treatment)?
Yes
No
Has the participant had moderate-severe cough or wheeze for ≥5 days during which APRIL therapy was used?
Yes
No
Go to Page 4
APRIL TREATMENT FAILURE
• Document that the child used APRIL therapy.
• Advise family to start child on OCELOT therapy as instructed on OCELOT action plan
• Call the clinical center during business hrs or provide clinical center documentation afterhours that an appointment needs to be scheduled for final visit for PRAM score in 36-72 hrs after initiation of OCELOT therapy.
• Remind family to give child albuterol treatments (neb or 4 puffs) every 4 hrs and call the triage center/clinical center if the symptoms worsen.


From Page 3
• The Child has not failed APRIL therapy.
• Advise family to start the child on APRIL therapy if not already started or continue child on APRIL therapy if already on it.
• Remind family to give child albuterol treatments every 4 hrs and call the clinical center if the symptoms fail to improve after 5 days or worsen.
Does the child have additional problems you wish to discuss with oncall physician?
Yes
• Call the oncall physician
• Document if that child did not fail April per protocol
No
End the Call
Notes:
**Albuterol treatment= one 2.5 mg neb or 2 puffs MDI
***3 back-to-back=3 albuterol treatments every 15-20 min within 1 hour

FLOW CHART PAGE 5



## 2.8 APRIL/OCELOT MEDICATION COMPLIANCE

**Visits 3-9, 20, 21**

Complete the APRIL Compliance Checklist (P2_APRIL_COMPLY) or the OCELOT Compliance Checklist (P2_OCELOT_COMPLY)

Adherence with the APRIL and OCELOT medications is assessed on the APRIL Compliance Checklist (P2_APRIL_COMPLY) and the OCELOT Compliance Checklist (P2_OCELOT_COMPLY). Since the participant will only be taking study medications when he/she is sick, adherence will only be assessed at the visit after the APRIL or OCELOT therapy is used. If the participant has used more than one APRIL therapy between visits, one form should be completed for each APRIL therapy that the participant has used.

If the participant is in the middle of taking APRIL or OCELOT medications at a scheduled visit, the COMPLY form should be set to missing for the current visit. Ask the parents to bring the medications to the next scheduled visit, at which time, adherence can be calculated and the correct COMPLY form can be completed.

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.

## 2.9 APRIL/OCELOT TREATMENT QUESTIONNAIRES

**Visits 2-9, 20, 21**
**Complete the APRIL Treatment Questionnaire (APRIL_TRTQX) - Visit 9 (or last visit see below for details)**
**Complete the OCELOT Treatment Questionnaire (OCELOT_TRTQX) - Visit 21**

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 question. The last question should be completed by the coordinator.

If a participant withdraws from the study following randomization and prior to Visit 9, the APRIL Treatment questionnaire should be completed at the time of the participant's final contact with the performance site. Participants who term early from APRIL for any reason (i.e. withdraw consent,4$^{th}$ APRIL therapy used, APRIL treatment failure) should complete the APRIL questionnaire at the time of the participant's final contact with the performance site. Only participants who start OCELOT therapy should complete the OCELOT Treatment Questionnaire at Visit 21.

## 2.10 BLOOD SAMPLING PROCEDURES

### Visit 2

The following blood samples will be drawn in APRIL/OCELOT at Visit 2. If you have difficulty drawing blood on the participant at Visit 2, you can draw blood at a later visit.

- ImmunoCap Testing for Food, AeroAllergen and IgE
- CBC (Total WBC and Eosinophils)
- Genetic Analysis (optional)

### General Blood Draw Procedures

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

2 ml for ImmunoCap Testing and IgE
1-2 ml blood for CBC and Eosinophil Count
4 ml (age: 12–60 months) or 10 ml (age: 60-72 months) blood for genetic analysis
The total amount of blood to be drawn should be 8-14 ml.

The processing and storage of each of these blood samples is discussed below. The CBC will be processed at the site's local lab. The ImmunoCap sample will be sent to the St. Louis Lab for processing. The blood for genetic analysis will be sent to the Tucson Genetics of Asthma Lab.

The results of the CBC (WBC and eosinophils) are recorded on the Laboratory Tests (P2_LAB) form. See Section 4 for more detail on completing this form.

### ImmunoCap and IgE Procedures (2 ml)

Specimen collection: A minimum of 2 ml of whole blood or 1 ml of serum should be collected in a serum separator tube (5 ml). Blood should be spun down to serum and poured off into a 5 ml cryovial. Alternatively, the serum can be put in the 5 ml cryovial using a pipette. The centrifuge speed and time will be dependent on the serum separator tube and centrifuge that are used. Therefore, each site will need to determine the speed and time based on the components they are using. Discard the remaining blood after the serum has been poured/pipette into the cryovial.

Blood collection tubes:
Fisher Scientific, externally-threaded 5.0 ml vials

Catalog #10-500-27, Pack of 50 for $34.02

### *Specimen Tracking – Collection Day*

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

Label specifications: Diversified Biotech (www.divbio.com).
Laser Cryo-Tags 1.69 x 1.75 (Catalog number: LCRY-1100), 1040/pk, $60.00

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 blood draw date). Print the shipment inventories for inclusion in the shipment. Samples must be shipped via FedEx priority overnight (using the DCC's APRIL FedEx account #337822355) Please record 'AsthmaNet – APRIL' in the reference section. 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 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

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

3. 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 St. Louis 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 tubes.

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. 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)


d. 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)


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

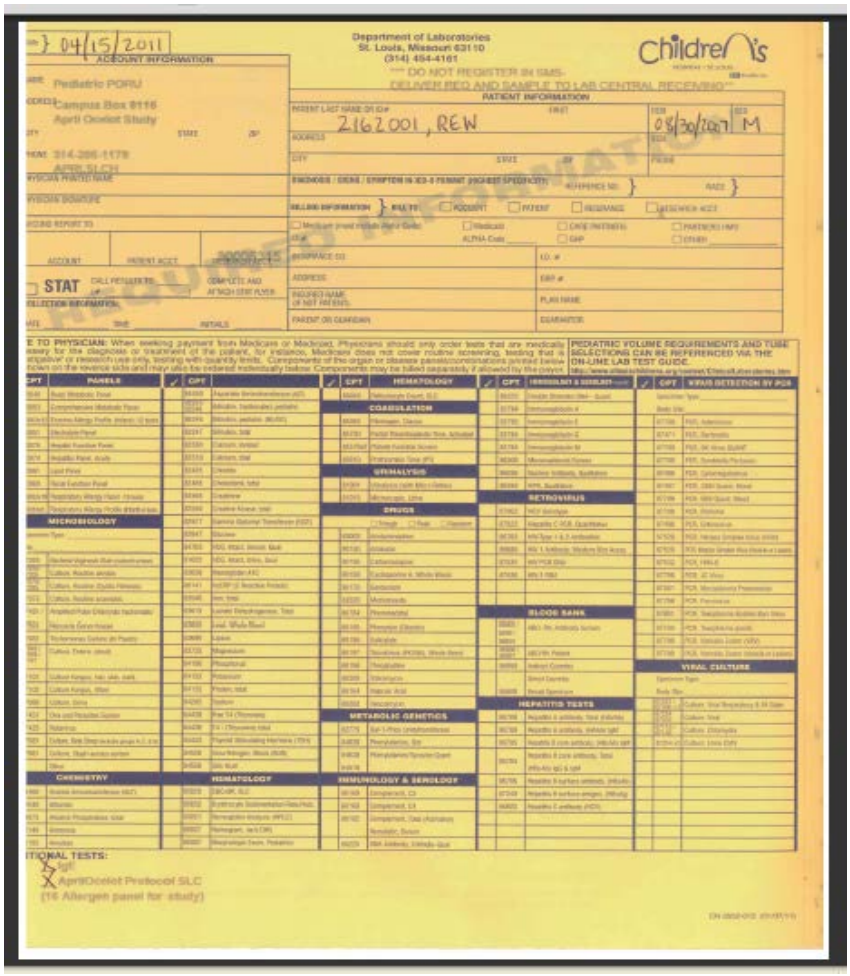
1. All blood specimens should be sent FedEx Priority Overnight (use DCC's APRIL FedEx account #337822355). Please record 'AsthmaNet – APRIL' in the reference section. No other form of shipping is acceptable. Blood samples should be shipped to St. Louis' Children's on the first Monday of each month (if Monday is a holiday, then ship on Tuesday). If you are unable to ship the samples on the designated shipping day, you **MUST** contact Tina Norris at St. Louis. She needs to make sure the lab person is available to receive the shipment on the alternate day.

For every sample that is shipped, a Gold-Req form **must** be completed and be shipped with the samples. Therefore, if 10 samples are being shipped, then 10 Gold-Req forms should be completed and shipped with the samples.

The following information should be completed on the Gold-Req forms:

- Date sample was drawn
- Patient Last Name of ID# - use participant ID without dashes and participant initials
- Date of Birth (DOB)
- Sex
- Additional Tests (at bottom of form) – place 'X's in the boxes for IgE and APRILOCELOT Protocol SLC

Note: If you were unable to collect the full amount of blood, please put a note on the Gold-Req form indicating that the sample is short.




Ship to:

St. Louis Children's Hospital
One Children's Place
St. Louis, MO 63110
Attn: Lab Receiving 2N21 – Mary Giedinghagen (314-454-4268)

## WBC and Eosinophil Count Procedures (1-2 ml)

For eosinophil percentage determination:

Use two 3 ml lavender top tubes containing EDTA anticoagulant or similar EDTA microtainer, if available for venipuncture specimen. Draw 1 ml of whole blood in each of the two tubes, invert immediately and gently mix with anticoagulant. The specimens cannot be used if stored more than 8 hours at room temperature or 24 hours at 4°C. One sample will be analyzed at the site's local laboratory, while the other sample should be held until the results from the first sample are received. Send to the local hematology laboratory to prepare the blood smear and determine differential count to report

percentage of eosinophils. A manual count is NOT required; an automatic count is sufficient. The second tube can be discarded once the results are obtained from the laboratory. Please note that if the first sample is sent to the lab on Friday and the sample clots, the lab personnel should alert the coordinator before the end of the day Friday, so that the second sample can be run immediately.

Record the participant's total WBC and relative eosinophil count on the Laboratory Tests form (P2_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 Procedures (4 ml for age 12-60 months, 10 ml for age >60 months)

Obtain blood sample for DNA extraction and genetic analysis (4 ml for participants age 12-60 months, 10 ml for participants age 60-72 months)
Complete Genetic Analysis Blood Draw (GABLOOD) form
Enter participant's genetics blood draw information into Genetics Sample Tracking module

Samples must be shipped via FedEx priority overnight (using the DCC's APRIL FedEx account #337822355) Please record 'AsthmaNet – APRIL' in the reference section. Please note that using the DCC's FedEx number for shipping genetic samples pertains to the APRIL study only.

See 'Genetic Analysis' later in this section for further details.

## 2.11 CERTIFICATION

Individuals who carry out APRIL/OCELOT study visits must be certified to do so. That is, personnel who complete any of the protocol-specific APRIL/OCELOT forms (designated by a P2 prefix in the form name) must possess APRIL/OCELOT study certification.

To obtain APRIL/OCELOT certification, clinical personnel must complete the following steps:

- Thoroughly read the APRIL/OCELOT protocol and this Manual of Operations.
- Pass the APRIL/OCELOT 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.

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).

## 2.12 CONCOMITANT MEDICATIONS

### Visits 1-9, 20, 21

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 APRIL/OCELOT 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 (RESCUE) 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 APRIL and OCELOT 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 (P2_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.

Note that participants must wash out of many medications for appropriate intervals prior to Visit 1. Washout periods are listed on the APRIL/OCELOT Exclusionary Drugs (P2_EXCLDRUG) reference card. If the participant is taking any of the drugs listed on P2_EXCLDRUG, confirm with the parent/guardian and with the study physician that he or she may discontinue use of this medication if he or she is eligible to enroll in the APRIL/OCELOT study. Also confirm that it is safe and appropriate for the participant to go off the medication for the appropriate washout period prior to Visit 1. Some institutions require that the parent/guardian read and sign the study informed consent document prior to washing out of medications for study enrollment.

### Visits 2-9

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 APRIL/OCELOT studies, the record should be marked 'ongoing at final visit.'

## 2.13 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 APRIL/OCELOT 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.

## 2.14 ELIGIBILITY CRITERIA

**Visit 1**

**Inclusion/Exclusion Criteria (P2_ELIG1)**

**INCLUSION CRITERIA**

The following inclusion criteria pertain to both APRIL and OCELOT. Participants who meet all of the following criteria are eligible for entry into APRIL and OCELOT, but OCELOT participation will begin once the participant achieves APRIL Treatment Failure. Participants may be reassessed if not initially eligible.

**1.** 12-71 months of age. Note: Participants who are 72 months old or older at the time of *enrollment* are not eligible for APRIL/OCELOT. A participant who is between 71 and 72 months old should be considered 71 months old until he/she reaches 72 months.

**2.** Recurrent significant wheezing in the past year (any of the following):

a. ≥3 episodes, ≥1 of which was clinically significant*; OR
b. ≥2 clinically significant* episodes; OR
c. ≥ 4 months of daily controller therapy AND ≥1 clinically significant* episode.

*Clinically significant episode: requiring any of the following: (1) systemic corticosteroids (oral or injectable), (2) unscheduled physician office visit, (3) ED visit, (4) urgent care visit, or (5) hospitalization.

**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.

**4.** Willingness to provide informed consent by the participant's parent or guardian. If the study consent form was signed in advance of Visit 1, they 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.

## 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. >4 courses of systemic corticosteroids in past 12 months.
2. More than 1 hospitalization for wheezing illnesses within the preceding 12 months.
3. Use of long-term controller medications for asthma, including inhaled corticosteroids, leukotriene modifiers, cromolyn/nedocromil, or theophylline for more than 8 months (cumulative use) in the past 12 months.
4. Current use of **higher than step 2** NAEPP asthma guideline therapy (e.g. medium-high dose ICS alone or combination therapy of low-medium-high dose ICS + LABA, montelukast, theophylline or cromolyn). If a participant's PCP agrees to stop combination therapy, there should be a 4 week washout prior to enrollment (i.e. If the participant is taking fluticasone + singulair and the PCP stops singulair, there should be a 4 week washout period prior to enrollment), NOTE: participants who have evidence of well-controlled symptoms immediately preceding study entry while receiving Step 2 controller therapy (presence of self-reported symptoms on average no more than 2 times per week and less than 2 nights per month of nocturnal awakenings, requiring albuterol, during the 4 weeks preceding visit 1) may be enrolled and will have their controller therapy discontinued upon study entry.
5. Use of OCS in the past 2 weeks.
6. Daily symptoms or ≥2 nocturnal awakenings, requiring albuterol, in the last 2 weeks.
7. Use of antibiotics in the past month.
8. Current treatment with antibiotics for diagnosed sinus disease.
9. Participation presently or in the past month in another investigational drug trial.
10. Evidence that the family may be unreliable or nonadherent, or may move from the site area before trial completion.
11. Contraindication of use of systemic corticosteroids or azithromycin.
12. Clinically relevant gastroesophageal reflux. Note: If a child takes medication daily to treat gastroesophageal reflux, it should be considered clinically relevant.
13. Concurrent medical conditions other than asthma that are likely to require oral or injectable corticosteroids during the study.
14. If receiving allergy shots, change in dose within the past 3 months. Participants should NOT change their maintenance regimen during the course of the APRIL/OCELOT study.

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, and may not be re-enrolled:

1. Gestation less than late preterm as defined as birth before 34 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 participant at increased risk of participating in the study.
4. Immunodeficiency disorders.
5. History of respiratory failure requiring mechanical ventilation.
6. History of hypoxic seizure.
7. History of significant adverse reaction to any study medication ingredient.
8. 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 < 10th 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, Q1780 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 P2_ELIG1 form. A data correction for Q1780 should be submitted once the growth charts are obtained.

NOTE: The DSMB recommended that children living in the same household should not be enrolled in the APRIL/OCELOT study at the same time to prevent a mix-up of study drugs and other materials. Once one child finishes/terms from the study, a second child can be enrolled.

**VISIT 2**

**EXCLUSION CRITERIA**

Participants will be ineligible for randomization if any of the following is documented, but may be re-enrolled if these exclusion criteria are resolved:

1. Persistent symptomatic asthma
   - **a.** For participants who are controller naïve at the time of enrollment, persistent asthma is defined as asthma-related symptoms/albuterol use $\geq$ 4 days/week or $\geq$ 1 nighttime awakenings, requiring albuterol, on average during the 2 week run-in OR

**b.** For participants who were receiving long-term controller medicine (low dose ICS or LTRA monotherapy) at the time of enrollment, persistent asthma is defined as asthma-related symptoms/albuterol use $\geq$ 4 days/week or $\geq$ 1 night awakenings, requiring albuterol, on-average during the last 2 weeks of the 4 week run-in

Please Note: Coordinators should stress to families that albuterol should be used for clinically meaningful symptoms related to asthma. Minor cough should not be treated with albuterol. If albuterol is not used at times that the coordinator thinks that it should have been used, that could be considered a sign of non-adherence to the directions. For these cases, by coordinator or MD discretion, a participant could be excluded.

If there is discordance between the diary symptoms and the albuterol use, the coordinator with the assistance of a study investigator, should evaluate the totality of the clinical situation on the specific days and decide whether albuterol use would have been appropriate. If albuterol use would have been appropriate, the day(s) should be added as albuterol day(s). If the participant meets the exclusion criteria due to persistent asthma owing from this situation, Question #9 should be marked 'Yes' and an explanation should be provided.

The Run-In Diary Cards should be reviewed with the parent. If the coordinator thinks that the parent exaggerated the severity of the participant's symptoms on the Diary Cards (and the parent agrees), the parent should make corrections to the Diary Cards as needed, and initial and date each change.

**2.** Inadequate adherence (< 80% of days) to diary card completion during the last 2 weeks of the Run-In period.

**3.** Use of oral corticosteroids or antibiotics during the 2-4 week observation run-in.

**4.** Use of asthma medication except prn albuterol during the 2-4 week observation run-in.

**Drugs to be withheld prior to Visit 1 and during the Run-In.**

| Excluded Drug | Generic Names (may not be inclusive) | Trade Names (may not be inclusive) | Washout Prior to Visit 1 |
|---|---|---|---|
| Oral or systemic steroids for any reason. | Prednisone, prednisolone, dexamethasone | Medrol, Decadron, Orapred, Prelone, Pediapred | 2 weeks |
| ORAL/INJECTABLE /INTRAVENOUS Antibiotics (topical antibiotics for ears, eyes,skin are permitted) | tetracycline, penicillin, cephalosporin, quinolones, monobactam, erythromycin, clarithromycin, telithromycin, azithromycin | Sumycin, Amoxicillin, Cipro, Aztreonam, E-Mycin, Biaxin, Ketek, Zithromax | 4 weeks |

## Exclusionary Medical Conditions during APRIL/OCELOT

- Addison's disease
- Cardiac arrhythmias (clinically significant)
- Cardiac disorder (except hemodynamically insignificant ASD, VSD, or heart murmur)
- Cataracts
- Chest surgery (call for exception)
- Congenital anomalies of the lung and chest, including growth abnormalities that affect predictability of expected lung function parameter
- 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)
- Failure to Thrive
- Gastroesophageal reflux (not controlled by standard medical therapy)
- 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, 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 (except febrile seizure in infancy)
- Peptic ulcer disease (active)
- Renal disease (active)
- Rheumatoid arthritis (if likely to require oral/systemic corticosteroid treatment)
- Thyrotoxicosis
- Tuberculosis (active)
- Vocal cord dysfunction (active)

## Allowed medications during APRIL/OCELOT

- acetaminophen
- acyclovir (e.g., Zovirax) for herpes
- non-macrolide antibiotics (e.g. tetracycline, penicillin, cephalosporin, quinolones, monobactam)
- 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
- non-steroidal anti-inflammatory medications (e.g. aspirin, ibuprofen, naproxen, ketoprofen)
- all oral decongestants (e.g., Sudafed)
- 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

## 2.15 FOLLOW-UP MEDICATION PRESCRIPTION

Visit 9 or Visit 21

**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 9 or Visit 21 date, and the 'ongoing at final visit' box should be checked.

## 2.16 FONEMED – AFTER HOURS NURSING TRIAGE SITE

**Visits1-2**

During the Run-In period, the parent/guardian should be instructed to call the site's normal after-hours call service for medical emergencies. Do not give them the phone number for FoneMed. If the participant calls FoneMed during the Run-In (since the phone number is listed in the consent form), FoneMed will direct the parent/guardian as indicated based on the participant's symptoms.

**Visits 2-9, 20, 21**
**Complete the FoneMed form (FONEMED)**

To assure consistent assignment of treatment and to have immediate access to personnel familiar with the APRIL/OCELOT study procedures, an after-hour nursing triage site will be available for calls placed primarily at night, holidays and weekends. In addition, FoneMed will also be available for calls placed during normal daytime hours, but will be unable to assist participants with issues not related to symptoms (i.e. rescheduling visits, lost study medications/supplies, follow-up phone call 36-72 hours after starting APRIL therapy, etc.)

The family should be instructed on the action plan when to contact the site and when to contact the after-hours nursing triage site. The families will be instructed to use a 1-800 phone number that identifies that the caller is part of the APRIL/OCELOT study and the caller's site. The nurses will have ready access to a computerized set of telephone algorithms for APRIL/OCELOT and the site's personnel coverage information. The protocols will allow the nurse to direct the caller to the appropriate care for his/her situation that may include starting study medication or advising the family to take the participant to the ER. The nurse will also contact the study coordinators and physicians in a timely manner to inform them of situation. Each site will have on-call study personnel available to the nurse 24 hours a day. A written summary of the call will be sent to the site where the participant is enrolled.

For every call that is placed to the after-hours nursing triage site, a FoneMed form (FONEMED) should be completed. Depending on the outcome of the call, other data collection forms may need to be completed as indicated by the FoneMed form.

Parents/guardians should be instructed to call the sites (and NOT FoneMed) for the following reasons:

- Reschedule visits
- Lost study medications/supplies
- Follow-up phone call 36-72 hours after starting APRIL therapy

However, if the parent/guardian calls FoneMed for any of the reasons listed above, FoneMed will contact the center and provide the details of the call.

The table below contains the site-specific FoneMed phone numbers:

| Group | Site Identifier | Performance Site | FoneMed number that parents will call |
|---|---|---|---|
| **Boston** | | | |
| | 112 | Children's Hospital | 855 855 6473 |
| **Chicago** | | | |
| | 122 | Children's Memorial | 855 855 6474 |
| | 124 | University of Chicago | 855 855 6475 |
| | 125 | StrogerHospital/Rush Univ. | 855 855 6476 |
| **Denver** | | | |
| | 132 | National Jewish | 855 855 6477 |
| | 133 | University of New Mexico | 855 855 6478 |
| **Madison** | | | |
| | 141 | University of Wisconsin | 855 855 6479 |
| | 143 | Milwaukee | 855 855 6480 |
| **Pittsburgh** | | | |
| | 152 | University of Pittsburgh | 855 855 6481 |
| | 153 | Case Western | 855 855 6482 |
| | 154 | Allegheny | 877 702 4742 |
| **St. Louis** | | | |
| | 162 | Washington University | 855 855 5778 |
| **San Francisco** | | | |
| | 172 | University of California (SF) | 855 855 5779 |
| | 173 | Children's Hospital Oakland | 855 855 5780 |
| **Tucson/Durham** | | | |
| | 181 | Univ. of Arizona | 855 855 5781 |
| **Winston-Salem/ Charlottesville** | | | |
| | 192 | University of Virginia | 855 855 5782 |
| | 194 | Emory University | 855 855 5783 |

## 2.17 FORGOTTEN STUDY MATERIALS

The table below details what to do regarding forgotten study materials at an APRIL/OCELOT 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, 8b, 8c, 8d, 20** |
|---|---|---|---|
| **Forgotten Item** | APRIL Run-In Diary Card | **Visit must be rescheduled,** since 80% compliance must be established firmly prior to randomization | NA |
| | APRIL MEDS | NA | Bring to next visit |
| | OCELOT MEDS | NA | Bring to next visit |
| | Nasal Samples | NA | Bring to next visit |
| | P2_PAD | NA | Bring to next visit |

## 2.18 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 APRIL/OCELOT 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 APRIL/OCELOT study. The genetic analysis participation rate for each clinical center partnership and performance site will be summarized on the APRIL/OCELOT 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) and 10 ml (age 60-72 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 be taken 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 6). 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.

