
2.1	Acute Asthma Assessment Questionnaire	6
2.2	Adherence Issues	9
	FACTORS THAT AFFECT ADHERENCE	9
	IMPROVING ADHERENCE	10
	TOOLS FOR MONITORING AND IMPROVING ADHERENCE DURING THE BARD TRIAL	11
	COUNSELING FOR NON-ADHERENCE	13
2.3	Adverse Events.....	15
	DEFINITION AND REPORTING.....	15
	ICD-9 CODES	17
2.4	Appointments: Confirming and Scheduling.....	19
2.5	Asthma Attack/Exacerbation Kit	20
2.6	Asthma Control Questionnaire.....	23
	GENERAL INFORMATION	23
	ADMINISTRATION INSTRUCTIONS	23
	SCORING INSTRUCTIONS	25
2.7	Asthma Control Test	26
	GENERAL INFORMATION	26
	CHILDHOOD ASTHMA CONTROL TEST (CACT).....	28
	ASTHMA CONTROL TEST (ACT).....	28
2.8	Blood Samples and Tests	29
2.9	Certification.....	31
	STUDY COORDINATORS AND TECHNICIANS	31
	LICENSED MEDICAL PRACTITIONERS (LMPS)	32
	DATA ENTRY PERSONNEL.....	33
2.10	Cold History	34
2.11	Complete Blood Count (CBC).....	35
2.12	Concomitant Medications	36
2.13	Contact Information	40
2.14	Dosing Compliance	42
2.15	Drop-out Status (Treatment Period).....	46
	DEFINITION AND TREATMENT	46

DOCUMENTATION	46
SPIROTEL [®] AND COMPLIANCE ASSESSMENTS	47
2.16 Eligibility Criteria (Screening)	48
GENERAL SUMMARY.....	48
NIGHTSHIFT WORKERS AND OTHERS WITH ALTERED SCHEDULES.....	49
VISIT 0A - INCLUSION CRITERIA	50
VISITS 0A AND 0B: ASTHMA VERIFICATION INCLUSION CRITERIA	58
VISIT 0A – EXCLUSION CRITERIA	63
2.17 Eligibility Criteria (Randomization)	79
RANDOMIZATION ELIGIBILITY EVALUATION AT VISITS 0B, 0C, 0D	79
INCLUSION CRITERIA FOR RANDOMIZATION.....	80
EXCLUSION CRITERIA FOR RANDOMIZATION - EXACERBATIONS	86
EXCLUSION CRITERIA FOR RANDOMIZATION – VISIT 1	87
2.18 Genetics Blood Draw	89
2.19 Geographic Information Systems (GIS) Add-on Study	92
2.20 Home Environment Questionnaire.....	95
2.21 Household Socio-Economic Information Form	96
2.22 Informed Consent.....	97
2.23 Inhalation Technique Assessment.....	101
METERED DOSE INHALER (MDI) TECHNIQUE	101
DISKUS [®] TECHNIQUE.....	103
2.24 Inhaled Corticosteroid (ICS) Step-Down Groups and Assessment	105
VISIT 0A AND VISIT 0A1	105
CLASSIFICATION OF ASTHMA GUIDELINE STEP.....	106
COMPARATIVE DAILY ICS DOSAGES TABLE.....	107
ASSIGNMENT OF STEP-DOWN GROUP.....	109
ASSESSMENT FOR RUN-IN ICS STEP-DOWN TO 1XICS.....	110
2.25 Medical History	114
2.26 Methacholine Challenge	117
2.27 Missed Visits.....	121
2.28 Participant Assignment Log and Protocol Enrollment	124
2.29 Participant Identification Card.....	126

2.30	Participant Status Report.....	128
2.31	Perceived Stress Scale	131
2.32	Phone Contacts and BARD Contact Information Form.....	133
	RUN-IN PHONE CONTACTS	133
	POST-RANDOMIZATION PHONE CONTACTS.....	133
	BARD CONTACT INFORMATION FORM.....	134
2.33	Physical Exams	135
	ADULT PROCEDURES	135
	PEDIATRIC PROCEDURES	137
2.34	Prednisone Washout Requirements	139
	VISIT 0A	139
	VISIT 1 AND CROSS-OVER VISITS (4, 7, 10).....	139
	BASELINE VISITS (2, 5, 8, 11)	139
2.35	Pregnancy Test.....	141
2.36	Protocol Age Tracks.....	144
2.37	Quality of Life Questionnaires.....	146
	GENERAL INSTRUCTIONS	146
	ASTHMA QUALITY OF LIFE QUESTIONNAIRE FOR 12 YEARS AND OLDER (AQLQ_12).....	147
	PAEDIATRIC ASTHMA QUALITY OF LIFE QUESTIONNAIRE (PAQLQS)	148
	PEDIATRIC QUALITY OF LIFE INVENTORY (PEDSQL™)	149
	RAND IMPACT OF ASTHMA ON QUALITY OF LIFE SF-12 (RAND_IAQL_12)	150
2.38	Randomization.....	153
	VISIT 1 PROCEDURES.....	153
	VISITS 2-12 PROCEDURES.....	155
	BACKUP DISKUS® ASSIGNMENTS	157
	BACKUP RANDOMIZATION PROCEDURES	157
2.39	Recruitment.....	158
2.40	Re-Enrollment.....	159
	VISIT 0A SCREEN FAILURES	159
	AFTER A SUCCESSFUL VISIT 0A AND PRIOR TO RANDOMIZATION.....	160
	AFTER RANDOMIZATION IN BARD	162
2.41	Reference Peak Flow (PEF)	163
	GENERAL INFORMATION	163
	VISIT 0A	165
	VISITS 0A1, 0B, 0C, 0D, 1	167
	VISITS 2-12	169

2.42	Registration.....	171
2.43	Satisfaction Questionnaire	172
2.44	Serum ImmunoCAP, Total IgE and Cotinine Tests.....	174
	SUPPLIES	174
	BLOOD COLLECTION, PROCESSING, AND STORAGE PROCEDURES	175
	SHIPPING SCHEDULE.....	178
	CREATING A SHIPMENT.....	178
	PACKAGING SAMPLES FOR SHIPMENT TO ADX LABS AT NATIONAL JEWISH IN DENVER	179
	SHIPPING CHARGES	181
	ADX LABORATORY CONTACTS.....	181
	LAB TEST RESULTS.....	182
	CONTINGENCY PLAN FOR DIFFICULT BLOOD DRAWS.....	182
2.45	Significant Asthma Exacerbation.....	183
	DEFINITION	183
	DOCUMENTATION	184
	RESCUE ALGORITHM	185
	PREDNISONE COURSES.....	187
	TIMING OF ASTHMA EXACERBATIONS AND TRIAL MANAGEMENT	189
2.46	Spirometry.....	191
	GENERAL INSTRUCTIONS	191
	DEMOGRAPHICS.....	192
2.47	Spirotel®	197
	PARTICIPANT INSTRUCTION.....	197
	SPIROTEL® PERFORMANCE CHECK	199
	PREPARING THE BARD SPIROTEL® FOR PARTICIPANT USE	199
	SPIROTEL® QUALITY CONTROL PROCEDURES.....	207
	LOGGING DISPENSATION AND RETURN OF SPIROTEL® EQUIPMENT.....	208
	BARD ASTHMA MONITORING LOG (P5_ASTHMA_LOG).....	208
	DOWNLOADING THE SPIROTEL®	210
	GENERAL E-DIARY AND PEAK FLOW COMPLIANCE ASSESSMENTS	210
	CLEANING REQUIREMENTS	212
	CHARGING REQUIREMENTS	212
	BARD SPIROTEL® REPORTS	213
	BARD SPIROTEL® ALERTS	221
	SPIROTEL® TRAFFIC LIGHT SETTINGS.....	222
	HANDLING PARTICIPANT TRAVEL.....	223
2.48	Sputum Induction	224
	PRE-SPUTUM INDUCTION SPIROMETRY	224
	EXACERBATIONS AND PREDNISONE TREATMENT PRIOR TO VISIT 1	224
	SPUTUM PROCESSING CRITERIA.....	225
	SPUTUM SHIPMENTS TO SAN FRANCISCO	225
	INTER-SITE SPUTUM PROCEDURES.....	226