Samples must be shipped via FedEx priority overnight (using the DCC's APRIL FedEx account #337822355) Please record 'AsthmaNet – APRIL' in the reference section. Please note that using the DCC's FedEx number for shipping genetic samples pertains to the APRIL study only.

## 2.19 GROWTH CHARTS

### Height/Length

**Visit 1-9, 20**

**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 1-9 and 20, 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 1-9, 20**

**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 1-9 and 20, 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.

## 2.20 GROWTH FAILURE PROTOCOL

### Visit 1

### Height/Length and Weight

If the participant's height/length or weight plots less than the 10$^{th}$ 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 2-9, 20

Plot height/length at each clinic visit (average every 2 months) 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 APRIL/OCELOT: Potential Growth Failure'.
- The email will also be forwarded to the lead PIs for the APRIL/OCELOT study.
- The email will contain all information related to the participant's growth while in the APRIL/OCELOT 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 APRIL/OCELOT study.

According to the APRIL/OCELOT 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 APRIL/OCELOT PIs will decide if the participant will continue in APRIL/OCELOT or be termed from the study.

## 2.21 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.

## 2.22 HOSPITALIZATIONS

Participants who are hospitalized for an acute wheezing exacerbation at any time during APRIL/OCELOT are assigned study failure status. 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 APRIL/OCELOT MOP and Section 4 of the General MOP for more information.

## 2.23 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.

## 2.24 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, cypress |
| **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 St. Louis lab. See 'Blood Sampling Procedures' for more details.

## 2.25 INFORMED CONSENT

**Visit 1**
**Acquire signed APRIL/OCELOT informed consent**

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 APRIL/OCELOT trial, should the potential participant be deemed eligible. Prior to implementation of Visit 1, a summary of the studies and their complementary nature should be presented to the parent/guardian. He or she should be given an opportunity to read and sign the consent document.

Guidelines for obtaining consent:

- At the beginning of Visit 1, provide the parent/guardian a copy of the informed consent form for one of the studies and ask him or her to read it thoroughly. The parent/guardian should not sign the form until after you have discussed its contents with him or her.

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

- If the parent/guardian is unable to read the informed consent form or seems to be struggling, offer to read it 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 study 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 form.

- Maintain the signed informed consent form in the participant's study folder. To ensure confidentiality, **do not send this form to the DCC**. This document 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 a clean copy of the consent document to review and sign. See the Reenrollment discussion in this section for further details.

If modifications are made to the APRIL/OCELOT consent document and approved by the local IRB while a participant is in the study, the parent/guardian must be re-consented following local IRB rules. All versions of the APRIL/OCELOT consent document 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 consent is recorded and tracked on Eligibility Checklist 1 (P2_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 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 APRIL/OCELOT 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 APRIL/OCELOT trial, he/she must be given the IRB-approved APRIL/OCELOT 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 APRIL/OCELOT 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.

## 2.26 MDI INHALATION TECHNIQUE ASSESSMENT *

*** Only required if participant is using MDI for rescue medication**

**Visit 1**

**Instruct Use of Albuterol (Rescue) Inhaler (TECH_MDI_FACE, HTMDI)**

If the participant will be using a rescue inhaler for albuterol during the Run-In phase of the study, 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. Participants will be given the choice of rescue medications by MDI or by nebulizer.

**Visits 2-8, 8b, 8c, 8d**

**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.

## 2.27 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.

## 2.28 MEDICATION ADHERENCE

**Visits 3-9, 20, 21**

Medication adherence will be assessed at the visit following use of APRIL or OCELOT medications. It is imperative that the parent/guardian does not throw away used medication bottles after the last dose of APRIL or OCELOT therapy is taken by the participant. They should save the used bottles and bring them to the next scheduled visit.

The contents remaining in the bottles should be weighed. The appropriate compliance form (P2_APRIL_COMPLY or P2_OCELOT_COMPLY) should be completed. If more than one APRIL therapy was used since the previous visit, a second P2_APRIL_COMPLY 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.

## 2.29 MISSED VISITS

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.

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, diary cards, nasal collection samples, etc.) to the participant by some other means.

## 2.30 NASAL SAMPLING PROCEDURES

**Visit 2 AND 9 or 21 (whichever one occurs)**

Day 1 and 4 of each APRIL medication usage

Nasal mucus samples will be taken by the coordinator during Visit 2 AND Visit 9 or 21. A participant will have either visit 9 or visit 21, not both. If he/she completes APRIL without starting OCELOT, his/her final visit will be visit 9. If he/she starts OCELOT, his/her final visit will be visit 21. Additional samples will be taken by the participant's parent on the first and fourth day of every APRIL respiratory illness. 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 Days 1 and 4. However, if the parent forgets on those days, the samples can still be collected within a few days of the ideal date. That is, the Day 1 sample could be collected on Days 2 or 3; the Day 4 sample could be collected on Days 5-7.

When a respiratory illness occurs and APRIL therapy is started, the parent is to call the site within 72 hours of starting APRIL. The P2_ILLNESS form is completed during that call and there are questions regarding whether the nasal samples were collected. The 'Daily Activities during Illness' Guide on the back of the APRIL/OCELOT Action Plan will serve as a reminder to collect nasal samples on Days 1 and 4 of each illness. For the in-clinic samples that are obtained at Visits 2 and 9/21, the P2_LAB form is part of the visit packet and includes questions regarding whether the nasal samples were 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 anytime. Written instruction provided to parents at the study Visit 2 and review 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.

If a participant has a respiratory illness the same day as Visit 2 or 9/21, it is not necessary to obtain an 'at-home' nasal sample, since one will already be obtained in the clinic. However, if they had a cold 5 days before the visit, an 'in-clinic' sample should still be obtained in addition to the 'at-home' sample that was obtained 5 days before.

Four nasal mucus sample kits should be sent home at Visit 2 and maintain four kits at the participant's home during the study (i.e. 2 for each illness). If the parent/guardian

calls the clinic reporting an APRIL therapy usage, the coordinator will need to send an additional two kits by mail, unless they are scheduled for a visit soon.

### Visit 9

Ongoing illnesses at Visit 9: If a participant is coming in for the final visit (Visit 9) and is in the middle of an APRIL therapy, please reschedule the visit so that at least 14 days have passed since the last dose was taken. Contact the DCC if a visit window exception is required.

### 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 (using the DCC's APRIL FedEx account #337822355). Please record 'AsthmaNet – APRIL' in the reference section. 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 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

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

7. 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.

8. Fill bottom of shipping box with dry ice

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

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


   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.
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 samples, using the following method. 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. In this way, at least 10 samples 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.
All samples should be sent FedEx Priority Overnight (use DCC's APRIL FedEx account #337822355). Please record 'AsthmaNet – APRIL' in the reference section. 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.

- 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).

## 2.31 OCELOT MEDICATIONS

### Visit 2

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

The use and purpose of the OCELOT medication should be explained to the parent/guardian. Make sure that the parent/guardian understands that he/she should not start OCELOT therapy without consulting the site personnel or after-hours call site. OCELOT therapy should be started when a participant is deemed an APRIL treatment failure.

It is important to remind the parent/guardian that albuterol should be used while taking OCELOT medications. Albuterol use while using OCELOT medications is: inhaler (4 puffs) with spacer or nebulizer (1 vial) taken every 4 hours (while awake) for 2 days, then 'as needed' to control symptoms.

If the participant is still taking the APRIL medications at the time OCELOT is started, he/she should finish the five day course of APRIL medications even if it overlaps with taking the OCELOT medications. APRIL medications and OCELOT medications can be taken at the same time.

The OCELOT therapy is dosed based on the participant's weight at Visit 2. Please refer to the OCELOT Prednisolone Dosing Reference Card for exact dose by weight.

The Preschool Asthma Diary (P2_PAD) should also be completed daily until the participant is symptom-free for 2 days. The parent/guardian should be encouraged to track albuterol use on the Albuterol Log which is on the reverse side of the Preschool Asthma Diary (P2_PAD).

Missed Doses (Please refer to the Tips for Taking APRIL and OCELOT medications handout): If the morning dose is missed, it should be taken as soon as possible. The prescribed dose should be resumed in the evening. If an evening dose is missed, it should be taken the next morning. If an entire day is missed, the prescribed dose should be resumed the next day. The prescribed dose should never be doubled.

## 2.32 OCELOT VISIT 20

**Visit 20**
**Complete the Ocelot Scheduling form (P2_OCELOT_SCHED) during Phone Contact 24 hours after starting OCELOT**

When a parent/guardian is instructed to start OCELOT medication, a follow-up phone call for safety should be placed between 1-24 hours after the medication is started. During the call, the OCELOT Scheduling Form (P2_OCELOT_SCHED) should be completed. Another purpose of the call is to schedule Visit 20.

The OCELOT visit 20 should take place 36-72 hours after the participant starts OCELOT medication. During the visit, a complete physical exam will be performed as well as an assessment of the PRAM score by a licensed medical practitioner. The licensed medical practitioner should be able to write prescriptions, if necessary.

If the participant requires inhaled steroids or oral steroids, they can be started immediately after completing Visit 20. If oral steroids are started prior to Visit 21, the participant should be assigned Study Failure status.

The participant's final visit (Visit 21) should be scheduled two weeks after Visit 20.

## 2.33 OCELOT VISIT 21

### Visit 21

Visit 21 is the final study visit for those participants who use the OCELOT medications. Procedures that will be performed during the final visit include: brief physical exam; collection of study drugs, nasal samples and other study materials; quality of life assessment; nasal sample collection and exit interview.

## 2.34 PARTICIPANT ASSIGNMENT LOG/PROTOCOL ENROLLMENT

### Visit 1

Assign participant ID number (P2_LOG)

A Participant Assignment Log (P2_LOG) has been developed for each performance site. This log includes columns for unique participant ID numbers, participant initials, participant's name, and assigned APRIL and OCELOT bottle numbers.

Participant ID numbers are preprinted on P2_LOG and are comprised of 8digits:

- The first two digits are the number of the AsthmaNet protocol. For the APRIL/OCELOT protocol the first two digits are 02.

- 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, 133=University of New Mexico, 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, 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 APRIL/OCELOT Participant Assignment Log. This number will be the primary participant identifier used during the APRIL/OCELOT 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 (P2_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 (P2_LOG)

Following assignment of the participant's ID number on the APRIL/OCELOT Participant Assignment Log (P2_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 3-9, 20**

Log assigned 3rd and 4th APRIL bottle number(s) or replacement medications (P2_LOG)

After accessing the randomization module to obtain the 3rd and 4th APRIL therapies or replacement bottle numbers for the participant, the new bottle numbers must be logged on P2_LOG. This log provides a single reference for all of an individual's medications over the life of the study.

## 2.35 PARTICIPANT HANDOUT FOLDER

At Visit 1 each participant is given an AsthmaNet folder containing 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 what to do during an APRIL illness (i.e. dosing with the APRIL therapy, completing the Pre-School Diary Card, collecting nasal samples, etc). The parent/guardian should store the study folder in a convenient location, as it will serve as a reference throughout the trial. The folder 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 APRIL/OCELOT study:

**Handouts Distributed at Visits**

| | |
|---|---|
| Visit 1 | Run-In Action Plan<br>Environmental Handouts (ENVIRONMENT)<br>How To Complete the Run-In Diary Card (P2_HTDIARY)<br>How To Use Your albuterol RESCUE Inhaler (P2_HTMDI)<br>How to Use Your Study Nebulizer® (HTNEBULIZER) |
| Visit 2 | A/O Action Plan Card / Respiratory Illness Daily Activities Guide<br>A/O Action Plan wallet-size ID Card<br>A/O Action Plan for Caregivers<br>APRIL Symptoms of Respiratory Illness (P2_SYMP_PARENT)<br>APRIL List of Symptoms of Respiratory Illness (P2_SYMPLIST)<br>Tips for Taking APRIL/OCELOT Medications (P2_TIPS_MED)<br>How to Contact the Study Team (P2_CONTACT_AO)<br>APRIL Nasal Swab (P2_HTNASAL_SWAB)/ APRIL Nasal Blow (P2_HTNASAL_BLOW)<br>Preschool Asthma Diary (PAD)/ Albuterol Log (P2_ALBUTEROL_LOG) |

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

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

### Environmental Handouts

The purpose of the Environmental Handouts (ENVIRONMENT) 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 Environmental Handouts includes:

Getting Rid of Cockroaches
Getting Rid of Mold
Pets
The Safe Sleeping Zone
Tobacco Smoke

### How to Complete the Diary Card (P2_HTDIARY)

These instructions can be used as a tool to introduce the Run-In Diary Card (P2_DIARY_RUNIN) to the parent/guardian at Visit 1. See "Run-In Diary Card" for further details.

### How to Use Your albuterol RESCUE Inhaler (P2_HTMDI) and How to Use Your Study Nebulizer® (HTNEBULIZER)

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

### APRIL Symptoms of Respiratory Illness (P2_SYMP_PARENT)/ APRIL List of Symptoms of Respiratory Illness (P2_SYMPLIST)

Parents/guardians should complete the APRIL Symptoms of Respiratory Illness form (P2_SYMP_PARENT) when they begin the APRIL medications. Parents are asked to complete the form while referring to the APRIL List of Symptoms of Respiratory Illness (P2_SYMPTLIST). The form has the parent/guardian identify the signs/symptoms that lead to a respiratory illness.

### Tips for Taking APRIL/OCELOT Medications (P2_TIPS_MED)

This handout provides some helpful tips for the parent/guardian when giving the participant the APRIL and OCELOT medications.

### How to Contact the Study Team (P2_CONTACT_AO)

This handout provides a quick reference for contacting the study team during normal business hours and holidays, weekends and nights.

### APRIL Nasal Swab (P2_HTNASAL_SWAB)/ APRIL Nasal Blow (P2_HTNASAL_BLOW)

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

### Preschool Asthma Diary (P2_PAD)/ Albuterol Log (P2_ALBUTEROL_LOG)

This Diary Card should be completed when taking the APRIL or OCELOT medications. There is one page per day. The reverse side of the Diary Card contains a place for the parent/guardian to record when/how often albuterol is given to the participant.

## 2.36 PERSISTENT SYMPTOMS

### APRIL Phone/Visit Symptom Assessment Form (P2_PHONE_CONTACT) and Persistent Symptoms Form (P2_PERS_SYMP)

**Definition of persistent symptoms:**

- Daytime symptoms of cough or wheeze which average 5 or more days a week over the past 4 weeks.
- Nighttime symptoms of cough or wheeze that wake the participant up and occur at least once a week on average over the past 4 weeks.

If symptoms have persisted for at least 4 weeks, the participant will be seen in the AsthmaNet site and evaluated for an alternative diagnosis for ongoing symptoms (such as sinusitis). If a diagnosis other than persistent asthma, such as sinusitis, is established, treatment of that condition may be prescribed (such as a course of oral antibiotics other than a macrolide) and the participant reassessed after completion of treatment. If symptoms do not resolve with this therapy, or if an alternative diagnosis is not established, the participant will be assigned STUDY FAILURE STATUS and Visit 9 should be scheduled. Blinded study participation will be discontinued. A PRAM score will not be recorded. A 5-day course of OCS will be considered per the AsthmaNet Site's physician discretion. The family will be asked to call the clinic back if the symptoms do not improve or worsen. Per the physician's discretion, the family may be provided with a 6-week supply of open-label inhaled corticosteroids. Communication regarding this study visit and any prescribed medications will be sent to the participant's primary care provider. If the symptoms worsen or do not improve, the participant will be evaluated by AsthmaNet clinic personnel (safety visit) or referred to urgent care or ED if symptoms severe. A second course of open label oral corticosteroids will be considered.

Two-weeks after the AsthmaNet Site visit, the family will be called by the AsthmaNet site personnel for a safety follow-up. Clinic coordinators will ask the parents at the two-week call if they have contacted the participant's primary care provider. Coordinators will emphasize the importance of contacting the participant's primary care provider for further treatment; both at the final visit and at the two-week follow up phone call. During this follow-up safety call, no data collection forms need to be completed. A note should be made in the participant's chart regarding the call.

## 2.37 PHONE CONTACTS

### Every 4 weeks after each visit starting with Visit 3

#### COMPLETE VISIT PROCEDURE CHECKLIST 3A-8A (P2_VISIT3A_8A)

Scheduled phone contacts during the APRIL/OCELOT 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.
- Review Action Plan.
- Answer any questions the parent/guardian may have.

**Persistent Symptoms**

If the participant has been having persistent symptoms for the past 2 weeks, a follow-up phone call should be scheduled in 2 weeks to assess whether the participant is continuing to have persistent symptoms. The Persistent Symptom Form (P2_PERS_SYMP) should be completed during the follow-up phone call.

**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 APRIL/OCELOT medications, collected nasal samples and completed Preschool Asthma Diaries (P2_PAD).

## 2.38 PHYSICAL EXAMS

**Visit 1, 20**
**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 APRIL/OCELOT 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 2-9, 21**
**Perform Short Physical Exam (SEXAM_PED)**

A brief physical exam is conducted at Visits 2-9. 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.

## 2.39 PRAM SCORE

**Visit 20**
**Complete the Pediatric Respiratory Assessment Measure form (PRAM)**

The **P**ediatric **R**espiratory **A**ssessment **M**easure (PRAM) will be scored 20 minutes post-bronchodilator in the AsthmaNet clinic 36-72 hours after the initiation of OCELOT therapy during Visit 20.

If the child used albuterol within 4 hours of Visit 20, additional albuterol should still be given prior to assessing the PRAM score.

The amount of albuterol that should be given is 4 puffs MDI or 1 nebulization.

The PRAM score is a 12-point validated measure assessing the severity of acute asthma in participants (aged 2-17 years). The PRAM score is copyrighted by Francine Ducharme and used with permission. This measure shows strong correlations with likelihood of admission for acute asthma, responsiveness to therapy with bronchodilator, face and content validity, and good levels of internal consistency and inter-rater reliability.

The PRAM score assessment should be performed by a licensed medical provider.

| PEDIATRIC RESPIRATORY ASSESSMENT MEASURE | | | | |
|---|---|---|---|---|
| **Signs** | **0** | **1** | **2** | **3** |
| **Suprasternal retractions** | Absent | | Present | |
| **Scalene muscle contraction** | Absent | | Present | |
| **Air entry**** | Normal | Decreased at bases | Widespread decrease | Absent/minimal |
| **Wheezing**** | Absent | Expiratory only | Inspiratory & expiratory | Audible without stethoscope/silent chest with minimal air entry |
| **$O_2$ saturation *** | ≥95% | 92-94% | <92% | |

*If oxygen supplementation, remove $0_2$ supplementation until oximetry level has stabilized for 1 minute or saturation has reached 90%, whichever comes first.

**In case of asymmetry such as between left and right lung fields or between the anterior and posterior regions of a lung, then rate the worst side/region.

## 2.40 PRE-SCHOOL ASTHMA DIARY / ALBUTEROL LOG

The Pre-School Asthma Diary is used to record participant symptoms during respiratory tract illnesses. The diary includes six symptom categories (cough, wheeze, sleep disturbance, lethargy, appetite, irritability and albuterol response). Each of the six symptom category is scored on a one through seven scale. The Pre-school Asthma Diary is copyrighted by Francine Ducharme and used with permission.

**Visit 2**
**Practice completion**

The parent/guardian should practice completion of the Pre-School Asthma Diary during Visit 2. That will ensure that he/she understands the questions and is prepared to complete it whenever the participant uses APRIL or OCELOT medications. The practice form should not be entered into the database. Instead, it should be filed in the participant's folder.

**Visits 2-9**
**Complete whenever using APRIL or OCELOT medications**

The Pre-School Asthma Diary (and corresponding Albuterol Log on reverse side) should be completed whenever APRIL or OCELOT medications are being used. The parent/guardian should have on hand enough diary cards to complete an illness. It is recommended that the participant has approximately 2 weeks of Diary Cards on hand. Note that the Diary Card is one page per day. The parent/guardian should continue to complete Diary Cards until the participant is symptom-free for 2 days.

The reverse side of the Diary Card is an Albuterol Log that can be used by the parent/guardian to track when the participant uses albuterol.

## 2.41 PROTOCOL VIOLATIONS and DEVIATIONS

The following is a list of protocol violations that may be assigned during the APRIL/OCELOT protocol:

Eligibility

- Participant with an exclusionary medical condition was enrolled.
- Participant taking an excluded medication within the defined washout period was enrolled.
- Participant who demonstrated lack of asthma control during Run-In period was randomized.
- Participant who used oral or systemic corticosteroids during the Run-In period was randomized.
- Participant who used antibiotics during the Run-In period was randomized.
- Participant with an exclusionary event (was hospitalized or intubated due to asthma or had a hypoxic seizure due to asthma) during the Run-In period was randomized.
- Participant was not 12 to 71 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 was randomized at Visit 2. (Adherence based on diary completion.)
- Participants living in the same household were enrolled at the same time.

Drug Dispensation

- No scheduled medications dispensed (participant left without drug due to clinic negligence).
- Incorrect medications for participant dispensed (wrong bottle number).

Serious Adverse Event

- Site failed to report a serious adverse event within the prescribed time limits.

Miscellaneous

- Site failed to recognize and document an APRIL treatment failure or study failure (unless details are unavailable due to participant being lost-to-follow-up, etc.).

The following is a list of protocol deviations that may be assigned during the APRIL/OCELOT protocol:

Certification

- Coordinator without APRIL/OCELOT protocol certification completed APRIL/OCELOT forms.

Blood Sampling

- Blood not drawn for ImmunoCap or CBC.
- Blood drawn after participant has been deemed ineligible.

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 or Registry Form sent to DCC. (includes breaches of confidentiality resulting from lost or stolen study documents)

Miscellaneous

- Site failed to notify DCC of use of a backup randomization.
- Physical exam not performed.
- Site incorrectly identified an APRIL treatment failure or study failure.
- A follow-up phone call was not made to assess persistent symptoms 2 weeks after possible identification during a phone contact.
- Incorrect Run-In length was used (2 or 4 weeks).

## 2.42 QUALITY OF LIFE QUESTIONNAIRE

**Visit 21**
**Effects of a Participant's Asthma Flare-Up on the Parents (PARENT_QOL)**

- The Effects of a Participant's Asthma Flare-Up on the Parents form (PARENT_QOL) is a validated quality of life tool from Francine Ducharme. Permission to use this copyrighted questionnaire has been obtained.

- The questionnaire has 23 questions and was developed according to the standardized procedures of item generation with 100 caregivers of acute ill asthmatic children; item reduction, again with another set of 100 caregivers; item presentation and scaling with another set of about 20 caregivers; and finally testing for psychometric properties which was done in the context of the *Pre-emptive use of High-Dose Fluticasone for viral-induced asthma in preschool-aged children: a randomized controlled trial.*

## 2.43 RANDOMIZATION

### Visit 2, 3rd APRIL therapy, 4th APRIL therapy, Lost/Replacement Drugs

The randomization module may be accessed for four reasons during the APRIL/OCELOT study: Visit 2 for the initial randomization, to obtain the 3rd APRIL treatment for a participant, to obtain the 4th APRIL treatment for a participant, and to obtain lost/replacement drugs.

The randomization will be stratified by the 9 performance sites and age group (12-41 months and 42-71 months).

The participant's weight will need to be checked since participants weighing > 20 kg will need 2 bottles of APRIL medication for each illness. Participants weighing <= 20 kg will only need 1 bottle of APRIL medication for each illness.

### Visit 2

The randomization module will provide bottle numbers for 2 APRIL therapies (i.e. 2 illnesses) and 1 OCELOT therapy. Participants weighing > 20 kg will receive a total of 5 bottles: 4 APRIL bottles and 1 OCELOT bottle. Participants weighing <= 20 kg will receive a total of 3 bottles: 2 APRIL bottles and 1 OCELOT bottle.

### Visits 2-9: 3rd APRIL therapy

Once the participant uses the first APRIL therapy, the 3rd APRIL therapy should be dispensed to the participant. The randomization module should used to obtain the bottle number(s).

### Visits 2-9: 4th APRIL therapy

Once the participant uses the second APRIL therapy, the 4th APRIL therapy should be dispensed to the participant. The randomization module should be used to obtain the bottle number(s). The 'Lost/Replacement' option on the randomization module should be chosen, and the reason of '4th APRIL therapy' should be typed into the application.

### Visits 2-9: Lost/Replacement Drugs

If the participant loses/spills the APRIL or OCELOT medications, 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.

NOTE: The participant's APRIL and OCELOT doses are based on their weight at the randomization visit and should NOT be adjusted if his/her weight changes during the study.

## 2.44 RECRUITMENT

APRIL/OCELOT visits will commence in March 2011. A total recruitment period of approximately 18 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 APRIL/OCELOT 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 APRIL protocol. Each of the 9 participating performance sites is expected to randomize approximately 67 participants for a Network total of 600 randomized participants in the APRIL protocol combined.

## 2.45 REGISTRATION

**Visit 1 or Prior**
**Register participant in AsthmaNet Registry**

Before a participant can be enrolled in the APRIL/OCELOT 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 (P2_VISIT1) in the participant's Visit 1 packet.

## 2.46 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 34 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. Immunodeficiency disorders.
5. History of respiratory failure requiring mechanical ventilation.
6. History of hypoxic seizure.
7. History of significant adverse reaction to any study medication ingredient.
8. 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 $10^{th}$ 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 (P2_LOG). However, specific data can be reused:

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

- The following forms may be reused from the original Visit 1: Participant Contact (CONTACT), Household Socio-Economic Information (HOUSEHOLD_SEI), 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 APRIL/OCELOT. These biological samples for non-randomized participants should be destroyed upon study termination.

## 2.47 RESPIRATORY TRACT ILLNESS/STARTING APRIL MEDICATIONS

### Parent Contact

Parents are instructed to call the AsthmaNet clinic within 72 hours of their child beginning a Respiratory Tract Illness (RTI) and/or the APRIL study medications.

Note: During a Phone Conference held on 10/21/2011, it was noted that some children seem to have a very rapid increase in symptoms which causes OCELOT to be missed and Study Failure to be achieved. Therefore, Dr. Bacharier suggested during that Phone Conference that all sites encourage parents to call the AsthmaNet clinic within 24 hours of starting an APRIL illness, rather than 72 hours.

Parents should be instructed to call the site during regular office hours for those call (i.e. FoneMed will not take these calls.). During this call to the clinic, two questionnaires should be completed, the APRIL/OCELOT Respiratory Illness Follow-up Contact (P2_ILLNESS) and the Symptoms of Respiratory Illness (P2_SYMP_CC). The purpose of these questionnaires is to determine the first symptoms of the illness, common symptoms of this illness, and whether the parents are following study procedures and taking APRIL medications. The call also allows the parents to ask any questions about the illness, action plan and study medications.

Parents should be asked to review the action plan and reminded to collect nasal samples on Days 1 and 4 of the illness. The nasal samples should be brought to the clinic at the next scheduled study visit. Parents should also be reminded to complete the Preschool Asthma Diary (P2_PAD) daily until the participant is symptom-free for 2 days in a row. Those diary cards should be brought to the next scheduled study visit.

The APRIL/OCELOT Respiratory Illness Follow-up Contact (P2_ILLNESS) asks about symptoms since the start of the illness, if the parents have started the study medications and whether nasal samples were collected. Ideally this form should be completed within 72 hours of the illness; however, the form may be completed up to 7 days after the illness if the parent fails to contact the site within the specified 72 hours.

APRIL therapy can be started on the day of randomization if the participant develops symptoms that were identified as indicating the start of a respiratory illness from the Symptoms of Respiratory Illness Questionnaire that was previously completed. However, if prior to randomization, the participant's symptoms are of a severity requiring a course of oral corticosteroids, the participant should not be randomized, but could be re-enrolled at a later time.

Albuterol should always be used as directed qid for the first 48 hours, even if the participant does not have specific asthma symptoms. Although there is inconvenience with qid dosing, parents should be reassured that during a respiratory illness, lung

changes are occurring that may benefit from albuterol even if the participant isn't having typical asthma symptoms.

Since azithromycin can stay in the system for up to 9 days after the last dose is taken, two consecutive APRIL therapies should be at least 14 days apart (i.e. there should be at least 14 days between the start of each APRIL therapy).

### Symptoms of Respiratory Illness (P2_SYMP_CC and P2_SYMP_PARENTS)

### Complete Symptoms of Respiratory Illness Form (P2_SYMPTOMS_CC)

Parents will have a copy of the Symptoms of Respiratory Illness (P2_SYMP_PARENTS and P2_SYMPTLIST) in their study folder. They should complete this questionnaire when they begin the APRIL medications. Parents are asked to complete the form while referring to the P2_SYMPTLIST. Coordinators will have a similar copy of the Symptoms of Respiratory Illness (P2_SYMP_CC). Coordinators will ask parents for their answers during the phone call and record the corresponding number (from the coded symptom list) in the line provided next to the question. This will allow parents to answer these questions as soon as the illness begins and enables the coordinator to collect the information for data entry. Parents should bring their copy of the completed survey to the clinic at the next visit. A new Symptoms of Respiratory Illness (P2_SYMP_PARENTS) should be given to the parent at that time. Since a new questionnaire is completed with each respiratory illness, the signs/symptoms that lead to a respiratory illness may change throughout the study.

Parents should be instructed to use 'Not Applicable' when the symptom/sign is not present. Similarly, they should be instructed to use 'Not very Important' when the symptom/sign occurs, but is not a very important part of the participant's reaction to viral infections.

The Symptoms of Respiratory Illness (P2_SYMP_CC) survey may be completed after the 72-hour window if the parents completed it at the start of the illness as instructed. Example: Parents fail to call within 72 hours (of the start of the illness) but bring their completed copy of the Symptoms of Respiratory Illness (P2_SYMP_PARENT) to the next study visit. Coordinators can use the answers from the Symptoms of Respiratory Illness (P2_SYMP_PARENT) to complete the Symptoms of Respiratory Illness (P2_SYMP_CC).

### Study Medications

Please instruct parents of participants who complete their course of APRIL medications and continue to have symptoms to call the site. A new course of study medication or illness kit should not be started at this time. APRIL therapy should be used for new illnesses only.

Parents should always have 2 courses of APRIL therapy available (unless they have already used 3). Once the participant has used the first course of APRIL therapy, the third course should be dispensed. Once the participant has used the second course of APRIL therapy, the fourth course should be dispensed.

## 2.48 RUN-IN DIARY CARDS

### General Information

The APRIL Run-In Diary Card (P2_DIARY_RUNIN) is a daily log of the participant's asthma medication use and symptom severity. Make sure the participant has 1 more Diary Card than the number of weeks between visits so that if the participant's next visit is postponed or a Diary Card is lost, a Diary card will be readily available.

See the handout "How to Complete the APRIL Run-In Diary Card" (P2_HTDIARY) for detailed information on completing this form.

The back of the APRIL Run-In Diary Card is an optional tool for the parent/guardian to record medications and medical problems that may occur during the week.

### Dispensing the Diary Cards

Before dispensing the Diary Cards, complete the upper right-hand corner and the day and dates (month and day) for each day on each card.

The parent/guardian should begin recording information for the nighttime evaluation *on the day of the visit*. **Cross out the morning evaluation portion of the card for the day of the visit,** since the parent/guardian should not complete this information. Bronchodilator puffs taken as part of visit procedures should NOT be recorded.

**Visit 1**

**Instruct Parent/Guardian on How to Complete the APRIL Run-In Diary Card (P2_HTDIARY)**

**Dispense Run-In Diary Cards (P2_DIARY_RUNIN)**

Using the P2_HTDIARY handout as a guide, show the parent/guardian how to complete the form, emphasizing that *blue or black ink* should be used. Be sure the parent/guardian understands the information that is required in each box. Encourage the parent/guardian to record the information each and every day. It is helpful if the recording of the data can be associated with specific daily activities (e.g., brushing teeth). Emphasize that data should not be *made up* or *recalled* more than one day back if days are missed.

When reviewing Question #1 (How much albuterol did your participant use since being put to bed?), tell parents that if the participant goes to bed for the night and falls asleep, but then is physically awakened during the night by asthma symptoms and must get up out of bed to take albuterol and then returns to sleep, then record the number of puffs or the number of nebulizer treatments.

### Reviewing the Diary Cards

Ask the parent/guardian to bring the Diary Cards that have been completed to Visit 2. Diary Cards are reviewed early in this visit so that problems with incomplete information can be addressed.

If numbers seem unclear, request clarification from the parent/guardian. If a Diary Card is difficult to read, ask the parent/guardian to copy the information onto a new Diary Card before leaving the clinic. Note that clinical personnel should not make changes to the Diary Cards; only the parent/guardian may alter this information.

Review the Diary Cards with the parent/guardian for use of rescue medications. If it appears that the participant has not been using his or her albuterol (RESCUE) inhaler for primary treatment of asthma symptoms, discuss this with the parent/guardian.

Examine the back of the Diary Card if it is completed. This information is helpful for the documentation of adverse events, and concomitant medications. If appropriate, complete the corresponding form(s) (AECLIN or CMED).

### Forgotten Diary Cards

Every effort should be made to ensure that parent/guardian remembers to complete and bring their Diary Cards to Visit 2, including reminder phone calls placed prior to the scheduled visit. At Visit 2, if the Diary Card is forgotten, then the visit should be rescheduled.

## 2.49 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 APRIL/OCELOT, it is present in the Visit 9 and Visit 21 packets. In addition, the questionnaire is also posted appended to the single APRIL Termination of Study Participation (P2_TERM) form for use with participants who terminate from the study before Visit 9.

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 APRIL/OCELOT 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 APRIL Termination of Study Participation (P2_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 P2_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.

## 2.50 SCREEN FAILURES

### Visit 1

If an APRIL/OCELOT 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.

## 2.51 STUDY FAILURES

**Visits 2-9, 20, 21**
**Complete the Study Failure Form (P2_STUDY_FAILURE)**

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

- Symptoms requiring immediate medical attention
- There is an unscheduled visit for acute asthma care (physician office, urgent care, emergency department) with 1 albuterol treatment lasting more than 1 hour or more than 1 albuterol treatment
- During an unscheduled visit for acute asthma care in a physician's office the participant is transferred to urgent care or the emergency department due to severity of respiratory symptoms
- Systemic steroids are needed for respiratory symptoms. This includes steroids given for 1 day to treat croup. Steroids given to treat conditions unrelated to breathing problems (i.e. poison ivy) should not count towards study failure.
- Hospitalization is needed for asthma
- Development of persistent symptoms
- Physician discretion

The Study Failure Form (P2_STUDY_FAILURE) should be completed and the participant should be evaluated at a safety visit within 72 hours and assigned study failure status. The safety visit should include an evaluation of the participant's asthma symptoms and whether or not APRIL or OCELOT medications were used. No data collection forms will be completed. If the participant is unable to be seen at the clinic within 72 hours, an evaluation by the participant's PCP/PMD within 72 hours can serve as the safety visit.

If OCELOT was started, Visit 21 should be scheduled 14 days after study failure (+/- 2 days).
If OCELOT was not started, but APRIL was started, Visit 9 should be scheduled 14 days after study failure (+/- 2 days).
If neither OCELOT nor APRIL was started, Visit 9 should be scheduled 14 days after study failure (+/- 2 days).

For those participants that did not receive open-label OCS, a 5 day course of open label OCS will be considered per physician discretion. If open label OCS is prescribed, a follow-up safety phone call should take place 2 weeks after starting OCS.

## 2.52 STUDY PATHS

Not all participants who are randomized into the APRIL study will enter the OCELOT study. There are various paths that the participant may take. It is not possible for a participant to have all APRIL and OCELOT visits. If they proceed to OCELOT, they will not have all APRIL visits, but will have OCELOT visits 20 and 21. If they do not proceed to OCELOT, they will not have OCELOT visits 20 and 21.

Here are several scenarios of how participants might navigate through APRIL and OCELOT:

- Participant completes APRIL through Visit 9 without proceeding to OCELOT.
- Participant uses 4 APRIL medications and is termed from APRIL.
- Participant becomes a study failure during APRIL and is termed from APRIL without proceeding to OCELOT.
- Participant is deemed an APRIL treatment failure and proceeds to OCELOT.

## 2.53 SYMPTOMS OF BREATHING ILLNESS

### Visits 1 and 2

### Complete the Symptoms of Breathing Illness Form (P2_SURVEY)

The Symptoms of Breathing Illness Form (P2_SURVEY) will be used to help parents identify their participant's symptoms that signal the onset of a breathing illness. This survey is very important in individualizing the participant's action plan. Please see the Action Plan Identification discussion earlier in this section for details on completing the Action Plan.

The Symptoms of Breathing Illness Form (P2_SURVEY) will be completed at Visit 1 by the coordinator. The parent's will be given a copy of the symptom list to help them answer the questions. Coordinators should use the coded copy of the symptom list to fill in the parent's answers. Parents will take a blank copy of the survey home with them. They should review the survey and take time to think about their answers. The Symptoms of Breathing Illness Form (P2_SURVEY) will be re-administered by the coordinators at Visit 2. The answers given by the parents at Visit 2 will be used on the Action Plan. Answers to the Symptoms of Breathing Illness Form (P2_SURVEY) will be data entered for both visits.

Parents should be instructed to use 'Not Applicable' when the symptom/sign is not present. Similarly, they should be instructed to use 'Not very Important' when the symptom/sign occurs, but is not a very important part of the participant's reaction to viral infections.

## 2.54 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 APRIL/OCELOT 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 APRIL/OCELOT 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 APRIL/OCELOT 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, or who fail to record information on their Run-In Diary Cards (P2_DIARY_RUNIN) 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 APRIL Termination of Study Participation Run-In (P2_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 drug packet 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 APRIL Study Treatment Questionnaire (P2_APRIL_TRTQX), 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 APRIL/OCELOT study. This questionnaire should be sent home with the parent/guardian. An APRIL Termination of Study Participation form (P2_TERM) should also be submitted.

If the parent/guardian of a randomized participant withdraws consent between visits, the APRIL Termination of Study Participation form (P2_TERM) should be completed and submitted. The study coordinator who was primarily responsible for the participant's study visits should complete the last question on the APRIL Treatment Questionnaire (P2_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 APRIL Termination of Study Participation (P2_TERM) form should also be submitted.

If the parent/guardian of a randomized participant withdraws consent between visits, the APRIL Termination of Study Participation (P2_TERM) form 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.

Add what constitutes 'Complete' and 'Not Complete'

## 2.55 THROAT SWAB (St. Louis site only)

### Visit 2 and 9/21 and during visit following 1st APRIL therapy

Throat swabs should be collected at the **St. Louis site only** at up to 3 time points:

- Visit 2
- The visit that follows the 1st course of APRIL therapy; this sample will be obtained if the visit occurs after a minimum of 14 days from the last dose of APRIL therapy (otherwise, it should be collected at the next visit). Note: if it has been between 10-14 days since the last dose of APRIL therapy was taken, the throat swab can still be collected and a comment should be included on the P2_LAB form, Q6000,
- Visit 9 or Visit 21; a minimum of 14 days after the last dose of APRIL therapy. Note: if it has been between 10-14 days since the last dose of APRIL therapy was taken, the throat swab can still be collected and a comment should be included on the P2_LAB form, Q6000.

Samples should be logged in Biological Sample tracking.

## 2.56 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 2-3 times during the study: Visits 1 and 2, and again at any point in the study if/when the participant has started OCELOT therapy and a follow-up visit is required. At Visit 1, the Visit Scheduler is run to schedule the Visit 2.There are 2 different options at Visit 1: a 2 week Run-In and a 4 week Run-In. (A 4 week Run-In is required if the participant is receiving step 2 or higher NAEPP asthma guideline therapy prior to Visit 1. The need for a 4 week Run-In is assessed on the P2_ELIG1 Checklist.) At Visit 2, the Visit Scheduler must be run again to produce the schedule for the remainder of the visits. If the participant starts OCELOT therapy, the Visit Scheduler should be run to determine the participant's OCELOT follow-up visit.

### Visit 1

Run the Visit Scheduler. It will determine the optimal date for Visit 2. You will need to choose a 2 week Run-In or a 4 week Run-In. A 4 week Run-In is required if the participant is receiving step 2 or higher NAEPP asthma guideline therapy prior to Visit 1. The need for a 4 week Run-In is assessed on the ELIG1 Checklist Q#19.

### Visit 2

At Visit 2, run the Visit Scheduler to determine the schedule for the remainder of the study.

The table below describes the APRIL/OCELOT 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:

2 week Run-In:

| 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 |

4 week Run-In:

| Visit at which the Visit Scheduler is run. | Visit Number | Ideal Date | Lower Window | Upper Window |
|---|---|---|---|---|
| Visit 1 | 2 | 28 days | 0 days, +7 days | 28-35 days |

Treatment Phase:

| Visit at which the Visit Scheduler is run. | Visit Number | Ideal Date | Lower Window | Upper Window |
|---|---|---|---|---|
| Visit 2 | 3 | 28 days | - 7 days | + 7 days |
| | PC | 56 days | - 7 days | + 7 days |
| | 4 | 84 days | - 14 days | + 14 days |
| | PC | 112 days | - 7 days | + 7 days |
| | 5 | 140 days | - 14 days | + 14 days |
| | PC | 168 days | - 7 days | + 7 days |
| | 6 | 196 days | - 14 days | + 14 days |
| | PC | 224 days | - 7 days | + 7 days |
| | 7 | 252 days | - 14 days | + 14 days |
| | PC | 280 days | - 7 days | + 7 days |
| | 8 | 308 days | - 14 days | + 14 days |
| | PC | 336 days | - 7 days | + 7 days |
| | 8b | 364 days | - 14 days | + 14 days |
| | PC | 392 days | - 7 days | + 7 days |
| | 8c | 420 days | - 14 days | + 14 days |
| | PC | 448 days | - 7 days | + 7 days |
| | 8d | 476 days | - 14 days | + 14 days |
| | PC | 502 days | - 7 days | + 7 days |
| | 9 * | 530 days | - 14 days | + 14 days |

*If a participant has used APRIL therapy within 14 days of Visit 9, Visit 9 should be rescheduled so that at least 14 days have passed since the last dose was taken. The DCC should be contacted if a visit extension is required.

OCELOT Follow-up Visit:

| Visit at which the Visit Scheduler is run. | Visit Number | Ideal Date | Lower Window | Upper Window |
|---|---|---|---|---|
| OCELOT Visit 20 | 21 | 14 days | - 2 days | + 2 days |

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## 2.1 ACTION PLANS and IDENTIFICATION CARDS

**APRIL Run-In Action Plan Card**
**APRIL Action Plan Card and wallet-sized ID Card**
**APRIL Caregiver Action Plan Card**

There are several different Action Plan Cards used during APRIL. 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 starting APRIL therapy, when the study team should be contacted and when to seek immediate help. The wallet-sized ID card includes instructions for treatment of asthma attacks by physicians and ER personnel who may not be familiar with the study and should be given to the parent/guardian to be kept with them at all times. The Action Plan should be reviewed at all study visits. The Action Plan Card contains the same information as the wallet-sized ID card, but has a Respiratory Illness Daily Activities Guide on the reverse side. The reverse side should be referenced by the parent/guardian whenever the participant has started APRIL or prednisolone.

**Visit 1**

**Dispense APRIL Run-in Action Plan Card**

- The APRIL Run-In Action Plan Card should be dispensed at Visit 1 and used during the Run-in.
- Complete the participant's name, date and the names and phone numbers of study contacts. During the Run-In, the 'After Hours Phone Number' should be the site's regular emergency contact. Do not use the FoneMed After-Hours phone number during the Run-In period.
- 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 or nebulizer, please try to contact one of the people listed on this card. Dr. Green is the Principal Investigator and Dr. Black is another physician working on this study. If you are unable to contact either of them, 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, including a record of any non-study medications taken. The back of the Diary Card can be used during the Run-In to keep track of illnesses, injuries and medications taken.

**Visit 2**

**Dispense APRIL action plan card, APRIL wallet-sized ID card and the APRIL caregiver action plan card (if needed)**

- Collect the APRIL Run-In Action Plan Card.
- The 'APRIL Action Plan Card' and the 'APRIL wallet-sized ID card' should be dispensed at Visit 2 and used for the remainder of the APRIL study. There is also an APRIL Caregiver Action Plan Card that can be dispensed at Visit 2 and given to Daycare providers, schools, etc.
- Write the participant's study ID number and the names and phone numbers of study contacts. The After Hours Phone Number should be the number provided to your site for FoneMed. Explain to the parent the purpose of the After Hours Phone Number.
- Review the contents of the card with the parent/guardian.

Due to the unique nature of the APRIL study, each action plan must be individualized. Coordinators need to use the parent's responses from the Symptoms of Breathing Illness Survey (P2_SURVEY) to complete the information on 'When to Start APRIL Illness Medication'. The P2_SURVEY form completed at Visit 2 should be used (not the P2_SURVEY form that was completed at Visit 1).

Coordinators will fill in the appropriate lines in the "When to Start APRIL Illness Medication" box. On the first line, fill in the answer to question 1010 on the Symptoms of Breathing Illness Survey (P2_SURVEY). The second line (most important symptom) should be the response to question 1040. The last line should be completed using the response from question 1070. If question 1020 is answered "no" and questions 1040 and 1070 are left blank, the second and third lines on the APRIL Action Plan and ID Card will be blank.

The back of the APRIL Action Plan contains a 'Respiratory Illness Daily Activities Guide'. The guide contains a simple summary of the study activities that must be carried out each day while taking APRIL medications. This handout serves as a checklist for the parents to help them remember the study activities. Parents do not need to actually fill out the checklist and it will not be collected at the site. The guide also reminds the parents to contact the clinic within 24 hours of starting the study medications or if they have any questions.

Coordinators will review with the parents the section on 'When to Contact the Study Team' and 'Get Medical Help!'

**Visit 3-8, 8b, 8c, 8d**

**Review the ID Card and 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 for 'When to Start APRIL Illness Medication' and 'When to Contact the Study Team' with the parents. Update the 'When to Start APRIL Illness Medication' section as needed based on discussions with the parents.
- 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 APRIL protocol are involved in study activities throughout the trial, especially when the participant is sick. 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 APRIL trial:

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

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

*Counseling for Non-Adherence*

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

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

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

**Visit 2**

It is very important at this visit to get a good sense of the ability of the parent/guardian to comply with protocol procedures, before allowing the participant to proceed and be randomized. The participant is required to have at least 80% adherence during the Run-In period with regards to the Run-In Diary completion in order to be eligible for APRIL. Since there are no Run-In study medications, there is no assessment of the participant's adherence with study medications. If the coordinator feels that the participant will not be able to comply with the study medications, the participant should not be randomized into APRIL.

Adherence with the Run-In Diary Card completion is assessed on Eligibility Checklist 2, Questions #6-#8. The participant must have at least 80% to be eligible.

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

## 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 <u>any</u> 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 subject 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 2-9

### 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 APRIL illness is being recorded, 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.

**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 APRIL 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 APRIL 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 APRIL MEDICATIONS

### Visit 2

The randomization module should be accessed at Visit 2 to obtain bottle numbers for 2 APRIL therapies.