2.49	Study Handout Folder	231
2.50	Study Medications	235
	RESCUE MEDICATIONS.....	235
	RUN-IN MEDICATIONS	235
	DOUBLE-BLIND TREATMENT PERIOD MEDICATIONS.....	236
	OPEN-LABEL FLOVENT [®] DISKUS [®] TREATMENT PERIOD MEDICATION	237
	DISPENSING TWO DISKUSES [®] AT ONE VISIT.....	238
2.51	Study Treatment Questionnaires	239
	GENERAL INSTRUCTIONS	239
	PARTICIPANT STUDY TREATMENT QUESTIONNAIRE	239
	COORDINATOR STUDY TREATMENT QUESTIONNAIRE	240
2.52	Transfer Participants.....	242
2.53	Treatment (Arm) Failure.....	245
	DEFINITION.....	245
	DOCUMENTATION.....	246
	ADJUSTMENT OF TRIAL MEDICATION	249
	ALTERATION OF VISIT SCHEDULE	249
	COMPLIANCE MONITORING (P5_COMPLY)	250
2.54	Urine Cortisol:Creatinine Laboratory Test	251
2.55	Visit Schedule.....	259
2.56	Visit Windows	262
2.57	Withdrawals	265
	VISIT 0A SCREEN FAILURES	265
	WITHDRAWALS DURING THE RUN-IN (VISIT 0A THROUGH VISIT 1).....	266
	EARLY WITHDRAWALS AFTER RANDOMIZATION.....	267
2.58	Work Productivity and Activity Impairment Questionnaire	271

2.1 Acute Asthma Assessment Questionnaire

This questionnaire is applicable only for the BARD Age 12-17 and Age 18+ Tracks.

The Acute Asthma Assessment Questionnaire (AAAQ) has been developed by AsthmaNet investigators in an effort to better characterize asthma exacerbations. Participants are asked to report the primary precipitating factor for the exacerbation (common cold, allergies, pollution or chemical irritants, too little asthma maintenance medication (and/or lack of adherence), or exercise). They are also asked to review their activity impairment due to asthma, asthma symptoms, rescue bronchodilator use, asthma awakenings, general amount of impairment, and stress level caused by asthma over a 3-day (72 hour) period. This tool will help evaluate exacerbation severity with the goal of establishing correlation between acute scores and the risk of subsequent adverse events.

This questionnaire appears as Appendix 2 in the BARD protocol. It will be administered to BARD participants, ages 12 and up, at the time of an acute exacerbation, as well as at the next study visit following an exacerbation. This tool will allow us to assess impairment associated with exacerbations and the extent to which recovery has occurred by the time of the next study visit.

Visit 0A, at the time of an exacerbation, and at post-exacerbation study visits Administer Acute Asthma Assessment Questionnaire (AAAQ)

To introduce the AAAQ and to establish a baseline, this questionnaire will be administered to participants ages 12 and up at the time of Screen Visit A (Visit 0A). The administration of the AAAQ is one of the early procedures performed at Visit 0A, in conjunction with the administration of the other asthma outcome questionnaires such as the ACT. Study coordinators should observe the order of procedures as they are laid out on the visit procedure checklists.

If the participant experiences an exacerbation between study visits, he/she should complete the copy of the AAAQ that resides in the Asthma Attack Kit that he/she has at home (see the discussion of the Asthma Attack/Exacerbation Kit in this section for further details). This form should be returned to the performance site at the next study visit, and the visit ID should be the number of the previous completed visit (the visit date should match the date the participant supplied in the source documentation box at the time of completion). At the first post-exacerbation study visit, the AAAQ should be completed again (as follow-up to the event), and the visit ID on this form should be the number of the current visit. These forms will be entered as single forms. Note that these instructions also apply if the participant is seen at the performance site for exacerbation

conditions between visits and he/she will start a prednisone course the same day. In that case the form should be completed and turned in to study personnel the same day.

If an exacerbation is identified at the time of a regular study visit and prednisone is prescribed and will be started the same day, then the participant should complete the AAAQ at the time of the visit (rather than waiting to complete it at home). The visit ID on this form should be the number of the current visit. At the participant's next (post-exacerbation) study visit, he/she should complete the AAAQ again (as follow-up to the event), using the number of the current visit as the visit ID. These forms will be entered as single forms.

At post-exacerbation visits the AAAQ is not part of the normal visit procedures. It has been added to the visit procedure checklists with a prompt for completion only if the participant experienced an exacerbation at the prior study visit or between study visits. This questionnaire should be administered after the last asthma questionnaire that is part of the visit structure and prior to recording adverse events and concomitant medications. That is, this questionnaire should be administered directly after the ACT and any quality of life questionnaires at the visit. It is administered in conjunction with the WPAI:Asthma questionnaire. See the Work Productivity and Activity Impairment Questionnaire discussion in this section for further details.

See section 4 of this MOP for data management instructions for handling AAAQ forms completed at various times during the trial.

Administration Instructions

The AAAQ is completed by the participant. When administering the questionnaire, request that the participant complete the entire form and provide answers as completely and as accurately as possible. No stated or implied time limit should be set.

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

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

The participant should provide source documentation on the AAAQ form by providing his/her initials and the date/time in the source documentation box. Review the source documentation provided by the participant to ensure that the date and time are accurate before collecting the form.

2.2 Adherence Issues

Participants enrolled in the BARD protocol are involved in study activities every day throughout the trial. A great deal is asked of participants, and the quality of the study results is a function of the participants' level of protocol adherence. Each participant 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 a participant's adherence level.

Participant Characteristics

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

Performance 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 participant 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 participant's life and work, not the other way around

Improving Adherence

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

- Associate the regimen with daily activities

Encourage the participant to associate the required study activities with his/her daily routine to help make these steps automatic. This point can be reinforced while reviewing the Daily Activities handout (P5_DAILYACT) at each visit. Daily activities do not change over the course of the BARD trial.
- Educate the participant
 - Make sure the study activities are understood
 - Demonstrate the activities and have the participant do the same
 - Present instructions as clearly as possible
 - Have the participant repeat instructions
 - 'Quiz' the participant on the instructions
 - Teach the regimen in a stepwise fashion (i.e., step 1, step 2, step 3 for AM and PM activities)
 - Review 1 or 2 of the participant handouts at each visit
 - Use phone contacts to reinforce instructions and to ensure that the participant is performing activities correctly
- Provide positive reinforcement for excellent participant adherence
- Encourage support of family and friends during study participation
- Prepare participants for what will happen at upcoming visits
- Run the clinic on schedule and make good use of the participant'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 participant'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 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.