### Visit 3-9

Once a participant uses the first APRIL therapy, the randomization module should be used to obtain bottle number(s) for the 3rd and 4th APRIL therapies.

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 APRIL therapy is dosed based on the participant's weight. Participants who weigh <=20 kg will require 1 bottle of APRIL therapy per RTI. Participants who weigh >20 kg will require 2 APRIL bottles per RTI. Thus, participants who weigh <=20 kg will be given 2 bottles of APRIL therapy at Visit 2. Participants who weigh > 20 kg will be given 4 bottles of APRIL therapy at Visit 2. Please refer to the APRIL Azithromycin Dosing Reference Card for exact dose by weight. The participant should take one dose per day for 5 days. The dose should be based on the participant's weight at Visit 2 and should remain the same throughout the study.

Special Instructions for APRIL dosing for participants weighing 20.1 to 20.8 kg:
There is a slight discrepancy between the randomization application and the APRIL Dosing Reference Card for the number of APRIL bottles needed per illness. The randomization application will issue 2 bottles per illness while the Dosing Reference Card indicates that only 1 bottle is needed. The Dosing reference card is correct. The Dosing Reference Card was created after the randomization application was programmed. While developing the Dosing Reference Card, it became apparent that ranges would need to be used since the measuring device could only measure to the closest 1/2 ml. (For example, a participant who weighs 20.5 kg, using a dosing of 12 mg/kg per day, should get a dose of 6.15 ml per day, which can't be measured with the device.) Since we have almost 25% of the participants randomized and this has only occurred one time, we expect this to be a rare event.

For sites that do not use a pharmacy: 2 of the 4 bottles should be dispensed to the parent for APRIL illnesses #1 and #2. The 3rd and 4th bottle should be clearly labeled with the participant's ID number and stored separately from the rest of the APRIL bottles. They can be used for the 3rd and 4th APRIL illnesses or as back-up medication, if needed. It is not necessary to use the randomization application for the 3rd and 4th APRIL therapies.

For sites that use a pharmacy to distribute medications: please ask the pharmacy for only 2 of the 4 bottles to be dispensed for APRIL illnesses #1 and #2. For these cases, it is necessary to use the randomization application for the 3rd and 4th APRIL therapies. The application will provide 2 APRIL bottle numbers for each illness, but you will only need to give the pharmacy 1 APRIL bottle number.

Please make a note on the Drug Dispensation Log (P2_DRG_AO) and APRIL Scheduled Medications (P2_MED) form indicating which bottles were dispensed.

APRIL therapy should be started at onset of a RTI based upon the individualized plan developed by the parent and site at Visits 1 and 2. The plan will consider both the pattern of symptoms identified by the participant's parent in the Parental Respiratory Illness Questionnaire that typically leads to episodes of LRT symptoms, as well as the clinician's judgment to promote as much consistency as possible and to avoid treating at the development of trivial symptoms. The subject-specific starting point will be based on the participant's previous history of symptom progression irrespective of whether symptoms originate in the upper or lower respiratory tracts. See the Respiratory Tract Illness/Starting APRIL Medications section for more details.

It is important to remind the parent/guardian that albuterol should be used while taking APRIL medications. Albuterol use while using APRIL medications is: inhaler (2 puffs) with spacer or nebulizer (1 vial) taken 4 times per day (while awake) for 2 days, then 'as needed' to control symptoms.

For each APRIL medication usage, the parent/guardian should collect a nasal sample on Days 1 and 4 of the illness. The Preschool Asthma Diary and corresponding Albuterol Log (on reverse side) should also be completed daily until the participant is symptom-free for 2 days.

Since azithromycin can stay in the system for up to 9 days after the last dose is taken, two consecutive APRIL therapies should be at least 14 days apart (i.e. there should be at least 14 days between the start of each APRIL therapy).

Missed Doses (Please refer to the Tips for Taking APRIL medications handout): If the morning dose is missed, it should be taken later in the day. If an entire day is missed, the prescribed dose should be resumed the next day (i.e. Do not take a double dose the next day.)

If a participant has used his/her 4th APRIL medications, he/she should be termed from the study. Visit 9 should be scheduled for 14 days after the last dose of APRIL medication is taken.

The APRIL Tracking Form should be completed each time the participant uses APRIL therapy. This is an administrative form that should be kept in the participant's folder at the center. Its purpose is to track the number of times APRIL therapy is used and provide instructions if the participant uses 4 APRIL therapies.

## 2.6 APRIL TREATMENT FAILURE/STARTING PREDNISOLONE

**Visits 2-9**
**Complete the APRIL Treatment Failure Form (P2_APRIL_TRTFAIL) and Study Failure Form (P2_STUDY_FAIL)**

A participant will be deemed an APRIL Treatment Failure by a study physician if any of the following criteria are met:

- Having symptoms that are more than mild after 3 albuterol treatments* in 1 hour
- Requiring albuterol treatment more than once every 4 hours**
- Requiring more than 6 albuterol treatments over a 24 hour period
- Having moderate-severe cough or wheeze for 5 or more days during which APRIL therapy was used.
- Physician Discretion – rationale must be clearly stated.

*An albuterol treatment is a 2.5 mg albuterol by nebulization with facemask or 2 puffs of albuterol via MDI/spacer/mask.

**For the purpose of determining treatment frequency, on one occasion up to 3 albuterol treatments may be administered back-to-back and counted as a single treatment.

If a participant is deemed an APRIL Treatment Failure, he/she is also a Study Failure. The P2_STUDY_FAIL form should also be completed.

The parent/guardian should be advised to start prednisolone immediately and to give the participant albuterol treatments every 4 hours. They should also be advised to call the site if the respiratory symptoms worsen. The action plan will direct them to call the site or after-hours triage site if a specific frequency of albuterol is used or significant symptoms develop.

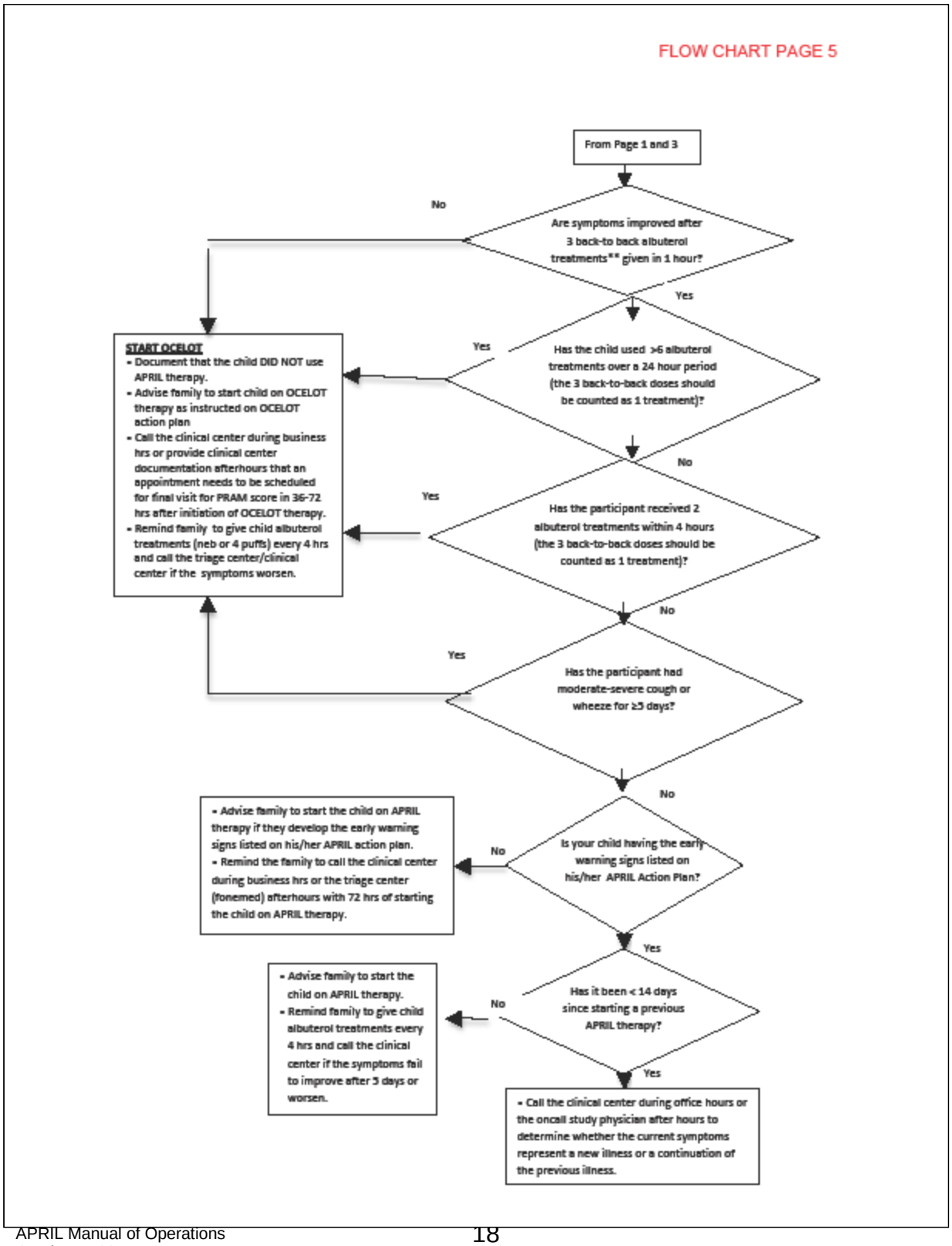
The prednisolone dose that should be given is 2 mg/kg/day for 2 days (max 60 mg), followed by 1 mg/kg/day for 2 days (max 30 mg). The Prednisolone Dosing Reference Card (P2_PRED_DOSE) should be referenced for dosing and the participant's weight at Visit 2 should be used

A follow-up phone call should be made to the parent/guardian 1-24 hours after telling the parent/guardian to start prednisolone. During that follow-up call, a final closeout visit (Visit 9) should be scheduled within 2 weeks or within 72 hours if the participant required urgent medical attention.

If the participant is still taking the APRIL medications at the time prednisolone is started, he/she should finish the five day course of APRIL medications even if it overlaps with taking the prednisolone. APRIL medications and prednisolone can be taken at the same time.

Record prednisolone use on the APRIL Prednisolone Medication Form (P2_PRED). 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.

## 2.7 APRIL/ TREATMENT FAILURE/STARTING PREDNISOLONE FLOWCHARTS



## 2.8 APRIL MEDICATION COMPLIANCE

**Visits 3-9**

Complete the APRIL Compliance Checklist (P2_APRIL_COMPLY)

Adherence with the APRIL medications is assessed on the APRIL Compliance Checklist (P2_APRIL_COMPLY). Since the participant will only be taking study medications when he/she is sick, adherence will only be assessed at the visit after the APRIL therapy is used. If the participant has used more than one APRIL therapy between visits, one form should be completed for each APRIL therapy that the participant has used.

If the participant is in the middle of taking APRIL medications at a scheduled visit, the COMPLY form should be set to missing for the current visit. Ask the parents to bring the medications to the next scheduled visit, at which time, adherence can be calculated and the correct COMPLY form can be completed.

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.

## 2.9 APRIL TREATMENT QUESTIONNAIRE

**Visits 2-9**
**Complete the APRIL Treatment Questionnaire (APRIL_TRTQX) - Visit 9 (or last visit see below for details)**

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 question. The last question should be completed by the coordinator.

If a participant withdraws from the study following randomization and prior to Visit 9, the APRIL Treatment questionnaire should be completed at the time of the participant's final contact with the performance site. Participants who term early from APRIL for any reason (i.e. withdraw consent,4$^{th}$ APRIL therapy used, APRIL treatment failure) should complete the APRIL questionnaire at the time of the participant's final contact with the performance site.

## 2.10 BLOOD SAMPLING PROCEDURES

### Visit 2

The following blood samples will be drawn in APRIL at Visit 2. If you have difficulty drawing blood on the participant at Visit 2, you can draw blood at a later visit.

- ImmunoCap Testing for Food, AeroAllergen and IgE
- CBC (Total WBC and Eosinophils)
- Genetic Analysis (optional)

### General Blood Draw Procedures

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

2 ml for ImmunoCap Testing and IgE
1-2 ml blood for CBC and Eosinophil Count
4 ml (age: 12–60 months) or 10 ml (age: 60-72 months) blood for genetic analysis
The total amount of blood to be drawn should be 8-14 ml.

The processing and storage of each of these blood samples is discussed below. The CBC will be processed at the site's local lab. The ImmunoCap sample will be sent to the St. Louis Lab for processing. The blood for genetic analysis will be sent to the Tucson Genetics of Asthma Lab.

The results of the CBC (WBC and eosinophils) are recorded on the Laboratory Tests (P2_LAB) form. See Section 4 for more detail on completing this form.

### ImmunoCap and IgE Procedures (2 ml)

Specimen collection: A minimum of 2 ml of whole blood or 1 ml of serum should be collected in a serum separator tube (5 ml). Blood should be spun down to serum and poured off into a 5 ml cryovial. Alternatively, the serum can be put in the 5 ml cryovial using a pipette. The centrifuge speed and time will be dependent on the serum separator tube and centrifuge that are used. Therefore, each site will need to determine the speed and time based on the components they are using. Discard the remaining blood after the serum has been poured/pipette into the cryovial.

Blood collection tubes:
Fisher Scientific, externally-threaded 5.0 ml vials
Catalog #10-500-27, Pack of 50 for $34.02

### *Specimen Tracking – Collection Day*

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

Label specifications: Diversified Biotech (www.divbio.com).
Laser Cryo-Tags 1.69 x 1.75 (Catalog number: LCRY-1100), 1040/pk, $60.00

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 blood draw date). Print the shipment inventories for inclusion in the shipment. Samples must be shipped via FedEx priority overnight (using the DCC's APRIL FedEx account #337822355) Please record 'AsthmaNet – APRIL' in the reference section. 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 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

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

3. 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 St. Louis 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 tubes.

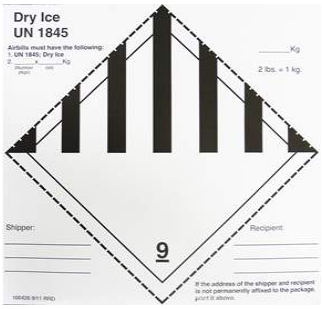
4. Fill bottom of shipping box with dry ice

   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. 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)


d. 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)




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

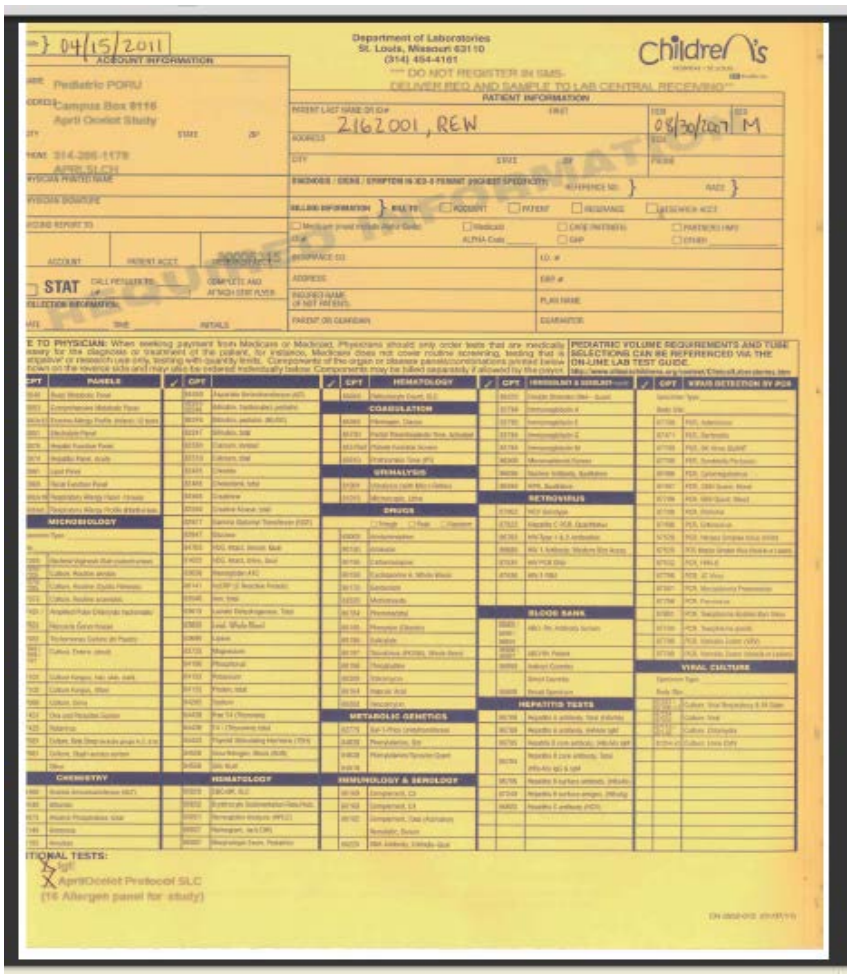
1. All blood specimens should be sent FedEx Priority Overnight (use DCC's APRIL FedEx account #337822355). Please record 'AsthmaNet – APRIL' in the reference section. No other form of shipping is acceptable. Blood samples should be shipped to St. Louis' Children's on the first Monday of each month (if Monday is a holiday, then ship on Tuesday). If you are unable to ship the samples on the designated shipping day, you **MUST** contact Tina Norris at St. Louis. She needs to make sure the lab person is available to receive the shipment on the alternate day.

For every sample that is shipped, a Gold-Req form **must** be completed and be shipped with the samples. Therefore, if 10 samples are being shipped, then 10 Gold-Req forms should be completed and shipped with the samples.

The following information should be completed on the Gold-Req forms:

- Date sample was drawn
- Patient Last Name of ID# - use participant ID without dashes and participant initials
- Date of Birth (DOB)
- Sex
- Additional Tests (at bottom of form) – place 'X's in the boxes for IgE and APRILOCELOT Protocol SLC

Note: If you were unable to collect the full amount of blood, please put a note on the Gold-Req form indicating that the sample is short.




Ship to:

St. Louis Children's Hospital
One Children's Place
St. Louis, MO 63110
Attn: Lab Receiving 2N21 – Mary Giedinghagen (314-454-4268)

## WBC and Eosinophil Count Procedures (1-2 ml)

For eosinophil percentage determination:

Use two 3 ml lavender top tubes containing EDTA anticoagulant or similar EDTA microtainer, if available for venipuncture specimen. Draw 1 ml of whole blood in each of the two tubes, invert immediately and gently mix with anticoagulant. The specimens cannot be used if stored more than 8 hours at room temperature or 24 hours at 4°C. One sample will be analyzed at the site's local laboratory, while the other sample should be held until the results from the first sample are received. Send to the local hematology laboratory to prepare the blood smear and determine differential count to report

percentage of eosinophils. A manual count is NOT required; an automatic count is sufficient. The second tube can be discarded once the results are obtained from the laboratory. Please note that if the first sample is sent to the lab on Friday and the sample clots, the lab personnel should alert the coordinator before the end of the day Friday, so that the second sample can be run immediately.

Record the participant's total WBC and relative eosinophil count on the Laboratory Tests form (P2_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 Procedures (4 ml for age 12-60 months, 10 ml for age >60 months)

Obtain blood sample for DNA extraction and genetic analysis (4 ml for participants age 12-60 months, 10 ml for participants age 60-72 months)
Complete Genetic Analysis Blood Draw (GABLOOD) form
Enter participant's genetics blood draw information into Genetics Sample Tracking module

Samples must be shipped via FedEx priority overnight (using the DCC's APRIL FedEx account #337822355) Please record 'AsthmaNet – APRIL' in the reference section. Please note that using the DCC's FedEx number for shipping genetic samples pertains to the APRIL study only.

See 'Genetic Analysis' later in this section for further details.

## 2.11 CERTIFICATION

Individuals who carry out APRIL study visits must be certified to do so. That is, personnel who complete any of the protocol-specific APRIL forms (designated by a P2 prefix in the form name) must possess APRIL study certification.

To obtain APRIL certification, clinical personnel must complete the following steps:

- Thoroughly read the APRIL protocol and this Manual of Operations.
- Pass the APRIL 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.

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).

## 2.12 CONCOMITANT MEDICATIONS

### Visits 1-9, 20, 21

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 APRIL 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 (RESCUE) 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 APRIL 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 (P2_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.

Note that participants must wash out of many medications for appropriate intervals prior to Visit 1. Washout periods are listed on the APRIL Exclusionary Drugs (P2_EXCLDRUG) reference card. If the participant is taking any of the drugs listed on P2_EXCLDRUG, confirm with the parent/guardian and with the study physician that he or she may discontinue use of this medication if he or she is eligible to enroll in the APRIL study. Also confirm that it is safe and appropriate for the participant to go off the medication for the appropriate washout period prior to Visit 1. Some institutions require that the parent/guardian read and sign the study informed consent document prior to washing out of medications for study enrollment.

### Visits 2-9

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 APRIL study, the record should be marked 'ongoing at final visit.'

## 2.13 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 APRIL study.

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.

## 2.14 ELIGIBILITY CRITERIA

**Visit 1**

**Inclusion/Exclusion Criteria (P2_ELIG1)**

**INCLUSION CRITERIA**

Participants who meet all of the following criteria are eligible for entry into APRIL. Participants may be reassessed if not initially eligible.

**1.** 12-71 months of age. Note: Participants who are 72 months old or older at the time of *enrollment* are not eligible for APRIL. A participant who is between 71 and 72 months old should be considered 71 months old until he/she reaches 72 months.

**2.** Recurrent significant wheezing in the past year (any of the following):

a. ≥3 episodes, ≥1 of which was clinically significant*; OR
b. ≥2 clinically significant* episodes; OR
c. ≥ 4 months of daily controller therapy AND ≥1 clinically significant* episode.

*Clinically significant episode: requiring any of the following: (1) systemic corticosteroids (oral or injectable), (2) unscheduled physician office visit, (3) ED visit, (4) urgent care visit, or (5) hospitalization.

**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.

**4.** Willingness to provide informed consent by the participant's parent or guardian. If the study consent form was signed in advance of Visit 1, they 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.

**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. >4 courses of systemic corticosteroids in past 12 months.
2. More than 1 hospitalization for wheezing illnesses within the preceding 12 months.
3. Use of long-term controller medications for asthma, including inhaled corticosteroids, leukotriene modifiers, cromolyn/nedocromil, or theophylline for more than 8 months (cumulative use) in the past 12 months.
4. Current use of **higher than step 2** NAEPP asthma guideline therapy (e.g. medium-high dose ICS alone or combination therapy of low-medium-high dose ICS + LABA, montelukast, theophylline or cromolyn). If a participant's PCP agrees to stop combination therapy, there should be a 4 week washout prior to enrollment (i.e. If the participant is taking fluticasone + singulair and the PCP stops singulair, there should be a 4 week washout period prior to enrollment), NOTE: participants who have evidence of well-controlled symptoms immediately preceding study entry while receiving Step 2 controller therapy (presence of self-reported symptoms on average no more than 2 times per week and less than 2 nights per month of nocturnal awakenings, requiring albuterol, during the 4 weeks preceding visit 1) may be enrolled and will have their controller therapy discontinued upon study entry.
5. Use of OCS in the past 2 weeks.
6. Daily symptoms or ≥2 nocturnal awakenings, requiring albuterol, in the last 2 weeks.
7. Use of antibiotics in the past month.
8. Current treatment with antibiotics for diagnosed sinus disease.
9. Participation presently or in the past month in another investigational drug trial.
10. Evidence that the family may be unreliable or nonadherent, or may move from the site area before trial completion.
11. Contraindication of use of systemic corticosteroids or azithromycin.
12. Clinically relevant gastroesophageal reflux. Note: If a child takes medication daily to treat gastroesophageal reflux, it should be considered clinically relevant.
13. Concurrent medical conditions other than asthma that are likely to require oral or injectable corticosteroids during the study.
14. If receiving allergy shots, change in dose within the past 3 months. Participants should NOT change their maintenance regimen during the course of the APRIL study.