Tools for Monitoring and Improving Adherence during the BARD Trial

The following tools are in place to improve and/or monitor adherence (form name is given in parentheses, where applicable):

Visit Scheduler Reports: Missed visits and poorly timed visits are forms of non-adherence. In order to allow the participant and the performance site to plan for upcoming visits, visit scheduler reports have been programmed that list the ideal dates and lower and upper regular and extended windows for upcoming visits per the protocol.

See the Visit Schedule discussion in this section and Section 3 of this manual for further details on the creation of visit scheduler reports.

Visit Handouts and Study Folder: A series of handouts is presented and reviewed with the participant at Visit 0A and at various subsequent visits as new procedures and concepts are introduced. Because it may be difficult to comprehend and execute all instructions initially, and because activities may change during the study depending on the study phase, participants are asked to bring this folder to each visit for review and replacement of certain materials. A description of each of the BARD handouts can be found in the Study Handout Folder discussion in this section.

Spirotek[®] device: The spirotek[®] device is an electronic diary (e-diary) and peak flow monitor in one unit that stores all measurements the participant provides between visits in its memory. The device has been customized for AsthmaNet to provide a participant-friendly screen and flow of procedures. Participants will have defined windows during which they can do their morning and evening assessments, including answering their diary questions and performing their peak flow maneuvers. This device will not allow 'backfilling' or 'recall' of data; it must be used on schedule twice daily. This customization requires participants to be conscientious about their home activities in

order to meet the compliance thresholds required for the study. Data from the Spirotek[®] device are downloaded at each visit and reports are generated for review with the participant. The Spirotek[®] Participant Visit Report shows the dates and times associated with each AM and PM session, along with the diary data the participant entered and his/her PEF measurements. The Spirotek[®] Participant Compliance Report (P5_COMPLY) provides metrics on how frequently the participant carried out all required home procedures between visits. Knowing that e-diary data will be reviewed at the next visit will encourage participants to be more compliant.

Daily diary records help participants assume more responsibility for their own care. Recall bias is minimized, as the e-diary device requires participants to complete their AM and PM diary assessments each day.

Specific BARD ‘alerts’ have been programmed into the Spirotek[®] device. These alerts will prompt participants to take their morning and evening medications and to activate their asthma action plan when their peak flow is in the yellow or red zone. These alerts should improve adherence with several aspects of the protocol.

See the Spirotek[®] discussion in this section and the Spirotek[®] Manual of Operations in Appendix 6 of the AsthmaNet General Manual of Operations for further details.

Spirotek[®] Performance Check (SPIROTEL_PERF): Peak flow measurement and diary question completion are important daily activities. Regular measurement of lung function and assessment of symptoms and rescue inhaler use will help the participant identify when he/she is trending towards exacerbation and will increase adherence with the onset of appropriate treatment and reporting of these events.

Improper peak flow technique is a form of non-adherence. Coaching the participant on the proper technique early in the study and reviewing this technique throughout the study improve adherence. The Spirotek[®] Performance Checklist (SPIROTEL_PERF) is used at Visit 0A to document that each participant has achieved proper peak flow technique.

Failure to complete diary assessments twice a day is another form of non-adherence. Instructing the participant in the proper way to use the Spirotek[®] device for entry of diary information improves adherence. The SPIROTEL_PERF checklist is used at Visit 0A to document that each participant has achieved an understanding of how to use the Spirotek[®] device correctly.

See the Spirotek[®] discussion in this section and the Spirotek[®] Manual of Operations in Appendix 6 of the AsthmaNet General Manual of Operations for further details.

Inhalation Technique Assessment (TECH_MDI_NOSP, TECH_MDI_SP): Proper inhalation technique using a metered-dose inhaler (MDI) (e.g., RESCUE Ventolin[®]) is important to the study. Improper technique is a form of non-adherence with study procedures. Instruction in proper technique and continual coaching serve to improve adherence. The MDI Inhalation Technique Checklist (Without Spacer) (TECH_MDI_NOSP) and MDI Inhalation Technique Checklist (With Spacer) (TECH_MDI_SP) are used to document that each participant has achieved proper MDI inhalation technique at Visit 0A. Each participant can determine if he/she wishes to use a spacer with the MDI and the appropriate checklist will be used for technique assessment. Documentation of proper technique is required to satisfy the eligibility criteria assessed at this visit. See the Inhalation Technique Assessment discussion in this section for further details.

Inhalation Technique Assessment (TECH_DISKUS): Proper inhalation technique using a dry powder inhaler Diskus[®] (e.g., Flovent[®] Diskus[®] and blinded study drug) is important to the study. Improper technique is a form of non-adherence with study procedures. Instruction in proper Diskus[®] technique and continual coaching serve to improve adherence. The Diskus[®] Inhalation Technique Checklist (TECH_DISKUS) is used to document that each participant has achieved proper Diskus[®] inhalation technique at Visit 0A. Documentation of proper technique is required to satisfy the eligibility criteria assessed at this visit. Diskus[®] technique assessment is repeated at every study visit to assure that participants continue to dose appropriately from their study inhalers. See the Inhalation Technique Assessment discussion in this section for further details.

Counseling for Non-Adherence

At each visit the participant'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 participant.

During each visit, review the necessity of correct study medication use and the importance of avoiding medications that are not allowed during the study. Discuss the importance of the information that is collected at home with the spirotel[®] device to the success of the trial. Remind the participant that correctly following study procedures is crucial to the study; it is a part of the commitment he/she made when agreeing to participate.

When addressing problems, try to be constructive and helpful:

Acceptable: “I noticed that you have not been using your spiroteI[®] regularly. Is there anything we can do to help you? Are you having trouble operating the device at home? Are you re-evaluating your ability to participate in the study?”

Unacceptable: “You are not doing what you are supposed to do. What is your problem?”

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 personnel and the participant. Ensure that the participant is aware of the resources available to help him/her understand the study procedures, such as study handouts and the availability and willingness of clinic personnel to answer questions whenever they arise.

2.3 Adverse Events

These procedures are applicable for all three BARD age tracks.

Definition and Reporting

Adverse events include the following:

- Clinical Adverse Events:

Any unintended worsening in structure or function of the body; any illness that occurs during the trial. These events are documented on the Clinical Adverse Events form (AECLIN).

The term 'study drug' on the AECLIN form should be interpreted to mean any drug dispensed as part of the study, including open-label Flovent[®] and blinded scheduled Diskus[®]. If an adverse event is thought to be related to one of these medications, this fact should be documented in Q1080 on the AECLIN form. In addition, if the dose of the medication was altered as a result of the adverse event, this should be noted in Q1090. Following randomization, if a change in the status of the participant's blinded scheduled Diskus[®] occurred because of an adverse event, a BARD Change in Scheduled Diskus[®] form (P5_CHANGE_DISKUS) also should be completed.

See section 10 of the AsthmaNet General Manual of Operations for further details on AECLIN form completion and submission.

- Laboratory Adverse Events:

Occurrences of abnormal laboratory tests or other test (e.g., ECG) results. These events are documented on the Clinical Adverse Events form (AECLIN).

- Treatment Failure and/or Significant Asthma Exacerbation:

Significant asthma exacerbations and treatment (arm) failure events should be recorded on the Significant Asthma Exacerbation form (P5_SIGEX). In addition, significant asthma exacerbations should be recorded on the AECLIN form using ICD-9 code 493.92, and treatment failures should be recorded on the AECLIN form using ICD-9 code 000.00. See the discussions of Treatment (Arm) Failures and Significant Asthma Exacerbations in this section for further details.

- Treatment Period Drop-Outs:

During the post-randomization portion of the study, if the study physician determines that continuation on the current double-blind treatment is not in the best interest of the participant, but that study termination is not warranted, the participant will be assigned treatment period drop-out status. These events will be recorded on the AECLIN form using ICD-9 code 000.99. See the discussion of Drop-Out Status (Treatment Period) in this section for further details.

- Serious Adverse Events:

Any experience that poses a significant hazard to a participant is considered a serious adverse event. With respect to human clinical experience, a serious adverse event includes any experience that meets at least one of the following criteria:

1. Results in death
2. Is life threatening (places the participant at immediate risk of death from the event as it occurred)
3. Results in a significant or persistent disability/incapacity
4. Requires inpatient hospitalization or prolongation of an existing hospitalization
5. Results in a congenital anomaly/birth defect
6. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition. Examples include allergic bronchospasm requiring intensive treatment in an emergency department or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or abuse.

Serious adverse events are reported on the Serious Adverse Events Reporting Form (SERIOUS) as well as on the Clinical Adverse Events form (AECLIN).

If an adverse event is deemed serious by the above definition, a SERIOUS form should be completed and faxed or e-mailed to the BARD scientific coordinator at the DCC as soon as possible, preferably within 72 hours of clinic notification. Promptly faxing this form to the DCC expedites communicating the details of the adverse event to the Steering Committee, Data and Safety Monitoring Board (DSMB), and Institutional Review Boards (IRBs) if the event was deemed unexpected and possibly related to the study. If the documentation cannot be assembled within 72 hours due to the need for access to medical records or

inability to contact the study participant, contact the BARD scientific coordinator so that the DCC has communications on file and can follow up.

For detailed information on adverse events, see section 4 in the AsthmaNet General Manual of Operations.

ICD-9 Codes

In general, ICD-9 codes describing an adverse event of any type should be obtained by searching the AsthmaNet ICD-9 Codes Excel spreadsheet. 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.

For AsthmaNet, reported ICD-9 codes should describe the underlying condition or disease that resulted in a particular adverse event. For example, if a participant is hospitalized for a hysterectomy that was necessitated by uterine fibroids, the ICD-9 code for uterine fibroids should be recorded on the Clinical Adverse Events form (AECLIN). The procedure code for hysterectomy is unavailable in the master spreadsheet and should not be recorded. In general, procedure codes will not be reported.

Specific ICD-9 codes of interest for the BARD study include:

- 000.00: Protocol-defined treatment failure event
- 000.99: Protocol-defined treatment period drop-out
- 493.92: Significant asthma exacerbation

Visit 0A

Record any adverse events that have occurred since the informed consent was signed on the Clinical Adverse Events form (AECLIN)

If the participant experienced any adverse events between the date he/she (or his/her parent/guardian) signed the informed consent form (original signature date) and the

date of Visit 0A, record the events on the Visit 0A AECLIN form. If no adverse events are recorded for the participant at Visit 0A, check the 'None' box.

A comprehensive medical history is taken during Visit 0A. As part of this history it is important to probe for pre-existing conditions, both those related to asthma and those unrelated to asthma. This baseline knowledge is necessary to determine if conditions experienced during the BARD study should be considered 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 Clinical Adverse Events form (AECLIN), but they should be noted in the clinic notes that are stored in the participant's study folder.

Visits 0A1, 0B, 0C, 0D, 1-13

Follow up clinical adverse events from previous visits and record any new events (AECLIN)

The Clinical Adverse Events form (AECLIN) should be updated each time the clinic has contact with a participant, whether for a scheduled visit or phone contact, impromptu visit, or unexpected phone call.

In preparation for each contact, review the participant's file to determine if there were any ongoing adverse events at the last visit/contact. If an ending date for an ongoing adverse event becomes available, update the AECLIN form with this new information. Probe the participant for the occurrence of any new adverse events and record these on AECLIN.

An AECLIN form should be completed for each participant at each visit, even if the participant has not experienced any new adverse events since the previous visit. If no new adverse events are being recorded for the participant at a visit, check the 'None' box. If new information is available, record it and have the participant review it for accuracy.

Visit 13 and early termination visits

Events that are ongoing at the time a participant leaves the study should be left open for stop dates (i.e., coded as 'ongoing at final visit'). The participant should be probed for any stop dates that are now known to close out previously-recorded events. All AECLIN forms for a given individual should be forwarded to the DCC following his/her study termination.

2.4 Appointments: Confirming and Scheduling

These procedures are applicable for all three BARD age tracks.

Visits 0A, 0A1, 0B, 0C, 0D, 1-12

Confirm/Schedule upcoming appointment(s)

Review Visit Preparation handout (P5_VISPRP)

At each visit, review the current BARD Visit Scheduler Report and confirm the dates of the next regular appointment and any upcoming phone contacts. Write the scheduled dates on the participant's copy of the Visit Scheduler Report for his/her reference, and enter the date into the clinic's appointment book or scheduling calendar.

Review the BARD Visit Preparation handout (P5_VISPRP) with the participant. Remind him/her of the substances that must be avoided prior to each scheduled visit that includes spirometry (all visits with the exception of 0C and 0D, unless methacholine challenge will be attempted at 0C or 0D). Also remind the participant to bring his/her study medications (used and not used), BARD Asthma Monitoring Log (P5_ASTHMA_LOG), spirotel device, and handout folder to each visit. Review the checklist on side 2 of the handout. Write reminders for special collection dates, such as the overnight urine collection, on P5_VISPRP and P5_ASTHMA_LOG.

Visits for a given participant should be scheduled for the same time of day (+/-3 hours) to avoid the introduction of circadian variability into the assessment of lung function. Once the participant is randomized, the time spirometry occurred at Visit 1 should be used as the reference. If a participant needs to be scheduled outside the 3-hour window, the BARD scientific coordinator at the DCC should be contacted to obtain an exception.

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

2.5 Asthma Attack/Exacerbation Kit

The Asthma Attack Kit is applicable only for the BARD Age 12-17 and Age 18+ Tracks.