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, and may not be re-enrolled:

1. Gestation less than late preterm as defined as birth before 34 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 participant at increased risk of participating in the study.
4. Immunodeficiency disorders.
5. History of respiratory failure requiring mechanical ventilation.
6. History of hypoxic seizure.
7. History of significant adverse reaction to any study medication ingredient.
8. 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 < 10th 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, Q1780 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 P2_ELIG1 form. A data correction for Q1780 should be submitted once the growth charts are obtained.

NOTE: The DSMB recommended that children living in the same household should not be enrolled in the APRIL study at the same time to prevent a mix-up of study drugs and other materials. Once one child finishes/terms from the study, a second child can be enrolled.

**VISIT 2**

**EXCLUSION CRITERIA**

Participants will be ineligible for randomization if any of the following is documented, but may be re-enrolled if these exclusion criteria are resolved:

1. Persistent symptomatic asthma
   - **a.** For participants who are controller naïve at the time of enrollment, persistent asthma is defined as asthma-related symptoms/albuterol use $\geq$ 4 days/week or $\geq$ 1 nighttime awakenings, requiring albuterol, on average during the 2 week run-in OR
   - **b.** For participants who were receiving long-term controller medicine (low dose ICS or LTRA monotherapy) at the time of enrollment, persistent asthma is defined as asthma-related symptoms/albuterol use $\geq$ 4

days/week or ≥ 1 night awakenings, requiring albuterol, on-average during the last 2 weeks of the 4 week run-in

Please Note: Coordinators should stress to families that albuterol should be used for clinically meaningful symptoms related to asthma. Minor cough should not be treated with albuterol. If albuterol is not used at times that the coordinator thinks that it should have been used, that could be considered a sign of non-adherence to the directions. For these cases, by coordinator or MD discretion, a participant could be excluded.

If there is discordance between the diary symptoms and the albuterol use, the coordinator with the assistance of a study investigator, should evaluate the totality of the clinical situation on the specific days and decide whether albuterol use would have been appropriate. If albuterol use would have been appropriate, the day(s) should be added as albuterol day(s). If the participant meets the exclusion criteria due to persistent asthma owing from this situation, Question #9 should be marked 'Yes' and an explanation should be provided.

The Run-In Diary Cards should be reviewed with the parent. If the coordinator thinks that the parent exaggerated the severity of the participant's symptoms on the Diary Cards (and the parent agrees), the parent should make corrections to the Diary Cards as needed, and initial and date each change.

2. Inadequate adherence (< 80% of days) to diary card completion during the last 2 weeks of the Run-In period.
3. Use of oral corticosteroids or antibiotics during the 2-4 week observation run-in.
4. Use of asthma medication except prn albuterol during the 2-4 week observation run-in.

**Drugs to be withheld prior to Visit 1 and during the Run-In.**

| Excluded Drug | Generic Names (may not be inclusive) | Trade Names (may not be inclusive) | Washout Prior to Visit 1 |
|---|---|---|---|
| Oral or systemic steroids for any reason. | Prednisone, prednisolone, dexamethasone | Medrol, Decadron, Orapred, Prelone, Pediapred | 2 weeks |
| ORAL/INJECTABLE /INTRAVENOUS Antibiotics (topical antibiotics for ears, eyes,skin are permitted) | tetracycline, penicillin, cephalosporin, quinolones, monobactam, erythromycin, clarithromycin, telithromycin, azithromycin | Sumycin, Amoxicillin, Cipro, Aztreonam, E-Mycin, Biaxin, Ketek, Zithromax | 4 weeks |

## Exclusionary Medical Conditions during APRIL

- Addison's disease
- Cardiac arrhythmias (clinically significant)
- Cardiac disorder (except hemodynamically insignificant ASD, VSD, or heart murmur)
- Cataracts
- Chest surgery (call for exception)
- Congenital anomalies of the lung and chest, including growth abnormalities that affect predictability of expected lung function parameter
- 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)
- Failure to Thrive
- Gastroesophageal reflux (not controlled by standard medical therapy)
- 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, 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 (except febrile seizure in infancy)
- Peptic ulcer disease (active)
- Renal disease (active)
- Rheumatoid arthritis (if likely to require oral/systemic corticosteroid treatment)
- Thyrotoxicosis
- Tuberculosis (active)
- Vocal cord dysfunction (active)

## Allowed medications during APRIL

- acetaminophen
- acyclovir (e.g., Zovirax) for herpes
- non-macrolide antibiotics (e.g. tetracycline, penicillin, cephalosporin, quinolones, monobactam)
- 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
- non-steroidal anti-inflammatory medications (e.g. aspirin, ibuprofen, naproxen, ketoprofen)
- all oral decongestants (e.g., Sudafed)
- 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

The following list of medications can lead to prolonged QT intervals. If there is a concern with the participant taking one of these medications, the study physician should be consulted.

Scheduled/prescribed medications that can lead to prolonged QT intervals:

**Antihistamines**
Diphenhydramine (Benadryl)

**Antibiotics**
Erythromycin or azithromycin (E-Mycin, EES, EryPed, PCE)
Trimethoprim and sulfamethoxazole (Bactrim, Septra)
Pentamidine (Pentam, intravenous)

**Heart medications**
Quinidine (Quinidine, Quinidex, Duraquin, Quinaglute) – rarely used in peds/preschoolers
Procainamide (Pronestyl)
Disopyramide (Norpace)
Sotalol (Betapace)
Dofetilide (Tikosyn)
Ibutilide (Corvert)

**Antifungal drugs**
Ketoconazole (Nizoral)
Fluconazole (Diflucan)
Itraconazole (Sporanox)

**Psychotropic drugs**
Tricyclic antidepressants (Norpramin, Vivactil) – Rarely used in preschoolers
Butyrophenones (Haloperidol) – rarely used in peds/preschoolers
Benzisoxazole (Risperdal) - rarely used in peds/preschoolers
Diphenylbutylpiperidine (Orap) – rarely used in preschoolers

## 2.15 FOLLOW-UP MEDICATION PRESCRIPTION

Visit 9

**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 9 date, and the 'ongoing at final visit' box should be checked.

## 2.16 FONEMED – AFTER HOURS NURSING TRIAGE SITE

**Visits1-2**

During the Run-In period, the parent/guardian should be instructed to call the site's normal after-hours call service for medical emergencies. Do not give them the phone number for FoneMed. If the participant calls FoneMed during the Run-In (since the phone number is listed in the consent form), FoneMed will direct the parent/guardian as indicated based on the participant's symptoms.

**Visits 2-9**
**Complete the FoneMed form (FONEMED)**

To assure consistent assignment of treatment and to have immediate access to personnel familiar with the APRIL study procedures, an after-hour nursing triage site will be available for calls placed primarily at night, holidays and weekends. In addition, FoneMed will also be available for calls placed during normal daytime hours, but will be unable to assist participants with issues not related to symptoms (i.e. rescheduling visits, lost study medications/supplies, follow-up phone call 36-72 hours after starting APRIL therapy, etc.)

The family should be instructed on the action plan when to contact the site and when to contact the after-hours nursing triage site. The families will be instructed to use a 1-800 phone number that identifies that the caller is part of the APRIL study and the caller's site. The nurses will have ready access to a computerized set of telephone algorithms for APRIL and the site's personnel coverage information. The protocols will allow the nurse to direct the caller to the appropriate care for his/her situation that may include starting study medication or advising the family to take the participant to the ER. The nurse will also contact the study coordinators and physicians in a timely manner to inform them of situation. Each site will have on-call study personnel available to the nurse 24 hours a day. A written summary of the call will be sent to the site where the participant is enrolled.

For every call that is placed to the after-hours nursing triage site, a FoneMed form (FONEMED) should be completed. Depending on the outcome of the call, other data collection forms may need to be completed as indicated by the FoneMed form.

Parents/guardians should be instructed to call the sites (and NOT FoneMed) for the following reasons:

- Reschedule visits
- Lost study medications/supplies
- Follow-up phone call 36-72 hours after starting APRIL therapy

However, if the parent/guardian calls FoneMed for any of the reasons listed above, FoneMed will contact the center and provide the details of the call.

The table below contains the site-specific FoneMed phone numbers:

| Group | Site Identifier | Performance Site | FoneMed number that parents will call |
|---|---|---|---|
| **Boston** | | | |
| | 112 | Children's Hospital | 855 855 6473 |
| **Chicago** | | | |
| | 122 | Children's Memorial | 855 855 6474 |
| | 124 | University of Chicago | 855 855 6475 |
| | 125 | StrogerHospital/Rush Univ. | 855 855 6476 |
| **Denver** | | | |
| | 132 | National Jewish | 855 855 6477 |
| | 133 | University of New Mexico | 855 855 6478 |
| **Madison** | | | |
| | 141 | University of Wisconsin | 855 855 6479 |
| | 143 | Milwaukee | 855 855 6480 |
| **Pittsburgh** | | | |
| | 152 | University of Pittsburgh | 855 855 6481 |
| | 153 | Case Western | 855 855 6482 |
| | 154 | Allegheny | 877 702 4742 |
| **St. Louis** | | | |
| | 162 | Washington University | 855 855 5778 |
| **San Francisco** | | | |
| | 172 | University of California (SF) | 855 855 5779 |
| | 173 | Children's Hospital Oakland | 855 855 5780 |
| **Tucson/Durham** | | | |
| | 181 | Univ. of Arizona | 855 855 5781 |
| **Winston-Salem/ Charlottesville** | | | |
| | 192 | University of Virginia | 855 855 5782 |
| | 194 | Emory University | 855 855 5783 |

## 2.17 FORGOTTEN STUDY MATERIALS

The table below details what to do regarding forgotten study materials at an APRIL 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, 8b, 8c, 8d** |
|---|---|---|---|
| **Forgotten Item** | APRIL Run-In Diary Card | **Visit must be rescheduled,** since 80% compliance must be established firmly prior to randomization | NA |
| | APRIL MEDS | NA | Bring to next visit |
| | Nasal Samples | NA | Bring to next visit |
| | P2_PAD | NA | Bring to next visit |

## 2.18 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 APRIL 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 APRIL study. The genetic analysis participation rate for each clinical center partnership and performance site will be summarized on the APRIL 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) and 10 ml (age 60-72 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 be taken 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 6). 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.

Samples must be shipped via FedEx priority overnight (using the DCC's APRIL FedEx account #337822355) Please record 'AsthmaNet – APRIL' in the reference section. Please note that using the DCC's FedEx number for shipping genetic samples pertains to the APRIL study only.

## 2.19 GROWTH CHARTS

### Height/Length

**Visit 1-9**

**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 1-9, 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 1-9**

**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 1-9, 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.

## 2.20 GROWTH FAILURE PROTOCOL

### Visit 1

### Height/Length and Weight

If the participant's height/length or weight plots less than the 10$^{th}$ 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 2-9

Plot height/length at each clinic visit (average every 2 months) throughout the 18 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 APRIL: Potential Growth Failure'.
- The email will also be forwarded to the lead PIs for the APRIL study.
- The email will contain all information related to the participant's growth while in the APRIL 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 APRIL study.

According to the APRIL 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 APRIL PIs will decide if the participant will continue in APRIL or be termed from the study.

## 2.21 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.

## 2.22 HOSPITALIZATIONS

Participants who are hospitalized for an acute wheezing exacerbation at any time during APRIL are assigned study failure status. 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 APRIL MOP and Section 4 of the General MOP for more information.

## 2.23 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.

## 2.24 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, cypress |
| **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 St. Louis lab. See 'Blood Sampling Procedures' for more details.

## 2.25 INFORMED CONSENT

**Visit 1**
**Acquire signed APRIL informed consent**

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 APRIL trial, should the potential participant be deemed eligible. Prior to implementation of Visit 1, a summary of the study 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 document.

Guidelines for obtaining consent:

- At the beginning of Visit 1, provide the parent/guardian a copy of the informed consent form for the study and ask him or her to read it thoroughly. The parent/guardian should not sign the form until after you have discussed its contents with him or her.

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

- If the parent/guardian is unable to read the informed consent form or seems to be struggling, offer to read it 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 study 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 form.

- Maintain the signed informed consent form in the participant's study folder. To ensure confidentiality, **do not send this form to the DCC**. This document 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 a clean copy of the consent document to review and sign. See the Reenrollment discussion in this section for further details.

If modifications are made to the APRIL consent document and approved by the local IRB while a participant is in the study, the parent/guardian must be re-consented

following local IRB rules. All versions of the APRIL consent document 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 consent is recorded and tracked on Eligibility Checklist 1 (P2_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 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 APRIL 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 APRIL trial, he/she must be given the IRB-approved APRIL 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 APRIL 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.

## 2.26 MDI INHALATION TECHNIQUE ASSESSMENT *

*** Only required if participant is using MDI for rescue medication**

**Visit 1**

**Instruct Use of Albuterol (Rescue) Inhaler (TECH_MDI_FACE, HTMDI)**

If the participant will be using a rescue inhaler for albuterol during the Run-In phase of the study, 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. Participants will be given the choice of rescue medications by MDI or by nebulizer.

**Visits 2-8, 8b, 8c, 8d**

**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.

## 2.27 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.

## 2.28 MEDICATION ADHERENCE

### Visits 3-9

Medication adherence will be assessed at the visit following use of APRIL medications. It is imperative that the parent/guardian does not throw away used medication bottles after the last dose of APRIL therapy is taken by the participant. They should save the used bottles and bring them to the next scheduled visit.

The contents remaining in the bottles should be weighed. The compliance form (P2_APRIL_COMPLY) should be completed. If more than one APRIL therapy was used since the previous visit, a second P2_APRIL_COMPLY 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.

## 2.29 MISSED VISITS

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.

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, diary cards, nasal collection samples, etc.) to the participant by some other means.

## 2.30 NASAL SAMPLING PROCEDURES

### Visit 2 AND 9

Day 1 and 4 of each APRIL medication usage

Nasal mucus samples will be taken by the coordinator during Visit 2 AND Visit 9. Additional samples will be taken by the participant's parent on the first and fourth day of every APRIL respiratory illness. 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 Days 1 and 4. However, if the parent forgets on those days, the samples can still be collected within a few days of the ideal date. That is, the Day 1 sample could be collected on Days 2 or 3; the Day 4 sample could be collected on Days 5-7.

When a respiratory illness occurs and APRIL therapy is started, the parent is to call the site within 72 hours of starting APRIL. The P2_ILLNESS form is completed during that call and there are questions regarding whether the nasal samples were collected. The 'Daily Activities during Illness' Guide on the back of the APRIL Action Plan will serve as a reminder to collect nasal samples on Days 1 and 4 of each illness. For the in-clinic samples that are obtained at Visits 2 and 9, the P2_LAB form is part of the visit packet and includes questions regarding whether the nasal samples were 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 anytime. Written instruction provided to parents at the study Visit 2 and review 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.

If a participant has a respiratory illness the same day as Visit 2 or 9, it is not necessary to obtain an 'at-home' nasal sample, since one will already be obtained in the clinic. However, if they had a cold 5 days before the visit, an 'in-clinic' sample should still be obtained in addition to the 'at-home' sample that was obtained 5 days before.

Four nasal mucus sample kits should be sent home at Visit 2 and maintain four kits at the participant's home during the study (i.e. 2 for each illness). If the parent/guardian calls the clinic reporting an APRIL therapy usage, the coordinator will need to send an additional two kits by mail, unless they are scheduled for a visit soon.

### Visit 9

Ongoing illnesses at Visit 9: If a participant is coming in for the final visit (Visit 9) and is in the middle of an APRIL therapy, please reschedule the visit so that at least 14 days have passed since the last dose was taken. Contact the DCC if a visit window exception is required.

### 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 (using the DCC's APRIL FedEx account #337822355). Please record 'AsthmaNet – APRIL' in the reference section. 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 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

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

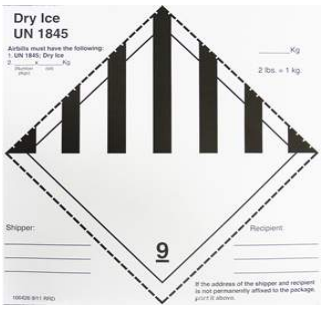
7. Use bubble wrap or cardboard to keep the samples stable should the dry ice dissipate.
    NOTE: There should be sufficient dry ice to keep the samples frozen until they reach the Madison lab.
    a. Suggestions:
        i. Plastic bubble wrap can be used at the bottom and top of the shipping container.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

8. Fill bottom of shipping box with dry ice

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

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


    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.
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 samples, using the following method. 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. In this way, at least 10 samples 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.
All samples should be sent FedEx Priority Overnight (use DCC's APRIL FedEx account #337822355). Please record 'AsthmaNet – APRIL' in the reference section. 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.

- 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).

## 2.31 PARTICIPANT ASSIGNMENT LOG/PROTOCOL ENROLLMENT

**Visit 1**

Assign participant ID number (P2_LOG)

A Participant Assignment Log (P2_LOG) has been developed for each performance site. This log includes columns for unique participant ID numbers, participant initials, participant's name, and assigned APRIL bottle numbers.

Participant ID numbers are preprinted on P2_LOG and are comprised of 8 digits:

- The first two digits are the number of the AsthmaNet protocol. For the APRIL protocol the first two digits are 02.

- 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, 133=University of New Mexico, 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, 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 APRIL Participant Assignment Log. This number will be the primary participant identifier used during the APRIL 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 (P2_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 (P2_LOG)

Following assignment of the participant's ID number on the APRIL Participant Assignment Log (P2_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 3-9**

Log assigned 3rd and 4th APRIL bottle number(s) or replacement medications (P2_LOG)

After accessing the randomization module to obtain the 3rd and 4th APRIL therapies or replacement bottle numbers for the participant, the new bottle numbers must be logged on P2_LOG. This log provides a single reference for all of an individual's medications over the life of the study.

## 2.32 PARTICIPANT HANDOUT FOLDER

At Visit 1 each participant is given an AsthmaNet folder containing 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 what to do during an APRIL illness (i.e. dosing with the APRIL therapy, completing the Pre-School Diary Card, collecting nasal samples, etc). The parent/guardian should store the study folder in a convenient location, as it will serve as a reference throughout the trial. The folder 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 APRIL study:

**Handouts Distributed at Visits**

| | |
|---|---|
| Visit 1 | Run-In Action Plan<br>Environmental Handouts (ENVIRONMENT)<br>How To Complete the Run-In Diary Card (P2_HTDIARY)<br>How To Use Your albuterol RESCUE Inhaler (P2_HTMDI)<br>How to Use Your Study Nebulizer® (HTNEBULIZER) |
| Visit 2 | APRIL Action Plan Card / Respiratory Illness Daily Activities Guide<br>APRIL Action Plan wallet-size ID Card<br>APRIL Action Plan for Caregivers<br>APRIL Symptoms of Respiratory Illness (P2_SYMP_PARENT)<br>APRIL List of Symptoms of Respiratory Illness (P2_SYMPLIST)<br>Tips for Taking APRIL Medications (P2_TIPS_MED)<br>How to Contact the Study Team (P2_CONTACT_AO)<br>APRIL Nasal Swab (P2_HTNASAL_SWAB)/ APRIL Nasal Blow (P2_HTNASAL_BLOW)<br>Preschool Asthma Diary (PAD)/ Albuterol Log (P2_ALBUTEROL_LOG) |

**Run-In Action Plan, APRIL Action Plan Card, APRIL Action Plan wallet-size ID Card, and APRIL Action Plan for Caregivers**

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

### Environmental Handouts

The purpose of the Environmental Handouts (ENVIRONMENT) 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 Environmental Handouts includes:

Getting Rid of Cockroaches
Getting Rid of Mold
Pets
The Safe Sleeping Zone
Tobacco Smoke

### How to Complete the Diary Card (P2_HTDIARY)

These instructions can be used as a tool to introduce the Run-In Diary Card (P2_DIARY_RUNIN) to the parent/guardian at Visit 1. See "Run-In Diary Card" for further details.

### How to Use Your albuterol RESCUE Inhaler (P2_HTMDI) and How to Use Your Study Nebulizer® (HTNEBULIZER)

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

### APRIL Symptoms of Respiratory Illness (P2_SYMP_PARENT)/ APRIL List of Symptoms of Respiratory Illness (P2_SYMPLIST)

Parents/guardians should complete the APRIL Symptoms of Respiratory Illness form (P2_SYMP_PARENT) when they begin the APRIL medications. Parents are asked to complete the form while referring to the APRIL List of Symptoms of Respiratory Illness (P2_SYMPTLIST). The form has the parent/guardian identify the signs/symptoms that lead to a respiratory illness.

### Tips for Taking APRIL Medications (P2_TIPS_MED)

This handout provides some helpful tips for the parent/guardian when giving the participant the APRIL medications.

### How to Contact the Study Team (P2_CONTACT_AO)

This handout provides a quick reference for contacting the study team during normal business hours and holidays, weekends and nights.

### APRIL Nasal Swab (P2_HTNASAL_SWAB)/ APRIL Nasal Blow (P2_HTNASAL_BLOW)

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

### Preschool Asthma Diary (P2_PAD)/ Albuterol Log (P2_ALBUTEROL_LOG)

This Diary Card should be completed when taking the APRIL medications. There is one page per day. The reverse side of the Diary Card contains a place for the parent/guardian to record when/how often albuterol is given to the participant.

## 2.33 PERSISTENT SYMPTOMS

### APRIL Phone/Visit Symptom Assessment Form (P2_PHONE_CONTACT) and Persistent Symptoms Form (P2_PERS_SYMP)

**Definition of persistent symptoms:**

- Daytime symptoms of cough or wheeze which average 5 or more days a week over the past 4 weeks.
- Nighttime symptoms of cough or wheeze that wake the participant up and occur at least once a week on average over the past 4 weeks.

If symptoms have persisted for at least 4 weeks, the participant will be seen in the AsthmaNet site and evaluated for an alternative diagnosis for ongoing symptoms (such as sinusitis). If a diagnosis other than persistent asthma, such as sinusitis, is established, treatment of that condition may be prescribed (such as a course of oral antibiotics other than a macrolide) and the participant reassessed after completion of treatment. If symptoms do not resolve with this therapy, or if an alternative diagnosis is not established, the participant will be assigned STUDY FAILURE STATUS and Visit 9 should be scheduled. Blinded study participation will be discontinued. A PRAM score will not be recorded. A 5-day course of OCS will be considered per the AsthmaNet Site's physician discretion. The family will be asked to call the clinic back if the symptoms do not improve or worsen. Per the physician's discretion, the family may be provided with a 6-week supply of open-label inhaled corticosteroids. Communication regarding this study visit and any prescribed medications will be sent to the participant's primary care provider. If the symptoms worsen or do not improve, the participant will be evaluated by AsthmaNet clinic personnel (safety visit) or referred to urgent care or ED if symptoms severe. A second course of open label oral corticosteroids will be considered.

Two-weeks after the AsthmaNet Site visit, the family will be called by the AsthmaNet site personnel for a safety follow-up. Clinic coordinators will ask the parents at the two-week call if they have contacted the participant's primary care provider. Coordinators will emphasize the importance of contacting the participant's primary care provider for further treatment; both at the final visit and at the two-week follow up phone call. During this follow-up safety call, no data collection forms need to be completed. A note should be made in the participant's chart regarding the call.

## 2.34 PHONE CONTACTS

### Every 4 weeks after each visit starting with Visit 3

#### COMPLETE VISIT PROCEDURE CHECKLIST 3A-8A (P2_VISIT3A_8A)

Scheduled phone contacts during the APRIL 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.
- Review Action Plan.
- Answer any questions the parent/guardian may have.

### Persistent Symptoms

If the participant has been having persistent symptoms for the past 2 weeks, a follow-up phone call should be scheduled in 2 weeks to assess whether the participant is continuing to have persistent symptoms. The Persistent Symptom Form (P2_PERS_SYMP) should be completed during the follow-up phone call.

### 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 APRIL medications, collected nasal samples and completed Preschool Asthma Diaries (P2_PAD).

## 2.35 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 APRIL study. 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 2-9**
**Perform Short Physical Exam (SEXAM_PED)**

A brief physical exam is conducted at Visits 2-9. 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.

## 2.36 PRE-SCHOOL ASTHMA DIARY / ALBUTEROL LOG

The Pre-School Asthma Diary is used to record participant symptoms during respiratory tract illnesses. The diary includes six symptom categories (cough, wheeze, sleep disturbance, lethargy, appetite, irritability and albuterol response). Each of the six symptom category is scored on a one through seven scale. The Pre-school Asthma Diary is copyrighted by Francine Ducharme and used with permission.

**Visit 2**
**Practice completion**

The parent/guardian should practice completion of the Pre-School Asthma Diary during Visit 2. That will ensure that he/she understands the questions and is prepared to complete it whenever the participant uses APRIL medications. The practice form should not be entered into the database. Instead, it should be filed in the participant's folder.

**Visits 2-9**
**Complete whenever using APRIL medications**

The Pre-School Asthma Diary (and corresponding Albuterol Log on reverse side) should be completed whenever APRIL medications are being used. The parent/guardian should have on hand enough diary cards to complete an illness. It is recommended that the participant has approximately 2 weeks of Diary Cards on hand. Note that the Diary Card is one page per day. The parent/guardian should continue to complete Diary Cards until the participant is symptom-free for 2 days.

The reverse side of the Diary Card is an Albuterol Log that can be used by the parent/guardian to track when the participant uses albuterol.

## 2.37 PROTOCOL VIOLATIONS and DEVIATIONS

The following is a list of protocol violations that may be assigned during the APRIL protocol:

Eligibility

- Participant with an exclusionary medical condition was enrolled.
- Participant taking an excluded medication within the defined washout period was enrolled.
- Participant who demonstrated lack of asthma control during Run-In period was randomized.
- Participant who used oral or systemic corticosteroids during the Run-In period was randomized.
- Participant who used antibiotics during the Run-In period was randomized.
- Participant with an exclusionary event (was hospitalized or intubated due to asthma or had a hypoxic seizure due to asthma) during the Run-In period was randomized.
- Participant was not 12 to 71 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 was randomized at Visit 2. (Adherence based on diary completion.)
- Participants living in the same household were enrolled at the same time.

Drug Dispensation

- No scheduled medications dispensed (participant left without drug due to clinic negligence).
- Incorrect medications for participant dispensed (wrong bottle number).

Serious Adverse Event

- Site failed to report a serious adverse event within the prescribed time limits.

Miscellaneous

- Site failed to recognize and document an APRIL treatment failure or study failure (unless details are unavailable due to participant being lost-to-follow-up, etc.).

The following is a list of protocol deviations that may be assigned during the APRIL protocol:

Certification

- Coordinator without APRIL protocol certification completed APRIL forms.

Blood Sampling

- Blood not drawn for ImmunoCap or CBC.
- Blood drawn after participant has been deemed ineligible.

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 or Registry Form sent to DCC. (includes breaches of confidentiality resulting from lost or stolen study documents)

Miscellaneous

- Site failed to notify DCC of use of a backup randomization.
- Physical exam not performed.
- Site incorrectly identified an APRIL treatment failure or study failure.
- A follow-up phone call was not made to assess persistent symptoms 2 weeks after possible identification during a phone contact.
- Incorrect Run-In length was used (2 or 4 weeks).

## 2.38 RANDOMIZATION

### Visit 2, 3rd APRIL therapy, 4th APRIL therapy, Lost/Replacement Drugs

The randomization module may be accessed for four reasons during the APRIL study: Visit 2 for the initial randomization, to obtain the 3rd APRIL treatment for a participant, to obtain the 4th APRIL treatment for a participant, and to obtain lost/replacement drugs.

The randomization will be stratified by the 9 performance sites and age group (12-41 months and 42-71 months).

The participant's weight will need to be checked since participants weighing > 20 kg will need 2 bottles of APRIL medication for each illness. Participants weighing <= 20 kg will only need 1 bottle of APRIL medication for each illness.

### Visit 2

The randomization module will provide bottle numbers for 2 APRIL therapies (i.e. 2 illnesses). Participants weighing > 20 kg will receive 4 APRIL bottles. Participants weighing <= 20 kg will receive 2 APRIL bottles.

### Visits 2-9: 3rd APRIL therapy

Once the participant uses the first APRIL therapy, the 3rd APRIL therapy should be dispensed to the participant. The randomization module should used to obtain the bottle number(s).

### Visits 2-9: 4th APRIL therapy

Once the participant uses the second APRIL therapy, the 4th APRIL therapy should be dispensed to the participant. The randomization module should be used to obtain the bottle number(s). The 'Lost/Replacement' option on the randomization module should be chosen, and the reason of '4th APRIL therapy' should be typed into the application.

### Visits 2-9: Lost/Replacement Drugs

If the participant loses/spills the APRIL medications, 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.

NOTE: The participant's APRIL doses are based on their weight at the randomization visit and should NOT be adjusted if his/her weight changes during the study.

## 2.39 RECRUITMENT

APRIL visits will commence in March 2011. A total recruitment period of approximately 18 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 APRIL accrual report. This report will be available on the secure website shortly after commencement of the study.

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 APRIL protocol. Each of the 9 participating performance sites is expected to randomize approximately 67 participants for a Network total of 600 randomized participants in the APRIL protocol combined.

## 2.40 REGISTRATION

**Visit 1 or Prior**
**Register participant in AsthmaNet Registry**

Before a participant can be enrolled in the APRIL 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 (P2_VISIT1) in the participant's Visit 1 packet.

## 2.41 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 34 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. Immunodeficiency disorders.
5. History of respiratory failure requiring mechanical ventilation.
6. History of hypoxic seizure.
7. History of significant adverse reaction to any study medication ingredient.
8. 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 $10^{th}$ 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 (P2_LOG). However, specific data can be reused:

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

- The following forms may be reused from the original Visit 1: Participant Contact (CONTACT), Household Socio-Economic Information (HOUSEHOLD_SEI), 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 APRIL. These biological samples for non-randomized participants should be destroyed upon study termination.

## 2.42 RESPIRATORY TRACT ILLNESS/STARTING APRIL MEDICATIONS

### Parent Contact

Parents are instructed to call the AsthmaNet clinic within 72 hours of their child beginning a Respiratory Tract Illness (RTI) and/or the APRIL study medications.

Note: During a Phone Conference held on 10/21/2011, it was noted that some children seem to have a very rapid increase in symptoms which causes Study Failure to be achieved. Therefore, Dr. Bacharier suggested during that Phone Conference that all sites encourage parents to call the AsthmaNet clinic within 24 hours of starting an APRIL illness, rather than 72 hours.

Parents should be instructed to call the site during regular office hours for those call (i.e. FoneMed will not take these calls.). During this call to the clinic, two questionnaires should be completed, the APRIL Respiratory Illness Follow-up Contact (P2_ILLNESS) and the Symptoms of Respiratory Illness (P2_SYMP_CC). The purpose of these questionnaires is to determine the first symptoms of the illness, common symptoms of this illness, and whether the parents are following study procedures and taking APRIL medications. The call also allows the parents to ask any questions about the illness, action plan and study medications.

Parents should be asked to review the action plan and reminded to collect nasal samples on Days 1 and 4 of the illness. The nasal samples should be brought to the clinic at the next scheduled study visit. Parents should also be reminded to complete the Preschool Asthma Diary (P2_PAD) daily until the participant is symptom-free for 2 days in a row. Those diary cards should be brought to the next scheduled study visit.

The APRIL Respiratory Illness Follow-up Contact (P2_ILLNESS) asks about symptoms since the start of the illness, if the parents have started the study medications and whether nasal samples were collected. Ideally this form should be completed within 72 hours of the illness; however, the form may be completed up to 7 days after the illness if the parent fails to contact the site within the specified 72 hours.

APRIL therapy can be started on the day of randomization if the participant develops symptoms that were identified as indicating the start of a respiratory illness from the Symptoms of Respiratory Illness Questionnaire that was previously completed. However, if prior to randomization, the participant's symptoms are of a severity requiring a course of oral corticosteroids, the participant should not be randomized, but could be re-enrolled at a later time.

Albuterol should always be used as directed qid for the first 48 hours, even if the participant does not have specific asthma symptoms. Although there is inconvenience with qid dosing, parents should be reassured that during a respiratory illness, lung

changes are occurring that may benefit from albuterol even if the participant isn't having typical asthma symptoms.

Since azithromycin can stay in the system for up to 9 days after the last dose is taken, two consecutive APRIL therapies should be at least 14 days apart (i.e. there should be at least 14 days between the start of each APRIL therapy).

**Symptoms of Respiratory Illness (P2_SYMP_CC and P2_SYMP_PARENTS)**

**Complete Symptoms of Respiratory Illness Form (P2_SYMPTOMS_CC)**

Parents will have a copy of the Symptoms of Respiratory Illness (P2_SYMP_PARENTS and P2_SYMPTLIST) in their study folder. They should complete this questionnaire when they begin the APRIL medications. Parents are asked to complete the form while referring to the P2_SYMPTLIST. Coordinators will have a similar copy of the Symptoms of Respiratory Illness (P2_SYMP_CC). Coordinators will ask parents for their answers during the phone call and record the corresponding number (from the coded symptom list) in the line provided next to the question. This will allow parents to answer these questions as soon as the illness begins and enables the coordinator to collect the information for data entry. Parents should bring their copy of the completed survey to the clinic at the next visit. A new Symptoms of Respiratory Illness (P2_SYMP_PARENTS) should be given to the parent at that time. Since a new questionnaire is completed with each respiratory illness, the signs/symptoms that lead to a respiratory illness may change throughout the study.

Parents should be instructed to use 'Not Applicable' when the symptom/sign is not present. Similarly, they should be instructed to use 'Not very Important' when the symptom/sign occurs, but is not a very important part of the participant's reaction to viral infections.

The Symptoms of Respiratory Illness (P2_SYMP_CC) survey may be completed after the 72-hour window if the parents completed it at the start of the illness as instructed. Example: Parents fail to call within 72 hours (of the start of the illness) but bring their completed copy of the Symptoms of Respiratory Illness (P2_SYMP_PARENT) to the next study visit. Coordinators can use the answers from the Symptoms of Respiratory Illness (P2_SYMP_PARENT) to complete the Symptoms of Respiratory Illness (P2_SYMP_CC).

**Study Medications**

Please instruct parents of participants who complete their course of APRIL medications and continue to have symptoms to call the site. A new course of study medication or illness kit should not be started at this time. APRIL therapy should be used for new illnesses only.

Parents should always have 2 courses of APRIL therapy available (unless they have already used 3). Once the participant has used the first course of APRIL therapy, the third course should be dispensed. Once the participant has used the second course of APRIL therapy, the fourth course should be dispensed.

## 2.43 RUN-IN DIARY CARDS

### General Information

The APRIL Run-In Diary Card (P2_DIARY_RUNIN) is a daily log of the participant's asthma medication use and symptom severity. Make sure the participant has 1 more Diary Card than the number of weeks between visits so that if the participant's next visit is postponed or a Diary Card is lost, a Diary card will be readily available.

See the handout "How to Complete the APRIL Run-In Diary Card" (P2_HTDIARY) for detailed information on completing this form.

The back of the APRIL Run-In Diary Card is an optional tool for the parent/guardian to record medications and medical problems that may occur during the week.

### Dispensing the Diary Cards

Before dispensing the Diary Cards, complete the upper right-hand corner and the day and dates (month and day) for each day on each card.

The parent/guardian should begin recording information for the nighttime evaluation *on the day of the visit*. **Cross out the morning evaluation portion of the card for the day of the visit,** since the parent/guardian should not complete this information. Bronchodilator puffs taken as part of visit procedures should NOT be recorded.

**Visit 1**

**Instruct Parent/Guardian on How to Complete the APRIL Run-In Diary Card (P2_HTDIARY)**

**Dispense Run-In Diary Cards (P2_DIARY_RUNIN)**

Using the P2_HTDIARY handout as a guide, show the parent/guardian how to complete the form, emphasizing that *blue or black ink* should be used. Be sure the parent/guardian understands the information that is required in each box. Encourage the parent/guardian to record the information each and every day. It is helpful if the recording of the data can be associated with specific daily activities (e.g., brushing teeth). Emphasize that data should not be *made up* or *recalled* more than one day back if days are missed.

When reviewing Question #1 (How much albuterol did your participant use since being put to bed?), tell parents that if the participant goes to bed for the night and falls asleep, but then is physically awakened during the night by asthma symptoms and must get up out of bed to take albuterol and then returns to sleep, then record the number of puffs or the number of nebulizer treatments.

### Reviewing the Diary Cards

Ask the parent/guardian to bring the Diary Cards that have been completed to Visit 2. Diary Cards are reviewed early in this visit so that problems with incomplete information can be addressed.

If numbers seem unclear, request clarification from the parent/guardian. If a Diary Card is difficult to read, ask the parent/guardian to copy the information onto a new Diary Card before leaving the clinic. Note that clinical personnel should not make changes to the Diary Cards; only the parent/guardian may alter this information.

Review the Diary Cards with the parent/guardian for use of rescue medications. If it appears that the participant has not been using his or her albuterol (RESCUE) inhaler for primary treatment of asthma symptoms, discuss this with the parent/guardian.

Examine the back of the Diary Card if it is completed. This information is helpful for the documentation of adverse events, and concomitant medications. If appropriate, complete the corresponding form(s) (AECLIN or CMED).

### Forgotten Diary Cards

Every effort should be made to ensure that parent/guardian remembers to complete and bring their Diary Cards to Visit 2, including reminder phone calls placed prior to the scheduled visit. At Visit 2, if the Diary Card is forgotten, then the visit should be rescheduled.

## 2.44 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 APRIL, it is present in the Visit 9 and Visit 21 packets. In addition, the questionnaire is also posted appended to the single APRIL Termination of Study Participation (P2_TERM) form for use with participants who terminate from the study before Visit 9.

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 APRIL 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 APRIL Termination of Study Participation (P2_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 P2_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.

## 2.45 SCREEN FAILURES

### Visit 1

If an APRIL 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.

## 2.46 STUDY FAILURES

**Visits 2-9**
**Complete the Study Failure Form (P2_STUDY_FAILURE)**

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

- Symptoms requiring immediate medical attention
- There is an unscheduled visit for acute asthma care (physician office, urgent care, emergency department) with 1 albuterol treatment lasting more than 1 hour or more than 1 albuterol treatment
- During an unscheduled visit for acute asthma care in a physician's office the participant is transferred to urgent care or the emergency department due to severity of respiratory symptoms
- Systemic steroids are needed for respiratory symptoms. This includes steroids given for 1 day to treat croup. Steroids given to treat conditions unrelated to breathing problems (i.e. poison ivy) should not count towards study failure.
- Hospitalization is needed for asthma
- Development of persistent symptoms
- Physician discretion

The Study Failure Form (P2_STUDY_FAILURE) should be completed. A follow-up phone call should be made to the parent/guardian 1-24 hours after telling the parent/guardian to start prednisolone. During that follow-up call, a final closeout visit (Visit 9) should be scheduled within 2 weeks or within 72 hours if the participant required urgent medical attention.

For those participants that did not receive open-label OCS, a 5 day course of open label OCS will be considered per physician discretion. If open label OCS is prescribed, a follow-up safety phone call should take place 2 weeks after starting OCS.

## 2.47 SYMPTOMS OF BREATHING ILLNESS

### Visits 1 and 2

### Complete the Symptoms of Breathing Illness Form (P2_SURVEY)

The Symptoms of Breathing Illness Form (P2_SURVEY) will be used to help parents identify their participant's symptoms that signal the onset of a breathing illness. This survey is very important in individualizing the participant's action plan. Please see the Action Plan Identification discussion earlier in this section for details on completing the Action Plan.

The Symptoms of Breathing Illness Form (P2_SURVEY) will be completed at Visit 1 by the coordinator. The parent's will be given a copy of the symptom list to help them answer the questions. Coordinators should use the coded copy of the symptom list to fill in the parent's answers. Parents will take a blank copy of the survey home with them. They should review the survey and take time to think about their answers. The Symptoms of Breathing Illness Form (P2_SURVEY) will be re-administered by the coordinators at Visit 2. The answers given by the parents at Visit 2 will be used on the Action Plan. Answers to the Symptoms of Breathing Illness Form (P2_SURVEY) will be data entered for both visits.

Parents should be instructed to use 'Not Applicable' when the symptom/sign is not present. Similarly, they should be instructed to use 'Not very Important' when the symptom/sign occurs, but is not a very important part of the participant's reaction to viral infections.

## 2.48 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 APRIL 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 APRIL 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 APRIL 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, or who fail to record information on their Run-In Diary Cards (P2_DIARY_RUNIN) 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 APRIL Termination of Study Participation Run-In (P2_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 drug packet 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 APRIL Study Treatment Questionnaire (P2_APRIL_TRTQX), 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 APRIL study. This questionnaire should be sent home with the parent/guardian. An APRIL Termination of Study Participation form (P2_TERM) should also be submitted.

If the parent/guardian of a randomized participant withdraws consent between visits, the APRIL Termination of Study Participation form (P2_TERM) should be completed and submitted. The study coordinator who was primarily responsible for the participant's study visits should complete the last question on the APRIL Treatment Questionnaire (P2_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 APRIL Termination of Study Participation (P2_TERM) form should also be submitted.

If the parent/guardian of a randomized participant withdraws consent between visits, the APRIL Termination of Study Participation (P2_TERM) form 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.

Add what constitutes 'Complete' and 'Not Complete'

## 2.49 THROAT SWAB (St. Louis site only)

### Visit 2 and 9 and during visit following 1st APRIL therapy

Throat swabs should be collected at the **St. Louis site only** at up to 3 time points:

- Visit 2
- The visit that follows the 1st course of APRIL therapy; this sample will be obtained if the visit occurs after a minimum of 14 days from the last dose of APRIL therapy (otherwise, it should be collected at the next visit). Note: if it has been between 10-14 days since the last dose of APRIL therapy was taken, the throat swab can still be collected and a comment should be included on the P2_LAB form, Q6000,
- Visit 9; a minimum of 14 days after the last dose of APRIL therapy. Note: if it has been between 10-14 days since the last dose of APRIL therapy was taken, the throat swab can still be collected and a comment should be included on the P2_LAB form, Q6000.

Samples should be logged in Biological Sample tracking.

## 2.50 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 2 times during the study: Visits 1 and 2. At Visit 1, the Visit Scheduler is run to schedule the Visit 2.There are 2 different options at Visit 1: a 2 week Run-In and a 4 week Run-In. (A 4 week Run-In is required if the participant is receiving step 2 or higher NAEPP asthma guideline therapy prior to Visit 1. The need for a 4 week Run-In is assessed on the P2_ELIG1 Checklist.) At Visit 2, the Visit Scheduler must be run again to produce the schedule for the remainder of the visits.

### Visit 1

Run the Visit Scheduler. It will determine the optimal date for Visit 2. You will need to choose a 2 week Run-In or a 4 week Run-In. A 4 week Run-In is required if the participant is receiving step 2 or higher NAEPP asthma guideline therapy prior to Visit 1. The need for a 4 week Run-In is assessed on the ELIG1 Checklist Q#19.

### Visit 2

At Visit 2, run the Visit Scheduler to determine the schedule for the remainder of the study.

The table below describes the APRIL 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:

2 week Run-In:

| 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 |

4 week Run-In:

| Visit at which the Visit Scheduler is run. | Visit Number | Ideal Date | Lower Window | Upper Window |
|---|---|---|---|---|
| Visit 1 | 2 | 28 days | 0 days, +7 days | 28-35 days |

Treatment Phase:

| Visit at which the Visit Scheduler is run. | Visit Number | Ideal Date | Lower Window | Upper Window |
|---|---|---|---|---|
| Visit 2 | 3 | 28 days | - 7 days | + 7 days |
| | PC | 56 days | - 7 days | + 7 days |
| | 4 | 84 days | - 14 days | + 14 days |
| | PC | 112 days | - 7 days | + 7 days |
| | 5 | 140 days | - 14 days | + 14 days |
| | PC | 168 days | - 7 days | + 7 days |
| | 6 | 196 days | - 14 days | + 14 days |
| | PC | 224 days | - 7 days | + 7 days |
| | 7 | 252 days | - 14 days | + 14 days |
| | PC | 280 days | - 7 days | + 7 days |
| | 8 | 308 days | - 14 days | + 14 days |
| | PC | 336 days | - 7 days | + 7 days |
| | 8b | 364 days | - 14 days | + 14 days |
| | PC | 392 days | - 7 days | + 7 days |
| | 8c | 420 days | - 14 days | + 14 days |
| | PC | 448 days | - 7 days | + 7 days |
| | 8d | 476 days | - 14 days | + 14 days |
| | PC | 502 days | - 7 days | + 7 days |
| | 9 * | 530 days | - 14 days | + 14 days |

*If a participant has used APRIL therapy within 14 days of Visit 9, Visit 9 should be rescheduled so that at least 14 days have passed since the last dose was taken. The DCC should be contacted if a visit extension is required.