Visit 0A

Distribute asthma exacerbation kit and review instructions (WPAI_ASTHMA, AAAQ, P5_ASTHMA_ATTACK)

One of the exploratory aims of the BARD trial is to evaluate the responsiveness of a range of tools to characterize the time-course (onset and resolution) and magnitude of morbidity associated with an asthma exacerbation and the use of systemic corticosteroids as part of the BARD action plan. The following questionnaires will be used to gather impairment data at the onset of an exacerbation (defined as the first day of prednisone dosing) and at the next study visit following an exacerbation (to examine exacerbation resolution):

- Asthma-Specific Work Productivity and Activity Impairment Questionnaire (WPAI_ASTHMA)

This questionnaire measures the effect of the participant's asthma on his/her ability to work, attend classes, and/or perform regular daily activities in a 7-day timeframe. See the discussion of the Work Productivity and Activity Impairment Questionnaire in this section for further details.

- Acute Asthma Assessment Questionnaire (AAAQ)

This questionnaire measures impairment level in terms of asthma symptoms, rescue bronchodilator use, nighttime awakenings, stress caused by asthma, and effects on usual activities in a 3-day timeframe. It also records the primary cause of the exacerbation. See the Acute Asthma Assessment Questionnaire discussion in this section for further details.

To facilitate collection of questionnaire data at the onset of an exacerbation, which may occur when the participant is at home or otherwise away from the performance site, an "Asthma Attack Kit" will be given to each participant (ages 12 and older) at Screen Visit A (Visit 0A). This kit should be kept at home with the participant's study materials and rescue prednisone bottle. The kit includes:

- One copy of the WPAI_ASTHMA questionnaire. Complete the participant's BARD ID and initials in the header field prior to dispensing the kit.

-
- One copy of the AAAQ questionnaire. Complete the participant's BARD ID and initials in the header field prior to dispensing the kit.
 - One copy of the Asthma Attack Kit Instructions handout

Review the kit instructions with the participant. Emphasize that one copy of each of the questionnaires should be completed on the day he/she takes the first dose of prednisone when it is prescribed to treat asthma symptoms. The questionnaires should be completed if a medical practitioner outside of the study prescribes prednisone to treat asthma, as well as when someone at the study site prescribes it. The participant should record the date he/she completed the questionnaire as part of the source documentation on the questionnaire. It is also helpful if the participant notes the first day of prednisone on his/her Asthma Monitoring Log and notes completion of the kit there, as well. The completion date is very important for analysis.

If the participant forgets to complete the questionnaires on the first day of prednisone dosing, but he/she remembers to complete them before the course has been finished (i.e., on days 2, 3, 4, or 5), the data are still useful. The participant should complete the actual date he/she completed the questionnaires in the source documentation box on both questionnaires. This information will be matched to the prednisone course information recorded on the Concomitant Medications form (CMED) so that the timing of the responses relative to use of prednisone can be determined and accounted for.

Visits 0A1-13

If the participant experienced an exacerbation between visits:

Collect completed asthma exacerbation kit materials (WPAI_ASTHMA, AAAQ)
Administer WPAI_ASTHMA and AAAQ during the visit

Visits 0B-12

If the participant experienced an exacerbation between visits:

Distribute new asthma exacerbation kit and review instructions (WPAI_ASTHMA, AAAQ, P5_ASTHMA_ATTACK)

Visits 0C-13

If the participant experienced an exacerbation at the previous visit (and completed questionnaires while at the visit):

Administer WPAI_ASTHMA and AAAQ during the visit

If an exacerbation is documented at the time of a regular visit and the participant will begin taking prednisone that day, he/she should complete the WPAI_ASTHMA and AAAQ questionnaires at the time of the visit (rather than waiting to do so at home). Clinic personnel should collect the questionnaires and review them for completion.

These forms will be entered as single forms with the current visit number. Ensure that the participant has copies of the questionnaires at home in the event that another exacerbation would occur prior to the next visit. At the next regular visit, he/she should complete the questionnaires a second time to document resolution of the exacerbation.

If an exacerbation occurs between regular visits, the participant should follow the instructions on the Asthma Attack Kit Instructions handout (P5_ASTHMA_ATTACK). He/she will complete WPAI_ASTHMA and AAAQ at home and return the forms to clinic personnel at the next regular visit. These forms will be entered as single forms using the visit number of the last visit completed. At the next regular visit, he/she should complete the questionnaires a second time to document resolution of the exacerbation. These forms will be entered as single forms using the current visit number. Kit supplies will be replenished at that time.

2.6 Asthma Control Questionnaire

The Asthma Control Questionnaire is applicable for all three BARD age tracks.

Visit 0A1

Administer Asthma Control Questionnaire (ACQ7)

General Information

The Asthma Control Questionnaire (ACQ) was developed by Dr. Elizabeth Juniper from the Department of Clinical Epidemiology and Biostatistics at McMaster University Medical Centre. AsthmaNet has received permission from Dr. Juniper to use this instrument in the BARD study.

The goal of the ACQ is to measure asthma control using recognized psychometric methods. The ACQ has strong measurement properties and can be used with confidence to measure the adequacy of clinical asthma control. It has been fully validated for use in both clinical practice and clinical trials. Lower scores indicate better asthma control; higher scores indicate worse asthma control. We will employ the self-administered version of the questionnaire for BARD for all age tracks.

The 7-item ACQ, which incorporates spirometry results, is being employed at the time of Visit 0A1 to determine if the participant's asthma has been adequately controlled on 2-2.5xICS during the past week. If the ACQ score at Visit 0A1 is less than 1.50, the participant's asthma is considered adequately controlled and he/she will be stepped down to the lower run-in inhaled corticosteroid (ICS) dose (1xICS). If the ACQ score at Visit 0A1 is greater than or equal to 1.50, the participant's asthma has not been adequately controlled on the intermediate ICS dose, and he/she is ineligible to have the ICS dose stepped down to 1xICS. In this case, the participant is ineligible to continue in the study. See the Inhaled Corticosteroid (ICS) Step-Down Groups and Assessment discussion in this section of the BARD MOP for further details.

Administration Instructions

The administration of the ACQ is one of the first procedures performed at Visit 0A1. This timing in the visit structure was intentional so that a participant's responses are not affected by other study procedures, such as spirometry and diary review. Study coordinators should observe the order of procedures as they are laid out on the Visit 0A1 Procedure Checklists (P5_VISIT0A1_A, P5_VISIT0A1_P) to ensure that ACQ results are not biased by other study activities.

If a given visit has been partially completed and then rescheduled for a later date, a new ACQ must be completed at the beginning of the rescheduled visit. Do not allow the participant to refer to or update his/her previously completed questionnaire. Old copies of the questionnaires should be filed in the participant's study folder or shredded; they should not be entered into the study database or forwarded to the DCC.

In administering the questionnaire, request that the participant complete the first six questions and provide answers as completely and as accurately as possible. The form is self-administered and participant completed. No stated or implied time limit should be set. If the participant requests help with or clarification of any question, the study coordinator should instruct the participant to reread the instructions and to give the best answer possible to each question. The coordinator should not provide an answer to any question. Providing guidance may bias the participant's responses.

Pediatric participants who may not be old enough to read and/or comprehend the questions on the ACQ should be assisted by their parent or guardian in the completion of the questionnaire.