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# 4 PROTOCOL SPECIFIC FORMS AND INSTRUCTIONS

This section provides specific instructions needed to correctly complete the forms for the APRIL 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 'P2' prefix are APRIL 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 APRIL 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: | | |
| APRIL Visit Procedure Checklist Visit 1 | P2_VISIT1 | |
| Registry Checklist | REG_CHK | * |
| APRIL Eligibility Checklist 1 | P2_ELIG1 | |
| BIOLINCC Consent Tracking Form | BIOLINCC | * |
| 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 | * |
| APRIL Symptoms of Respiratory Illness Survey | P2_SURVEY | |
| Visit 2: | | |
| APRIL Visit Procedure Checklist Visit 2 | P2_VISIT2 | |
| APRIL Run-In Diary | P2_DIARY_RUNIN | |
| APRIL Eligibility Checklist 2 | P2_ELIG2 | |
| APRIL Symptoms of Respiratory Illness Survey | P2_SURVEY | |
| Pediatric Short Physical Exam | SEXAM_PED | * |
| APRIL Laboratory Results | P2_LAB | |
| Genetic Analysis Blood Draw | GABLOOD | * |
| APRIL Scheduled Medications | P2_MED | |
| Visit 3 – 8, 8b, 8c, 8d: | | |
| APRIL Visit Procedure Checklist Visits 3-8 | P2_VISIT3_8 | |
| APRIL Compliance Checklist | P2_APRIL_COMPLY | |
| Pre-School Asthma Symptom Diary | P2_PAD | |
| Pediatric Short Physical Exam | SEXAM_PED | * |
| APRIL Phone Contact | P2_PHONE_CONTACT | |
| Visit 3a – 8a, 8b1, 8c1, 8d1: | | |
| APRIL Phone Contact Visit Procedure Checklist | P2_VISIT_PC | |
| APRIL Phone Contact | P2_PHONE_CONTACT | |

| | | |
|---|---|---|
| Visit 9: | | |
| APRIL Visit Procedure Checklist Visit 9 | P2_VISIT9 | |
| APRIL Compliance Checklist | P2_APRIL_COMPLY | |
| Pre-School Asthma Symptom Diary | P2_PAD | |
| Pediatric Short Physical Exam | SEXAM_PED | * |
| APRIL Laboratory Results | P2_LAB | |
| APRIL Study Treatment Questionnaire | P2_APRIL_TRTQX | |
| Termination of APRIL | P2_APRIL_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 APRIL study. Some forms (example: Termination of Study Participation) 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 APRIL protocol. 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 |
|---|---|---|---|---|
| APRIL Compliance Checklist | P2_APRIL_COMPLY | * | | |
| APRIL Eligibility Checklist 1 | P2_ELIG1 | * | | |
| APRIL Eligibility Checklist 2 | P2_ELIG2 | * | | |
| APRIL Laboratory Tests | P2_LAB | * | * | |
| APRIL Persistent Symptoms | P2_PERS_SYMPTOMS | | * | |
| APRIL Phone Contact | P2_PHONE_CONTACT | * | * | |
| APRIL Respiratory Illness Follow-up Contact | P2_ILLNESS | | * | |
| APRIL Run In Diary | P2_DIARY_RUNIN | * | * | |
| APRIL Run in Termination of Study Participation | P2_TERMR | | * | |
| APRIL Scheduled Medications | P2_MED | * | * | |
| APRIL Prednisolone Medication | P2_PRED | | * | |
| APRIL Study Treatment Questionnaire | P2_APRIL_TRTQX | * | * | |
| APRIL Symptoms of Respiratory Illness Survey | P2_SURVEY | * | | |
| APRIL Symptoms of Respiratory Illness | P2_SYMP_CC | | * | |
| APRIL Treatment Failure | P2_TRTFAIL | | * | |
| Biolincc Consent Tracking Form | BIOLINCC | * | | |
| Clinical Adverse Events | AECLIN | | | * |

| Form Name | Form Code | Packet | Single | Concurrent |
|---|---|---|---|---|
| Concomitant Medications for Asthma/Allergy Related Drugs | CMED_AS | | | * |
| Effect's of a Child's Asthma Flare-Up on the Parents | PARENT_QOL | * | | |
| FONEMED | P2_FONE_MED | | * | |
| Genetic Analysis Blood Draw | GABLOOD | * | | |
| Home Environment Questionnaire | HEQ | * | * | |
| Household Socio-Economic Information | HOUSEHOLD_SEI | * | | |
| Pediatric Asthma and Allergy History | ASTHMA_HX_PED | * | | |
| Pediatric Long Physical Exam | LEXAM_PED | * | | |
| Pediatric Respiratory Assessment Measure | PRAM | * | | |
| Pediatric Short Physical Exam | SEXAM_PED | * | | |
| Pre-School Asthma Symptom Diary | P2_PAD | * | * | |
| Prior Conditions for All Participants | PRIOR_COND_ALL | * | | |
| Prior Asthma/Allergy Treatment | PRIOR_TRT | * | | |
| Registry Checklist | REG_CHK | * | | |
| Serious Adverse Event Reporting Form | SERIOUS | | * | |
| Study Failure | P2_STUDY_FAIL | | * | |
| Termination of APRIL | P2_APRIL_TERM | * | * | |

### 4.2.1 APRIL Compliance Checklist (P2_APRIL_COMPLY)

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

**Who:** An AsthmaNet Coordinator completes the form.

**When:** Visits 3 – 9, 20.

Form Instructions:

This form is to establish the participant's adherence for the APRIL therapy use at visits 3 through 9, and visit 20.

Question 1000. Record if the participant used APRIL therapy since the last visit. If the participant is using APRIL therapy at the time of the visit, Q1000 should be answered 'No' and compliance will be determined at the next visit. If Q1000 is answered 'No', ***stop*** completion of the form. Otherwise complete Q1010.

Question 1010. Record the start date of the APRIL therapy usage.

Question 1020. Record the number of bottles of medication the participant required. If the participant required two bottles of medication, skip to Q1080. The APRIL therapy is dosed based on the participant's Visit 2 (randomization) weight. Participants who weigh less than 20 kg at the time of initial randomization will be given 2 bottles of APRIL therapy at Visit 2 and participants who weigh more than 20 kg will be given 4 bottles of APRIL therapy at Visit 2.

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.

Question 1050. Record the participant's daily dose in milliliters.

Question 1060. Calculate and record the total dosage in grams. Q6 X 5 X 1.9

Question 1070. Calculate and record the participant's adherence percentage. Use the weight of a full bottle, which is 74. ((74 – Q5)/Q7) X 100

The field constraint on Q1070 has a maximum value of 150. If the calculated percentage is greater than 150, enter 150 into Q1070 and include the real value in the comment field (Q6000). Do not leave the value missing. There will be an error indicating that the compliance calculation is incorrect. This should be marked as unresolvable with the comment that the calculated value is greater than 150.

Complete the Questions 1080 – 1150 for participant's who needed two bottles of APRIL therapy.

Questions 1080 - 1110. Record the bottle number and bottle weight in grams for both bottles. Round to the closest whole gm when completing 1090 and 1110 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.

Question 1120. Record the total weight of both bottles in grams (Q1090 + Q1110).

Question 1130. Record the participant's daily dose in ml.

Question 1140. Calculate and record the total dosage in grams. Q14 X 5 X 1.9

Question 1150. Calculate and record the participant's adherence. Use the weight of a full bottle which is 74 and multiply that by 2. ((148 - Q13)/Q15) X 100

The field constraint on Q1150 has a maximum value of 150. If the calculated percentage is greater than 150, enter 150 into Q1150 and include the real value in the comment field (Q6000). Do not leave the value missing. There will be an error indicating that the compliance calculation is incorrect. This should be marked as unresolvable with the comment that the calculated value is greater than 150.

Question 6000. If the medications are not returned and the compliance calculation cannot be completed, please provide a comment. If you know that the calculated adherence is not correct for reasons such as the parent spilled the medication, etc., please provide a comment. If the calculated value in Q1070 or Q1150 is greater than 150, provide the actual compliance calculation in the comment field.

If more than one APRIL therapy was used since the last visit, please complete a P2_APRIL_COMPLY form for **each** APRIL therapy usage. The P2_APRIL_COMPLY form is a repeating form which means that more than one usage can be recorded within the same visit. Record ID's were created in the database to uniquely identify each usage. The record ID for the P2_APRIL_COMPLY form is the page number. Record ID's cannot be repeated within a visit.

Complete the 'Form Page __ of __' fields at the bottom center of the form for each APRIL therapy usage. For example, if the participant used two APRIL therapies since the last visit, the first P2_APRIL_COMPLY form should be numbered 'Form Page 1 of 2', and the second as 'Form Page 2 of 2'.

When collating and mailing this form to the DCC, all P2_APRIL_COMPLY forms completed for the same participant on the same day should be organized together as one form in the order in which they were completed.

### 4.2.2 APRIL Eligibility Checklist 1 (P2_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 2.12 of the APRIL MOP.

Questions 1000 – 1010. The child's parent or guardian must display willingness to provide informed consent. 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 – Q1040. The participant must be able to take the study medications. If the participant has an intolerance or allergy to azithromycin, oral corticosteroids (Decadron, Dexamethasone, Orapred, Prelone, Pediapred, prednisone) or albuterol he/she is not eligible for APRIL.

Question 1050. The participant must be 12 to 71 months old at time of enrollment. Persons who are less than 12 months old **OR** 71 months old or older at the time of *enrollment* are not eligible for APRIL.

Question 1060. If the participant was born earlier than 34 weeks gestation, he/she is not eligible for APRIL.

Questions 1070 – 1080. The participant must be up-to-date with immunizations to be eligible for APRIL. 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 1090 – 1100. 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 APRIL.

Questions 1110 – 1150. 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, or any other significant medical illness as listed on the P2_EXCLMED reference card, he/she is not eligible to participate in APRIL.

Questions 1160 – 1170. Record the use of oral or systemic corticosteroid courses the participant has had within the past 12 months. If the number of courses is greater than or equal to 5, he/she is not eligible to participate in APRIL.

Question 1180. Record the use of oral or systemic corticosteroid for any reason within the past 2 weeks.

Question 1190. Record the use of antibiotics during the past 4 weeks.

Questions 1200 – 1230. Record the use of daily controller therapies taken by the participant during the past 12 months. If the response to Q1200 is 'No' skip to Q1710. Otherwise, complete Q1210. If the participant has been on daily controller therapy for greater than or equal to 9 months out of the past 12 months, he/she is not eligible to participate in APRIL.

Questions 1240 – 1700. 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 the response to Q1240 is NO, skip to Question 20. The participant should enter a 2-week Run-In period.

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, he/she is not eligible to participate in APRIL.

If none of the doses are greater than the limit, but the participant has been using any controller therapy during the last 4 weeks, the participant needs to stop the controller medication and enter a 4 week Run-In period.

Questions 1710 - 1770. The participant must have had:

- at least 3 wheezing episodes in the past 12 months and at least one of them must have been clinically significant **OR**
- the participant must have had at least 2 wheezing episodes in the past 12 months **AND** both episodes were clinically significant **OR**
- the participant must have had 1 or 2 wheezing episodes AND at least 1 was a clinically significant wheezing episode **AND** the participant used a daily controller therapy for at least 4 months (Q1220 = 1).

Question 1780. If the participant has significant developmental delay or failure to thrive he/she is not eligible to participate in APRIL.

Questions 1790 – 1840. 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 2 or more times, has had daily symptoms or 2 or more nocturnal awakenings during the past 2 weeks, has experienced respiratory failure resulting in mechanical ventilation or resulting in a hypoxic seizure, 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 APRIL.

Question 1850. If there is any other reason why the participant cannot be included in the study and the response to Q1850 is 'Yes', please provide a description of the reason in Q1850D.

Question 1860. 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.

### 4.2.3 APRIL Eligibility Checklist 2 (P2_ELIG2)

**Purpose:** This eligibility form is completed during Visit 2. The purpose is to determine the eligibility of a participant based on medication use during the run-in period, asthma related symptoms during the run-in period, and diary adherence during the run-in period.

**Who:** An AsthmaNet Coordinator completes the form.

**When:** Visit 2.

Form Instructions:

For further guidance refer to the Eligibility Criteria in Section 2.12 of the APRIL MOP.

Questions 1000 - 1010. If the participant has used any asthma medication other than albuterol, oral corticosteroids or anti-biotics since Visit 1 he/she is not eligible to participate in the study.

Question 1015. Record the number of days between the Visit 1 visit date and the Visit 2 visit date. If the participant is in a 2 week Run-In, all days should be used (excluding today and Visit 1 day). If the participant is in a 4 week Run-In, only the last 14 days should be used (excluding today) and the count should be 13 days.

Question 1020. Review the Run-In Diary Cards and complete this question regarding the asthma-related symptoms or albuterol use recorded by the parent/guardian for the past 2 weeks. Do not count any day more than one. If P2_DIARY_RUNIN Q1020 is greater than or equal to 2, count that day. If P2_DIARY_RUNIN Q1030 – Q1080 is greater than or equal to 1, count that day.

Questions 1030 – 1040. Calculate the average number of days with asthma-related symptoms or albuterol use and record in Q1030. If Q1030 is greater than or equal to 4, the participant is not eligible to continue in APRIL.

Questions 1050 – 1060. Review the Run-In Diary Cards and complete these questions regarding night time awakenings recorded on the P2_Run-In Diary Card during the past two weeks. Do not count any night more than once. If P2_DIARY_RUNIN Q1000 OR Q1010 is greater than or equal to 1, count that night. If the number of night-time awakenings recorded in Q1050 is greater than or equal to 2, the participant is not eligible to continue in APRIL.

Questions 1070 - 1090. Complete these questions regarding the participant's diary card adherence during the last 2 weeks. The diary card questions that count towards adherence include Q1000 – Q1080. If the participant's adherence is less than 80%, he/she is not eligible to participate in the study.

Question 1100. If there is any other reason why the participant should not be included in the study and the response to Q1100 is 'Yes', please enter a description in Q1100D.

Question 1110. If the participant is ineligible based on P2_ELIG2 form, please complete P2_TERMR form.

### 4.2.4 APRIL Laboratory Tests (P2_LAB)

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

**Who:** An AsthmaNet Coordinator completes the form.

**When:** Packet form at Visits 2, 9, 21 and single form at Visits 2 – 8, 21.

Form Instructions:

The Laboratory Tests (P2_LAB) form can be entered into the database as a packet form at Visits 2, 9 and 21 and as a single form at Visits 2 – 8 and V21. If Nasal Samples are collected by the parent/guardian at home between visits, the AsthmaNet Coordinator records this information on the P2_ILLNESS form.

Questions 1000 – 1010. (VISIT 2 ONLY) Record the White Blood Count (WBC) and Eosinophil results from the samples collected at Visit 2. If blood is obtained after Visit 2, enter the form as a single form and mark entry errors unresolvable.

Question 1000. For the WBC, 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 P2_LAB form as 8000/cu.mm.

Question 1010. 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 - 1040. For clinic visits 2, 9, and 21 record whether the Nasal Sample was collected and the collection technique that was used. If Q1030 is answered 'Yes', complete Q1040. Otherwise, stop here (except for the St. Louis site).

ST. LOUIS ONLY:
Question 1050. Record the Throat Swab collection completed in the clinic at Visits 2, 9, or 21, and V3-V8, 8b, 8c, 8d if applicable. It would be completed at visits 3 – 8, 8b, or 8c, 8d if the visit occurred after the first APRIL illness was used, and if it has been at least 14 days since the last dose was taken.

Submit the original 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.

### 4.2.5 APRIL Persistent Symptoms (P2_PERS_SYMP)

**Purpose:** To record symptoms the participant has experience within the past 2 weeks.

**Who:** An AsthmaNet Coordinator completes the form.

**When:** This form is completed during the 2 week follow-up phone call.

Form Instructions:

This form is completed based on responses to the P2_PHONE_CONTACT completed during the scheduled Visit 3a – 8a phone calls. If the participant reported more than 8 days with wheeze or cough OR more than 2 night awakenings during the 2 week period prior to the scheduled phone call, the coordinator must schedule a follow up phone call and complete the P2_PERS_SYMP form at that time.

Question 1000. If the participant has had wheezing or cough during the past 2 weeks and the answer to Q1000 is 'Yes' complete Q1010. Otherwise, skip to Q1040.

Question 1010. If Q1010 is greater than 8 the participant is having persistent symptoms and has met Study Failure Criteria. Stop completion of the P2_PERS_SYMP form and complete the Study Failure form. Refer to Section 2.49 and Section 4.2.19 of the APRIL mop for more details.

Question 1040. If the participant has had night time awakenings greater than 2 during the past 2 weeks and the answer to Q1040 is 'Yes' complete Q1050. Otherwise, skip to Q1020.

Question 1050. If Q1050 is greater than 2 the participant is having persistent symptoms and has met Study Failure Criteria. Stop completion of the P2_PERS_SYMP form and complete the Study Failure form. Refer to Section 2.49 and Section 4.2.19 of the APRIL mop for more details.

Questions 1020 – 1030. If the participant has had to slow down his/her play or activities during the past 2 weeks due to asthma symptoms and the answer to Q1020 is 'Yes' complete Q1030. Otherwise, skip to Q1060.

Questions 1060 – 1070. If the participant has taken albuterol (excluding pre-exercise) during the past 2 weeks and the answer to Q1060 is 'Yes' complete Q1070. Otherwise, stop completion of the form here.

### 4.2.6 APRIL Phone/Visit Symptom Assessment (P2_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 – 8a.

Form Instructions:

Questions 1000 – 1010. If the participant was absent from school or daycare due to breathing problems during the past 2 weeks and the answer to Q1000 is 'Yes' complete Q1010. Otherwise, skip to Q1020.

Questions 1020 – 1030. If the participant's parent/guardian was unable to go to work or school due to the child's breathing problems during the past 2 weeks and the answer to Q1020 is 'Yes' complete Q1030. Otherwise, skip to Q1040.

Questions 1040 – 1050. If the participant has been to a doctor for breathing problems during the past 2 weeks and the answer to Q1040 is 'Yes' complete Q1050. Otherwise, skip to Q1060.

Question 1060. If the participant been to an ER/urgent care facility for breathing problems during the past 2 weeks, refer to Section 2.3 of the APRIL MOP for further details.

Question 1070. If the participant has been hospitalized for breathing problems during the past 2 weeks, refer to Section 2.3 of the APRIL MOP for further details.

Questions 1080 – 1090. If the participant has had wheezing or cough during the past 2 weeks and the answer to Q1080 is 'Yes' complete Q1090. Otherwise, skip to Q1100. Q1090 is greater than 8, a follow up phone call should be scheduled for 2 weeks to assess if the child is having persistent symptoms. The Persistent Symptoms (P2_PERS_SYMP) form should be completed during this phone call.

Questions 1100 – 1110. If the participant has had night time awakenings due to asthma during the past 2 weeks and the answer to Q1100 is 'Yes' complete Q1110. Otherwise, skip to Q1120. If Q1100 is greater than 2, a follow up phone call should be scheduled for 2 weeks to assess if the child is having persistent symptoms. The Persistent Symptoms (P2_PERS_SYMP) form should be completed during this phone call.

Questions 1120 – 1130. If the participant has had to slow down his/her play or activities during the past 2 weeks due to asthma symptoms and the answer to Q1120 is 'Yes' complete Q1130. Otherwise, skip to Q1140.

Questions 1140 – 1150. If the participant has taken albuterol (excluding pre-exercise) during the past 2 weeks and the answer to Q1140 is 'Yes' complete Q1150. Otherwise, skip to Q1160.

Questions 1160 – 1170. If the participant has started APRIL therapy since the last visit or phone contact, and the answer to Q1160 is 'Yes', complete Q1170. Otherwise stop completion of the form with Q1160.

If the usage recorded in Q1160 and Q1170 was the participant's fourth usage of APRIL therapy and APRIL treatment failure has not been achieved, then the participant should be termed from APRIL.

### 4.2.7 APRIL Respiratory Illness Follow-up Phone Contact (P2_ILLNESS)

**Purpose:** This form collects information on the start of the illness and assesses the severity of the participant's breathing problems, shortness of breath and wheezing since the start of the illness.

**Who:** An AsthmaNet coordinator completes this form

**When:** Completed within 72 hours of starting the APRIL medication.

Form Instructions:

This form is completed when the parent/guardian calls within 72 hours of beginning the APRIL medication. This form can only be entered as a single form. The visit number should be the same as the last completed visit and the visit date is the date that the phone call occurred.

Question 1000. The respondent is the person answering the questions from the coordinator. It is preferred that the parent/legal guardian be the contact person for the completing the form, but if necessary, another respondent may answer the questions

Question 1010. Record the date the illness started.

Questions 1020 – 1060. Ask each question to the parent/legal guardian (other respondent) and record their response. Each response should indicate the symptoms since the start of the illness.

Questions 1070 – 1110. These questions refer to the study medication usage by the participant since the start of the illness. If the parent/guardian indicates the APRIL medication has not been started and the answer to Q1070 is 'No', instruct them to start the APRIL medication immediately and skip to Q1110. Otherwise, complete Q1080. Record the date and time the APRIL medication was started in Q1080 and Q1090.

Question 1130 – 1170. These questions refer to the nasal sample collection performed by the parent/guardian since the start of the illness. If the parent/guardian indicates that the nasal sample was not collected and the answer to Q1130 is 'No', instruct them to collect a nasal sample immediately.

### 4.2.8 APRIL Run-In Diary (P2_DIARY_RUNIN)

**Purpose:** To record daily symptoms and medication use during the run-in period.
.

**Who:** The parent/legal guardian completes the form.

**When:** Visit 2.

Form Instructions:

See Section 2.46 'Diary Cards for information on initiating the Diary Cards.

The participant should complete the Run In Diary Card on a daily basis during the run-in period. At Visit 1, carefully review the "How to Complete the APRIL Run-In Diary Card" (P2_HTDIARY_RUNIN) instructions with the participant's parent/legal guardian before distributing the Diary Cards. The APRIL Run-In Diary Cards are distributed at Visit 1 and collected and entered into the database at Visit 2.

Questions 1000 - 1010. These questions are to be completed in the morning. The Parent/legal guardian should refer to the time from when the child was put to bed for the night until he/she awoke in the morning.

Questions 1020 – 1080. These questions are completed in the evening after the child goes to bed. The parent/legal guardian should refer to the time since the child awoke in the morning of each day. For Q1070 - Q1080 remind the parent that they should not count albuterol given for pre-treatment prior to exercise or play.

Question 1060. ***Yes*** or ***No*** should be circled for Question #6 and a response should be recorded for each diary day.

**Distributing** the Diary Cards to the participant:

Complete the upper left and right-hand corner of each card. Write the return visit number and the proposed return visit date on which the Diary Cards will be returned.

Complete the days and dates (month and day) for each day on each card and be careful not to miss any days. Check the calendar for the last day in a given month.

Remind the parent/legal guardian to complete all applicable sections on the card. The Diary Cards must be legible and completed in blue or black ink.

**Collecting** the Diary Cards from the parent/legal guardian:

Make sure the 'Return Visit Number' and 'Return Visit Date' match the current visit number and current date.

Review the Diary Cards for completeness and legibility. The Diary Cards must be completed in blue or black ink. If necessary, have the participant's parent/legal guardian recopy the cards before they are sent to the DCC.

The back of the Diary Card has been designed to help the participant's parent/legal guardian record non-study medications or medical problems that happened during the week. It is an optional tool that can be used throughout the study to keep track of illnesses, injuries and medications between study visits.

Non-Study Medications: The parent/legal guardian can record any prescription or over-the-counter medications that he or she has taken during the week.

Medical Problems: The parent/legal guardian can indicate and rate the severity of any medical problems he or she has during the week and rate the severity of each problem as mild, moderate, or severe.

The Diary Card is a repeating form, which means that more than one day can be recorded within the same visit. Record ID's were created in the database to uniquely identify each day. The record ID for the Diary Card is date. Record ID's cannot be repeated within a visit. When entering a Diary Card the user must first enter the month and day of the first diary day, the diary days thereafter the diary date will auto-populate for the user once the final field of the record is entered.

When collating this form, all Diary Card(s) returned on the same date should be organized together as one form in date order but the Diary Card(s) should not be stapled together. Complete the 'Form Page __ of __' fields at the bottom center of each page. For example, if three Diary Card(s) are returned, the first Diary Card should be numbered 'Form Page 1 of 3', the second as 'Form Page 2 of 3', and the third as 'Form Page 3 of 3'.

A photocopy of the Diary Card(s) should be made and filed in the participant's study folder, while the original is sent to the DCC.

### 4.2.9 APRIL Run-In Termination of Study Participation (P2_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 P2_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 1010. Indicate the primary reason the participant has withdrawn from the study. If Q1010 is answered 8 or 9 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.

If the participant if 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 P2_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.

### 4.2.10 APRIL Scheduled Medications (P2_MED)

**Purpose:** To record the dispensation of study drugs.

**Who:** An AsthmaNet Coordinator completes the form.

**When:** Visit 2, 3 – 8.

Form Instructions:

The Scheduled Medications form must be completed ***every*** time study drugs are dispensed at scheduled or unscheduled visits. The form will be entered as a packet form ***only*** at Visit 2 and as a single form at Visits 3 – 8 as needed

An unscheduled visit is a visit which occurs between two scheduled visits. At unscheduled visits (between Visits 2 through 8) where drug is dispensed, enter the Scheduled Medications (P2_MED) form into the database as a single form. The visit date should be the date the form is completed and the visit number should be the last visit number completed.

**Labels.** Affix the labels to the APRIL Scheduled Medications (P2_MED) form.

After affixing the labels and signing and dating the source documentation box, copy the drug label number onto the spaces provided in Questions 1030, 1060, 1090, 1120 and 1150.

**DO NOT COMPLETE Q1150 AFTER THE PARENT HAS CONSENTED TO STOP OCELOT.**
To verify that the information collected on this form is correct; the Clinic Coordinator should sign and date the source documentation box in Q1160 and 1170.

### 4.2.11 APRIL Prednisolone Medication (P2_PRED)

**Purpose:** To record prednisolone medication use during study.

**Who:** An AsthmaNet Coordinator completes the form.

**When:** As a single form at Visits 2 – 9.

Form Instructions:

This form should be completed when 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.

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

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.

### 4.2.12 APRIL Study Treatment Questionnaire (P2_APRIL_TRTQX)

**Purpose:** To assess how well controlled the child'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 or clinic coordinator thinks the child was receiving during the study.