Dr. Juniper gives the following guidelines for ACQ administration to ensure the best quality data:

- Provide the participant (and his/her parent/guardian, if needed) a quiet place to complete the questionnaire.
- Before the participant/guardian completes the ACQ, the study coordinator should do the following:
 - Tell the participant that all questions from 1 through 6 should be answered. Question 7 should be left blank. The coordinator will complete that question following the spirometry session at the visit.
 - Tell the participant that only one response may be given for each question. It is not possible to score a question in between values. The participant/guardian must choose one or the other as most representative of the participant's asthma in the past week.
 - Remind the participant that he/she is scoring problems experienced due to asthma and not because of any other problems.
 - Remind the participant that the ACQ is collecting data about his/her asthma over the past week (7 days).

Participants should use a black pen to complete the questionnaire. If the participant or guardian wishes to change a response, the original response should be crossed out with a single line and then dated and initialed by the participant/guardian. The final response should be circled for clarification. Once the participant returns the

questionnaire to study personnel, no changes are allowed unless they are to resolve data discrepancies or to fill in a missing response. The form should be returned to the participant/guardian to have these changes made; clinical personnel should not alter participant/guardian-completed forms.

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

No source documentation can be provided on this questionnaire due to constraints imposed by Dr. Juniper on the formatting of the instrument.

Scoring Instructions

Before scoring the ACQ, retrieve the participant's spirometry report for the visit. Note the FEV₁ percent of predicted value on the line provided next to Question 7 on the ACQ7 form. Choose the category in which the %predicted FEV₁ value falls and circle the corresponding numerical response.

A 'Clinic Use Only' box has been provided on ICS Step-Down Assessment form (P5_STEPDOWN_ASSESS) to assist in computing the ACQ score at Visit 0A1. Write the number (ranging from 0-6) corresponding to the response provided for each question in the blank line above each question number. Sum the responses across all seven questions and complete the 'Total' line. Divide the total by 7 and round to the second decimal place. Record the score on the lines provided. The ACQ score is simply the average of the scores of the seven questions.

If the participant's score is less than 1.50, he/she is eligible to step down his/her ICS to the 1xICS level. The dose reduction can take place even if the participant has not met the 75% level with compliance for study dosing and/or spirotel[®] procedures. Additional training and counseling should be done if the participant's compliance does not meet study requirements.

If the participant's score is greater than or equal to 1.50, he/she is ineligible to step down his/her ICS to the 1xICS level. In this case the participant is ineligible to continue in the study.

2.7 Asthma Control Test

Asthma Control Tests are applicable for all three BARD age tracks. This section describes the two Asthma Control Tests used in the BARD study and the participants to whom each is applicable.

Asthma Control Tests are administered at Visits 0A, 0B, 1-13

General Information

The Asthma Control Test (ACT) is administered at almost every BARD visit. Results of the ACT are used at Screen Visit A (Visit 0A) to determine the participant's eligibility for the study based on his/her asthma control level and asthma treatment step at study entry. The results of the ACT also will be analyzed longitudinally as a secondary outcome for the study.

Two versions of the ACT have been developed through research by GlaxoSmithKline:

- Childhood Asthma Control Test (CACT)

The CACT has been validated for use in children ages 4-11. This version of the ACT will be administered to participants in the BARD Age 5-11 Track. These participants will complete the CACT at all of their study visits, even if they turn 12 while in the study.

- Asthma Control Test (ACT)

The ACT has been validated for use in adolescents and adults ages 12+. This version of the ACT will be administered to participants in the BARD Age 12-17 and Age 18+ Tracks.

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

If a given visit has been partially completed and then rescheduled for a later date

because of the participant's time constraints on that day, a new CACT/ACT form must be completed at the beginning of the rescheduled visit. Do **not** allow the participant to refer to or update his/her previously completed questionnaire. Old copies of the questionnaires should be filed in the participant's study folder and clearly marked or shredded; they should not be entered into the study database or forwarded to the DCC.

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

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

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

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

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

Childhood Asthma Control Test (CACT)

This questionnaire is applicable for participants in the BARD Age 5-11 Track only.

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

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

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

Asthma Control Test (ACT)

This questionnaire is applicable for participants in the BARD Age 12-17 and Age 18+ Tracks.

The ACT is a trade-marked 5-item questionnaire that was developed through research by GlaxoSmithKline and is now managed by QualityMetric Incorporated. AsthmaNet has paid a licensing fee for the use of the ACT in the BARD trial. QualityMetric supplied the version of the form that we are using, and AsthmaNet was refused permission to implement any formatting changes to make it more compatible with our database. See the data management guidelines for this form in section 10 of the AsthmaNet General Manual of Operations for more information.

The ACT gathers information on asthma control using a 4-week recall window. The form is self-administered and participant completed. The ACT website is: www.asthmacontrol.com.

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

2.8 Blood Samples and Tests

All of the following blood tests are applicable for all three BARD age tracks.

At Visit 1, blood samples will be drawn, in the order presented below, for the following tests:

- Serum ImmunoCAP/Total IgE

The ImmunoCAP test provides a clinically relevant means of confirming or excluding the presence of atopic disease in patients with upper respiratory disease. It allows for accurately identifying specific allergen sensitivities in patients with confirmed allergy. The test measures allergen-specific IgE in serum. The specific allergens that will be tested for BARD include: cat (e1), dog (E5), mouse (E72), mold mix (Mx1), German cockroach (i6), grass mix (gx2), tree mix (Tx4, Tx6), weed mix (Wx1), weed (W3), mite (D2, D1), and rat (E74).

Total IgE, which is a general marker of atopic status, will also be measured.

For blood collection, storage and shipment procedures for these tests, see the discussion of Serum ImmunoCAP, Total IgE and Cotinine Tests in this section of the BARD MOP.

- Serum Cotinine

This test is being done to assess each participant's exposure to cigarette smoke.

For blood collection, storage and shipment procedures for this test, see the discussion of Serum ImmunoCAP, Total IgE and Cotinine Tests in this section of the BARD MOP.

- Complete Blood Count with Differential (CBC)

The CBC provides information on the total number of white blood cells and the number of each type of white blood cell the participant has. We are specifically interested in the number and percentage of eosinophils, as they are a marker for allergy and asthma.

For details on this test, see the discussion of Complete Blood Count in this section of the MOP.

- DNA Extraction (Genetics Blood Draw)

Blood sample for genetic analyses, including the ancestry analysis needed for this study. Procedures for the genetics blood draw can be found in the Genetics Blood Draw discussion in this section of the BARD MOP and in the Genetics MOP in Appendix 4 of the AsthmaNet General Manual of Operations.

Blood samples must be drawn in the order specified above. This order is also reflected on the Visit 1 Procedure Checklists (P5_VISIT1_A, P5_VISIT1_P).

2.9 Certification

Certification procedures are applicable for all three BARD age tracks.

Study Coordinators and Technicians

Coordinators who carry out BARD study visits must be certified to do so. That is, personnel who complete pregnancy tests (PREG_TEST form) or any of the protocol-specific BARD forms (designated by a P5 prefix in the form name) must possess BARD protocol certification. *Note that this includes completion of the BARD Pulmonary Procedure Checklist (P5_PULMONARYCHK).*

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

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

Any individual who performs spirotel[®] procedures, spirometry, sputum induction or methacholine challenge as part of a BARD visit must be AsthmaNet certified in these procedures or be supervised by a certified technician, as applicable. Certification for these procedures is tracked independently of BARD study certification. It is acceptable for these procedures to be performed during the BARD study by technicians who possess only individual procedure certification and not BARD protocol certification, but it is preferred that technicians review the protocol and take the certification exam, as well. If a technician is only certified in spirometry and not in the BARD protocol, a BARD-certified coordinator must complete the BARD Pulmonary Procedure Checklist (P5_PULMONARYCHK) to qualify participants for spirometry and methacholine challenge testing.

It should be noted that the spirotel[®] certification required for BARD is the “peak flow/e-diary” certification. If a coordinator currently possesses only spirotel[®] e-diary certification, he/she must complete the requirements for peak flow/e-diary certification. This certification can be done with a VIDA or BARD/SIENA spirotel[®].

It should further be noted that if a site is planning to screen participants in the Age 5-11 Track, then technicians need to possess pediatric spirometry certification. Requirements to achieve this certification are outlined in the AsthmaNet Spirometry MOP. Individuals who are certified for pediatric spirometry can also perform spirometry on adolescents and adults (their spirometry certification is transferrable to the adult category). Individuals who are certified for adolescent/adult spirometry must fulfill the requirements for pediatric spirometry certification prior to performing spirometry on a participant in the Age 5-11 Track.

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

The quality of AsthmaNet data is tracked and reported on a regular basis to the individual performance sites, clinical center partnerships, the AsthmaNet QCC, and to the Data and Safety Monitoring Board (DSMB). It is possible to become decertified in some of the procedures (e.g., spirometry, sputum induction) if lack of quality becomes an issue and the study data begins to be affected adversely. The DCC will contact individuals who are in danger of becoming decertified to discuss the situation before they are decertified formally in the certification tracking system. It is also possible to become decertified if a coordinator or technician leaves the Network and returns later, not having performed spirometry or other procedures for an extended period of time. See the individual procedure MOPs in the AsthmaNet General MOP for details.

Licensed Medical Practitioners (LMPs)

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

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

Data Entry Personnel

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

2.10 Cold History

This questionnaire is applicable for all three BARD age tracks.

Respiratory tract infections (i.e., “colds”) are known to be associated with worsening asthma symptoms and asthma exacerbations. During the detailed medical history collected at the first screening visit, a short cold history is taken. This information will be used to characterize the participant’s asthma and may be used to define predictor variables when examining factors that predict responses to the different study treatments.

Visit 0A

Administer Cold History form (COLD_HX)

The Cold History form (COLD_HX) was created by AsthmaNet researchers. This form collects baseline information on the frequency, severity, and effects on asthma of colds the participant experienced in the past year.

The cold history is obtained by participant interview. Read each question to the participant in a consistent, even tone, exactly as written on the form. Provide clarification when asked.

See Section 10 of the AsthmaNet General Manual of Operations for further details regarding the completion of the COLD_HX form.

2.11 Complete Blood Count (CBC)

This blood test is applicable for all three BARD age tracks.

Visit 1

Obtain blood sample for CBC with differential (local lab)

CBC (with Differential) Blood Draw Procedures

At Visit 1, for randomized participants only, fill a purple-top tube with blood for CBC/differential determination as follows (check with local lab to verify tube type and size in case their procedures differ):

BARD Age 5-11 Track: Obtain one small purple top tube
BARD Age 12-17 Track: Obtain one small purple top tube
BARD Age 18+ Track: Obtain one 4 ml purple top tube

The order of blood draws outlined in the Blood Samples and Tests discussion in this section must be observed.

Blood samples for CBC will be analyzed in the performance site's local lab. This lab does not have to possess CLIA certification. Samples should be labeled according to local requirements and transported to the lab within **two hours** of the blood draw.

After the results are available, record the participant's white blood cell (WBC) count, absolute eosinophil count, and eosinophil differential in Question #1 on the BARD Laboratory Results form (P5_LAB). Note that absolute eosinophil values must be recorded in number of cells per μL . No other units are acceptable. Any necessary conversions must be made prior to recording data on the form and entering the data into the study database.

A copy of the local lab report should be forwarded to the DCC with the P5_LAB form. All identifying information (name, medical record number, etc.) must be blackened out prior to sending the report to the DCC. Include the participant's ID number on the report.

Refer to Section 4 for more details on how to complete the P5_LAB form.

2.12 Concomitant Medications

These procedures are applicable for all three BARD age tracks.

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 he/she is 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 or treatment failure event.

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

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

Medications not taken for asthma, allergies or adverse events should be recorded on the CMED_NON form. Examples include multivitamins and herbs the participant is taking for health maintenance and maintenance drugs taken for a pre-existing condition (e.g., Paxil for depression). Other non-asthma, non-allergy drugs the participant takes chronically, such as oral contraceptives, should also be recorded on this form.

Study medications, including run-in open-label Flovent[®], Ventolin[®] rescue medication, and blinded scheduled Diskuses[®], should not be regarded as concomitant medications and should not be recorded on CMED or CMED_NON. Prednisone taken to treat an asthma exacerbation or other adverse event should be recorded on the CMED form as a concomitant medication and linked to the appropriate adverse event on the Clinical Adverse Events form (AECLIN). If a randomized participant experiences a treatment (arm) failure or becomes a treatment period drop-out and is given open-label Flovent[®] per protocol, the open-label medications should be recorded on CMED in order to track their dose and duration of use. Open-label Flovent[®] should be linked to the treatment failure or treatment period drop-out adverse event. Note that open-label Flovent[®] is only recorded if it is used post-randomization.

Any non-study asthma medications (e.g., Alvesco[®]) are considered concomitant medications and should be recorded on the CMED form if they are prescribed during the study (note that these drugs are excluded during the study and their use should be avoided if at all possible).

The following classes of drugs/solutions/products 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
- Novacaine 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
- Allergy shots (i.e., immunotherapy injections)
- Vaccinations (e.g., flu vaccine)

Visit 0A

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

Thorough questioning about medication use during the initial study visit will prevent the presentation of unexpected information when it is time to randomize a participant. It also will help to prevent misinterpretation of medications reported at subsequent contacts, particularly if the participant interacts with a different coordinator.

During the first visit, prompt participants with the following questions:

- What over-the-counter medications do you 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 do you typically take during a given month, including continuous use and as-needed medications?
- What over-the-counter medications do you typically pack when you go on vacation or away for business? What prescription medications?

- What over-the-counter medications do you keep in your desk drawer or purse? What prescription medications?

If the participant has taken any medications for asthma or allergies or adverse events that have occurred since he/she (or his/her parent or guardian) signed the informed consent (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 0A, even if the participant has agreed to stop taking them after completing the visit. List the consent date as the start date for the medication (i.e., when the use of the medication became concomitant with study participation) if the participant started taking the drug prior to his/her original consent signature date.

Note: BARD requires that participants who will need an intranasal steroid during the study begin using one as of Visit 0A. These drugs also must be listed on CMED.

Any medications that were used to treat conditions other than asthma, allergies or adverse events since the participant signed the informed consent should be recorded on the Concomitant Medications for Non-Asthma Drugs (CMED_NON) form. This includes substances like multivitamins, vitamin D and calcium supplements, and herbs the participant is taking for health maintenance. It also includes maintenance drugs for a pre-existing condition (e.g., Paxil for depression or insulin for diabetes) and other drugs the participant takes chronically, such as oral contraceptives.