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

**When:** Visits 2 – 9 when a participant completes/leaves the study.

Form Instructions:

This form can be entered as a packet form at Visit 9. This form can also be entered as a single form at Visits 2 – 8 if the participant withdraws consent to participate in the study or is termed early for any other reason.

Page 2 should be completed by the clinic coordinator. Q1110 is on the last page and should be completed prior to the parent/guardian completing Q1000 – Q1100 so that the Clinic Coordinator is not influenced by the parent/guardian responses.

After a randomized participant has completed the APRIL study or his/her participation was terminated, give the APRIL Study Questionnaire (P2_APRIL_TRTQX) to the participant's parent/guardian to complete. Do not give the parent/guardian page 2 of the form.

Page 1 (Q1000 – Q1100) is completed by the parent/guardian. Please be sure that the parent/guardian cannot see the response to Q1110 (coordinator completed question) when completing Q1000 – Q1100.

This form should NOT be reviewed with the parent/guardian during the clinic visit following the guidelines outlined in Section 5.1.6 of the Standard MOP. This form is separated and completed individually to avoid undue influence on the responses

### 4.2.13 APRIL Symptoms of Respiratory Illness Survey (P2_SURVEY)

**Purpose:** This form is completed to assess the symptoms of participant's respiratory illnesses

**Who:** An AsthmaNet coordinator completes the form.

**When:** Visit 1 and 2.

Form Instructions:

This form is completed at Visit 1 and Visit 2 and can only be entered as a packet form.

The APRIL Symptoms of Respiratory Illness Survey (P2_SURVEY) will be used to help parents identify their child's symptoms that signal the onset of a respiratory illness. This survey is very important in individualizing the participant's action plan.

The APRIL Symptoms of Respiratory Illness Survey (P2_SURVEY) will be completed at Visit 1 by the coordinator. The parent's will be given a copy of the symptom list (P2_SYMPLIST) to help them answer the questions. The APRIL Symptoms of Respiratory Illness Survey (P2_SURVEY) will be re-administered by the coordinators at Visit 2. The answers given by the parents at Visit 2 will be used on the APRIL Action Plan. Data from the APRIL Symptoms of Breathing Illness Questionnaire (P2_SURVEY) will be entered at both visits.

Questions 1000 – 1010. Ask the parent/legal guardian what is usually the very first symptom that leads them to believe their child is starting to get sick and record the response in the appropriate space on the form. They will choose the symptoms from the list (P2_SYMPLIST) provided by the Clinic Coordinator.

Question 1020. Ask the parent/legal guardian if there is usually a symptom they notice that makes them very certain the illness will lead to significant breathing problems. If Q1020 is answered 'No', skip to Q1080. Otherwise, complete Q1030 and Q1040.

Questions 1050. Ask the parent/legal guardian if there is usually a second symptom that they notice that makes them very certain the illness will lead to significant breathing problems. If the answer to Q1050 is 'No', skip to Q1080. Otherwise, complete Q1060 and Q1070. .

Questions 1080 – 1190. Ask the parent to rate each of the symptoms when the child has a respiratory illness. Each symptom should have one response selected

### 4.2.14 APRIL Symptoms of Respiratory Illness (P2_SYMP_CC)

**Purpose:** This form assesses the symptoms of participant's respiratory illnesses

**Who:** An AsthmaNet coordinator completes the form.

**When:** Visits 2 – 9, 20.

Form Instructions:

This form is a single form only and can be entered at Visits 2 - 9.

This form is completed over the phone within 72 hours of beginning the respiratory illness medication. This form is very similar to the P2_SURVEY form but instead of asking what usually happens, it asks the parent what actually happened with this specific illness. Instruct the parent/legal guardian to refer to the Symptoms of Breathing Illness (P2_SYMP_PARENT) form and record their responses onto this form using the symptom codes provided on P2_SYMPLIST.

Questions 1000 – 1010. Ask the parent/legal guardian what was the very first symptom that led them to believe their child was starting to get sick and record the response in the appropriate space on the form. The parent/legal guardian will be giving the specific symptom based on their response to the APRIL Symptoms of Breathing Illness (P2_SYMP_PARENT) form they completed at home. The code for this response will be entered into Q1010. The coordinator will complete Q1000 based on this specific response indicated by the parent, finding the code for the general category on the symptoms of list (P2_SYMPLIST) handout.

Questions 1020 – 1030. Ask the parent/legal guardian what was the most important symptom he/she noticed that made them feel certain this illness would lead to significant breathing problems and record the response in the appropriate space on the form. The parent/legal guardian will be giving the specific symptom based on their response to the APRIL Symptoms of Breathing Illness (P2_SYMP_PARENT) form they completed at home. The code for this response will be entered into Q1030. The coordinator will complete Q1020 based on this specific response indicated by the parent, finding the code for the general category on the symptoms of list (P2_SYMPLIST) handout.

Questions 1040 – 1070. Ask the parent/legal guardian, what were the two most important symptoms that led them to start the study medication. The parent/legal guardian will be giving the specific symptoms based on their responses to the APRIL Symptoms of Breathing Illness (P2_SYMP_PARENT) form they completed at home. The code for these responses will be entered into Q1040 and Q1060. The coordinator will complete Q1050 and Q1070 based on the code for these specific responses indicated by the parent, finding the general categories on the symptom list (P2_SYMPLIST) handout.

Questions 1080 – 1190. Ask the parent to rate each of the symptoms when the child has a respiratory illness. Each symptom should have one response selected

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 header information.

### 4.2.15 APRIL Treatment Failure (P2_TRTFAIL)

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

**Who:** An AsthmaNet Coordinator completes this form.

**When:** This form is completed when a participant has met the treatment failure criteria at Visits 2 – 9.

Form Instructions:

For more details on Treatment Failures, see the Treatment Failure discussion in Section 2.6 of the APRIL MOP.

Complete the APRIL Treatment Failure (P2_TRTFAIL) form ***only*** if the participant has met the treatment 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 APRIL Treatment Failure (P2_TRTFAIL) form must be entered into the database as a single form.

If the participant is deemed a treatment failure at a study visit complete the current visit number and current date on the APRIL Treatment Failure (P2_TRTFAIL) form.

Questions 1000 – 1040. If the answer to any of these questions is 'Yes' the participant is a treatment failure. If Q1040 is answered 'Yes', please provide a detailed description in Q1040D.

Question 1050. If any of the shaded boxes are selected (Q1000 - Q1040), the participant is a treatment failure.

Question 1060. Indicate the date treatment failure status occurred.

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 FONEMED (P2_FONE_MED)

**Purpose:** To record the results of a participant call with FoneMed

**Who:** An AsthmaNet Coordinator completes the form .

**When:** Any time a report is sent to the site from FONEMED.

Form Instructions:

This form is completed by the clinic coordinator each time a report is received from FoneMed indicating that a participant has placed a called to the FoneMed Call Center.

Complete the FONEMED (P2_FONE_MED) form ***only*** when a report is faxed to the clinical center by the FoneMed Call Center. If the form is completed between visits, specify the ***Last Visit Number completed*** and ***Current Date*** in the upper right-hand corner. The FONEMED (P2_FONE_MED) form must be entered into the database as a single form.

Question 1000. Record the date the call was made to the FoneMed Call Center.

Question 1010. Check the primary reason the phone call was made. The only reason to go on and complete this form would be if the child was having respiratory symptoms, number 1 box is checked.

If the call was to reschedule or cancel a clinic visit, then ***stop*** completion of the form.

If the call was due to the participant starting APRIL medication, ***stop*** completion of the form. If the parent has not called into the clinical center within 72 hours of starting the APRIL medications, the clinical coordinator must contact the parent/guardian.

If the response to Q1010 is 'other', then ***stop*** completion of the form and specify the reason for the call in Q6000 on page 2 of this form. Refer to the APRIL MOP for further details.

Question 1020 and 1030. Respond as to whether the participant was taking either APRIL or OCELOT medications.

**DO NOT COMPLETE Q1040 AFTER THE PARENT HAS CONSENTED TO STOP OCELOT.**
Question 1040. If the participant had symptoms that required immediate medical attention [severe respiratory distress, including (but not limited to) nasal flaring, retractions not immediately responsive to bronchodilator, altered level of consciousness, cyanosis, signs of dehydration, rapidly progressive symptoms], and Q1040 is answered 'Yes', complete Q1050. Otherwise, skip to Q1060.

Question 1050. If the participant was referred to an urgent care facility or emergency department for evaluation, the response to Q1050 should be 'Yes', and coordinator should stop completion of the form. Refer to the APRIL MOP for further details. Otherwise, proceed to Q1060.

Question 1060. If the participant is a study failure, the response to Q1060 should be 'Yes' and the coordinator must complete the Study Failure (P2_STUDY_FAIL) form.

Question 1070. If the participant is an APRIL treatment failure, the response to Q1070 should be 'Yes' and the coordinator must complete the APRIL Treatment Failure (P2_TRTFAIL) form.

**DO NOT COMPLETE Q1080 AFTER THE PARENT HAS CONSENTED TO STOP OCELOT.**

Question 1080. If the parent or guardian was instructed to start the OCELOT medications, the response to Q1080 should be 'Yes' and the coordinator must complete the OCELOT scheduling (P2_OCELOT_SCHED) form.

Question 1090. If the parent or guardian was instructed to start the APRIL medications, the coordinator MUST contact them within 72 hours to complete APIRL Respiratory Illness Follow-Up Contact (P2_ILLNESS) form and the APRIL Symptoms of Respiratory Illness (P2_SYMP_CC) form.

Question 1100. If the participant had additional problems that the parent or guardian wanted to discuss with the on-call physician, please provide a description in Q6000.

The FoneMed form is entered into the database as a single form.

### 4.2.17 Pre-School Asthma Symptom Diary (P2_PAD)

**Purpose:** To record participant's daily symptoms during an illness.

**Who:** Parent/guardian completes the form.

**When:** Visits 2 – 9 whenever using APRIL medications

Form Instructions:

The Pre-School Asthma Diary (and corresponding Albuterol Log on reverse side) should be completed whenever APRIL medications are being used. The Diary Card is **one page per day** and the parent/guardian should continue to complete Diary Cards **until the participant is symptom-free for 2 days**.

Coordinator must update Q1190 on the P2_PAD prior to distribution. Please cross out OCELOT and write in prednisolone.

The back of each Diary Card page contains an Albuterol Log that can be used by the parent/guardian to track when the participant uses albuterol.

The date should be recorded on each diary card in the 'Today's Date' field.

Questions 1000 – 1060. Parent/Guardian should record HOW OFTEN the child experienced each of the symptoms in the last 24 hours. A response should be checked for each symptom.

Questions 1070 – 1160. Parent/Guardian should record the DEGREE to which each symptom was a problem observed in the child in the last 24 hours.

Question 1170. Parent/Guardian should record any change in the child's asthma over the past 24 hours, either an improvement or worsening of symptoms.

Questions 1180 – 1210. Record the number of albuterol treatments given within the past 24 hours, whether prednisolone was started, how much time the respondent has spent with the child during the past 24 hours, and who the respondent is.

**Collecting** the Diary Cards from the parent/legal guardian:

Make sure the 'Return Visit Number' and 'Return Visit Date' match the current visit number and current date.

Review the Diary Cards for completeness and legibility. The Diary Cards must be completed in blue or black ink. If necessary, have the participant's parent/legal guardian recopy the cards before they are sent to the DCC.

The P2_PAD is a repeating form, which means that more than one day can be recorded within the same visit. Record ID's were created in the database to uniquely identify each day. The record ID for the P2_PAD is 'today's date'. Record ID's cannot be repeated within a visit. When entering a P2_PAD the user must enter the entire date for the 'today's date' field on every diary card.

When collating this form, all Diary Card(s) returned on the same date should be organized together as one form in date order but the Diary Card(s) should not be stapled together.

A photocopy of the Diary Card(s) should be made and filed in the participant's study folder, while the original card(s) is sent to the DCC.

### 4.2.18 Study Failure (P2_STUDY_FAIL)

**Purpose:** To record the date and the events that occurred when a participant is deemed a 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 – 9.

Form Instructions:

For more details on Study Failures, see the Study Failure discussion in Section 2.49 of the APRIL MOP.

Complete the Study Failure (P2_STUDY_FAIL) form ***only*** if the participant has met the 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 Study Failure (P2_STUDY_FAIL) form must be entered into the database as a single form.

If the participant is deemed a study failure at a study visit complete the current visit number and current date on the Study Failure (P2_STUDY_FAIL) form.

Questions 1000 – 1110. If the answer to any of these questions is 'Yes' the participant is a study failure. If Q1110 is answered 'Yes', please provide a detailed description in Q1110D.

Question 1120. If any of the shaded boxes are selected (Q1000 - Q1110), the participant is a treatment failure.

Question 1130. Indicate the date treatment failure status occurred.

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.

The Study Failure Form (P2_STUDY_FAILURE) should be completed and the participant should be evaluated within 72 hours and assigned study failure status. A safety visit should occur within 72 hours. Visit 9 should be scheduled 14 days after study failure.

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### 4.2.19 Termination of Study Participation (P2_APRIL_TERM)

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

**Who:** An ASTHMANET Coordinator completes the form.

**When:** May be completed at or between Visits 2 - 8 as a single form or at Visit 9 as a packet form. It would be completed for Visit 2 only if the participant had been randomized.

Form Instructions:

A participant should be terminated from the study when he/she is deemed ineligible, parent/guardian has withdrawn consent, 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 in the key variable information.

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

The participant has completed the APRIL study if.
She/he has used <4* APRIL courses over the 78 week follow up She/he has used all 4* APRIL courses and is not a treatment failure or study failure. The form would be entered as part of the Visit 9 follow up visit She/he is deemed a treatment failure or study failure.
*For participants enrolled prior to the addition of the 4$^{th}$ APRIL treatment, this will remain 3.

If a participant was deemed a study failure, Visit 9 will occur 14 days after the study failure was identified and the P2_APRIL_TERM form will be completed as part of the Visit 9 packet at that time. The participant has not completed the APRIL study in this case and the response to Q1000 should be 'No; and Q1010 should be completed.

If the participant was deemed a treatment failure (and not a study failure), the P2_APRIL_TERM form is completed at the time the treatment failure is identified and Q1000 should be answered 'Yes', and Q1010 not completed.
Question 1010. Indicate the primary reason the participant has withdrawn from the study. If Q1010 is answered 3, 4, 7, 12, or 14 an additional explanation is required in Q1010D. If the participant experienced a serious adverse event, please complete a Serious Adverse Event Reporting (SERIOUS) form.

**DO NOT COMPLETE Q3 AND Q3A AFTER THE PARENT HAS CONSENTED TO STOP OCELOT.**

Question 1020 - 1030. Record if the participant has proceeded to OCELOT. If Q1020 is answered 'No', complete Q1030. Otherwise, skip to Q1040.

If the response to Q1030 is 'Yes' Visit 9 should be scheduled 14 days after the last dose of APRIL therapy.

Questions 1040 – 1070. 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 Q1060 to verify that all data collected for this participant are correct to the best of their knowledge.

## 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 APRIL study administrative forms, the corresponding form code and related instructions.

| Administrative Form Name | Form Code |
|---|---|
| APRIL Back-Up Randomization | P2_BACKUP |
| APRIL Drug Dispensing Log: Albuterol MDI | P2_ALB_MDI |
| APRIL Drug Dispensing Log: Albuterol Vials | P2_ALB_VIAL |
| APRIL Drug Dispensing Log: APRIL/OCELOT Medications | P2_DRG_AO |
| APRIL Medication Tracking Form | P2_APR_TRK |
| APRIL Nasal Mucus Collection Log | P2_NASAL_LOG |
| APRIL Participant Assignment Log | P2_LOG |
| APRIL Drug Accountability Log: Prednisolone | P2_PRED_LOG |
| APRIL Visit Procedure Checklists | P2_VISIT1, P2_VISIT2, P2_VISIT3_8, P2_VISIT3a_8a, P2_VISIT9 |

### 4.3.1 APRIL Backup Randomization (P2_BACKUP)

**Purpose:** To document a manual backup randomization and to record the assigned drug bottle number.

**Who:** An AsthmaNet Coordinator completes the form.

**When:** When you are unable to access the computer randomization module and cannot reach the DCC to perform a randomization.

Form Instructions:

Completion of the Backup Randomization (P2_BACKUP) form is **ONLY** necessary in the event the AsthmaNet Coordinator is unable to access the computer randomization module **AND** they are also unable to reach the DCC to perform a randomization.

If the answer to Question #5 is shaded, then proceed with the backup randomization.

To verify that the information collected on this form is correct; the Clinic Coordinator should sign and date the source documentation box.

Upon completion, fax this form ***immediately*** to the APRIL Primary Data Manager at (717) 531-4359. Call the AsthmaNet voicemail (717) 531-3663 and leave a message. For use only at the Clinical Center, this form is not data entered.

### 4.3.2 APRIL Drug Dispensing Log: Albuterol MDI (P2_ALB_MDI)

**Purpose:** To record the Subject ID number, the Subject's initials, the date the pulmicort is dispensed and returned, the dispenser's and the collector's initials, and whether the MDI Albuterol was returned.

**Who:** An AsthmaNet Coordinator completes the log

**When:** When MDI Albuterol is dispensed, returned, or lost between visits

Form Instructions:

When MDI Albuterol is dispensed, returned, or lost, complete the appropriate part of this log.

When MDI Albuterol is dispensed, record the date dispensed, the Subject ID number, the Subject's initials, and the dispenser's initials in the next available row on the log.

When MDI Albuterol is returned, record the date returned, and the collector's initials. If MDI Albuterol is lost or not returned, check the corresponding column to ensure that the records are accurate. Indicate the reason the MDI Albuterol was not returned, if known.

Shipment 1, in the title of the drug log, will be updated in sequential order as new shipments are sent to your center.

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.

### 4.3.3 APRIL Drug Dispensing Log: Albuterol VIALS (P2_ALB_NEB)

**Purpose:** To record the Subject ID number, the Subject's initials, the date the pulmicort is dispensed and returned, the dispenser's and the collector's initials, and whether the Nebulized Albuterol was returned.

**Who:** An AsthmaNet Coordinator completes the log

**When:** When nebulized Albuterol is dispensed, returned, or lost between visits

Form Instructions:

When nebulized Albuterol is dispensed, returned, or lost, complete the appropriate part of this log.

When nebulized Albuterol is dispensed, record the date dispensed, the Subject ID number, the Subject's initials, and the dispenser's initials in the next available row on the log.

When nebulized Albuterol is returned, record the date returned, and the collector's initials. If nebulized Albuterol is lost or not returned, check the corresponding column to ensure that the records are accurate. Indicate the reason the nebulized Albuterol was not returned, if known.

Shipment 1, in the title of the drug log, will be updated in sequential order as new shipments are sent to your center.

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.

### 4.3.4 APRIL/OCELOT Drug Dispensing Log: Study Medications (P2_DRG_AO)

**Purpose:** To record the date the study medication is dispensed and returned, the dispenser's and the collector's initials, the medication bottle number(s) and the weight of the bottle(s) if the study medications were returned.

**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 APRIL medication bottle number(s) for the initials APRIL study medication.

If the participant uses the first medication for an illness during APRIL, the second medication bottle will be dispensed.

For participants enrolled prior to the addition of the 4$^{th}$ APRIL treatment who re-consent, the coordinator can edit the original APRIL Drug Dispensing Log: Study Medications (P2_DRG_AO) and handwrite the two bottle numbers for the 4$^{th}$ course on the form.

For participants enrolled after the change, please print the latest version (version 1.1, 05/17/2012). This version has two additional rows for the bottle numbers for Course 4. Record the OCELOT medication information in the second part of the table including the date dispensed, the dispenser's initials, and the OCELOT medication bottle number. When the study medications are returned, record the date returned, and the collector's initials. Also record the weight of the bottle(s). If the bottle is not returned, check the box in the last column on the log. If study medications are lost and replacement medications are needed record these on the log in the shaded rows marked with an asterisk. This replacement medication should be the exception rather than the rule.

For replacement medications due to the expiration dates, please print the latest version and complete the required information for each bottle dispensed on page 2.

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.

### 4.3.5 APRIL Medication Tracking Form (P2_APR_TRK)

**Purpose:** To record and track a participant's APRIL medication use.

**Who:** An Asthmanet Coordinator completes the form.

**When:** Update the form each time an APRIL medication is used.

Form Instructions:

Use this form to track APRIL therapy use during the treatment phase. Update the form each time an APRIL medication course is started or completed.

If four APRIL medication courses are initiated during the study and the participant does not initiate OCELOT therapy (i.e., the participant is not a treatment failure or study failure), study participation is complete. Visit 9 should be scheduled for 14 days after last APRIL dose was taken.

For participants enrolled prior to the addition of the 4th APRIL treatment who re-consent, the coordinator can edit the original APRIL Medication Tracking form (P2_APR_TRK) and handwrite the 4th course on the form.

For participants enrolled after the change, please print the latest version (version 1.1, 05/17/2012). This version has a row added for Course 4.

If the participant initiates OCELOT therapy (i.e., the participant is a treatment failure), complete P2_TRTFAIL and schedule Visit 20.

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

DO NOT forward to the DCC.

### 4.3.6 APRIL Nasal Mucus Collection Log (P2_NASAL_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 P2_NASAL_LOG for the participant ID. All samples collected during the study must be recorded on this log, whether in clinic or at home.

For participants enrolled prior to the addition of the 4th APRIL treatment who re-consent, the coordinator can edit the original APRIL Nasal Mucus Collection Log (P2_NASAL_LOG) and handwrite APRIL kit 4 on the back of the existing forms.

For participants enrolled after the change, please print the latest version (version 1.2, 05/17/2012). This version a second page added with two rows for the APRIL kit 4 dispensation.
A P2_LAB form should be completed and entered into the database for each visit (2, 9, 21) during which a clinic sample has been collected. The samples collected at home visits will be recorded on the P2_ILLNESS form which is entered as a single form whenever it is completed. .

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 APRIL Participant Assignment Log (P2_LOG)

**Purpose:** To track all participants enrolled in the APRIL study by their study-specific Participant ID numbers.

**Who:** An AsthmaNet Coordinator completes the form.

**When:** Visits 1 and 2, and as bottles are distributed throughout the study.

Form Instructions:

A Participant Assignment Log (P2_LOG) has been developed for Clinical Sites to use for recording the assignment of ID's. It includes columns for unique participant ID numbers, participant initials, participant's name, and medication bottle numbers (to be completed at Visit 2).

The first digit is the number of the AsthmaNet protocol. For APRIL this digit is 2.

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 (P2_LOG) **must** be used every time a **new** Participant ID number is assigned. The Participant Assignment Log (P2_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, complete the Assigned Bottle Numbers column with the participant's APRIL and OCELOT assigned bottle numbers.
If all 14 pages of the P2_LOG were printed at the start of the study, you can continue to use the existing assignment log. For participants enrolled prior to the addition of the 4th APRIL treatment who re-consent and for all participant who enroll/consent after the additional of the 4th APRIL treatment, you can write the additional numbers anywhere on the line for that participant that has an open space, i.e., in the participant name field, in the margin to the right of the OCELOT number, etc.

If all 14 pages of the P2_LOG were not printed at the start of the study **OR** you want to replace currently un-used pages of the existing P2_LOG, please be sure to print out the newest version of the P2_LOG (version 1.1, dated 5/17/12).

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.

### 4.3.8 APRIL Drug Accountability Logs: Prednisolone (P2_PRED_LOG)

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

**Who:** An AsthmaNet Coordinator completes the log

**When:** When 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.

### 4.3.9 APRIL Visit Procedure Checklists: P2_VISIT1, P2_VISIT2, P2_VISIT3_8, P2_VISIT3a_8a, P2_VISIT9

**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.

If a Treatment Failure occurs, enter the P2_TRTFAIL and P2_APRIL_TERM forms as single forms, and set forms for procedures not performed to missing.

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

This form is not entered during data entry.