Probing for medication use during Visit 0A affords an opportunity to recognize clinically significant medical problems early in the study. For example, a participant may take several medications to treat hypertension. The participant's condition may be deemed unstable and poorly controlled, therefore, he/she is 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/her from study participation, first check the BARD Exclusionary Medical Conditions reference card (P5_EXCLMED). If the applicable condition is not listed specifically, contact the DCC for guidance.

When scheduling Visit 0A, the potential participant should be asked to bring all over-the-counter and prescribed medications and supplements he/she is currently taking to the visit. Alternatively, the participant may write down the names of the medications and supplements and the date he/she started taking each medication and bring this list to the visit.

Visits 0A1, 0B, 0C, 0D, 1-13

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 phone contact, impromptu visit, or unexpected phone call, 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/she was taking, update the stop date on the CMED or CMED_NON form, as appropriate. Probe the participant for any new medications that may have been taken and record these on the appropriate form for the next visit. If the participant began taking a new medication for a condition or disease that existed prior to study enrollment at Visit 0A and no adverse event (i.e., worsening of the condition) is associated with the change in medication, record this information on the CMED_NON form. 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.

Visit 13 and early termination visits

Medications that are still in use at the time of the final study visit or contact should be left open for stop dates. On the CMED form, these are coded as 'ongoing at final visit.' On the CMED_NON form these are coded as 'ongoing at end of study.' During the participant's final visit or contact with the clinical site, finalize his/her CMED and CMED_NON forms. All CMED forms for a given individual should be forwarded to the DCC following his/her study termination. CMED_NON forms are not sent to the DCC.

2.13 Contact Information

These procedures are applicable for all three BARD age tracks.

Visit 0A

Administer Adult or Pediatric Participant Contact Information form (CONTACT_ADULT or CONTACT_PED)

Administer the following Contact Information form depending on the participant's age track:

- Age 5-11 Track: CONTACT_PED
- Age 12-17 Track: CONTACT_PED
- Age 18+ Track: CONTACT_ADULT

Adult Participant Contact Information form (CONTACT_ADULT)

The CONTACT_ADULT form is completed by the participant. 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 participant through work, family, or friends. It also includes contact information for the participant's health care provider.

Pediatric Participant Contact Information form (CONTACT_PED)

The CONTACT_PED form is completed by the participant's parent or guardian. Its purpose is to collect pertinent participant identification information such as full name, address, and telephone number. The parent/guardian's information is also collected, along with contact information for the participant's pediatrician and asthma care doctor. Contact information for alternative contacts (family, friends, neighbors) is also collected.

General Information

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

- It is important to obtain complete and accurate phone number information for the participant during Visit 0A. The participant or his/her parent/guardian will need to be contacted via phone if he/she misses a visit and for regular phone contacts as part of the BARD trial.
- Store the CONTACT_ADULT or CONTACT_PED form in the participant's study folder; do not forward it to the DCC. This form contains the participant's name, address, and other identifying information. A protocol violation may be assigned if this form is misdirected to the DCC or another off-site group affiliated with AsthmaNet (e.g., sputum lab, ADx Lab, etc.).

2.14 Dosing Compliance

Compliance procedures are applicable for all three BARD age tracks.

During the BARD trial participants are expected to use their study Diskus[®] consistently, taking 1 puff BID. Compliance with medication dosing is checked and documented at all visits to give coordinators an opportunity to retrain participants, as needed. Dosing compliance is documented on the following BARD forms depending on the visit:

- Visits 0B, 0C, 0D, 1: Randomization Eligibility Checklist (P5_RAND_ELIG)
- Visit 0A1: ICS Step-Down Assessment (P5_STEPDOWN_ASSESS)
- Visits 2-13: Spirotel[®] Participant Compliance Report (P5_COMPLY)

The Diskus[®] includes a counter that shows the number of puffs remaining (out of a total of 60 puffs in a new Diskus[®]). The counter will be used to assess the participant's compliance with dosing from the scheduled Diskus[®] during the run-in and during the blinded treatment periods post-randomization.

The number of scheduled puffs should include all doses the participant should have taken since leaving the last clinic visit, including the evening dose on the day of the visit. During the post-randomization treatment periods, the participant should be holding his/her morning dose from the scheduled, double-blind Diskus[®] prior to the visit to accommodate the 12-hour hold on long-acting beta-agonists. Do not count the skipped morning dose in the number of scheduled puffs. If the participant is being seen very early in the morning for a visit, then he/she may also have held the evening dose the night before the visit. In that case, do not count the evening or morning doses in the number of scheduled puffs.

If the participant has been switched to open-label Flovent[®] due to treatment failure or an exacerbation late in the treatment period, no medication hold is required prior to the next visit. In that case, count the morning dose in the number of scheduled puffs. Include a comment on the P5_COMPLY form to explain the circumstances.

Example Diskus[®] Compliance Calculations at Visit 0B

The following chart shows the number of scheduled open-label Flovent[®] Diskus[®] puffs a participant should have taken between Visit 0A and Visit 0B (2-week interval). Visit 0A took place on 1/13/2014 and Visit 0B is taking place on 1/27/2014. The Diskus[®] returned by the participant has a counter value of 42.

Date	1/27 Visit 0B	1/26	1/25	1/24	1/23	1/22	1/21	1/20	1/19	1/18	1/17
Scheduled Puffs	1 (AM dose only)	2	2	2	2	2	2	2	2	2	2

Date	1/16	1/15	1/14	1/13 Visit 0A
Scheduled Puffs	2	2	2	1 (PM dose only)

Compliance assessment (follow P5_RAND_ELIG, Questions #5a-5d):

5a. Number of scheduled puffs (from above table): 28

5b. Number of remaining puffs (from Diskus counter): 42

5c. Number of puffs taken:

The number of puffs taken is equivalent to the number of puffs packaged in the Diskus[®] – the number of puffs remaining in the Diskus[®].

The number of puffs taken is equivalent to $60 - 42 = 18$.

5d. Percent compliance = # puffs taken / # puffs scheduled x 100
 $= 18 / 28 \times 100$
 $= 64.3\%$.

∴ Because the participant's compliance percentage is below the 75% goal defined for the study, the participant should be retrained on appropriate dosing procedures, assuming this is his/her first attempt at Visit 0B. After retraining the participant, Visit 0B may be rescheduled in 2 weeks. The example participant's Diskus[®] has enough doses left on it to accommodate the additional period of time. As long as it will not exceed its

30-day expiration date, he/she can be given the same Diskus[®] to use until the new visit. At the new Visit 0B, a new P5_RAND_ELIG form will be completed.

Compliance Assessments with One Diskus[®] Used Across Run-In Visits

When assessing Diskus[®] compliance at a new visit when the Diskus[®] was used and assessed at the previous visit, the number of puffs taken will be calculated by subtracting the number of remaining puffs on the Diskus[®] from the number of remaining puffs at the initial visit. For example, suppose the participant described in the above example arrives for his/her rescheduled Visit 0B and the Diskus[®] counter reflects 16 remaining puffs. The number of puffs taken since the participant left the last clinic visit is calculated as: 42- 16 = 26 puffs taken.

Note: Participants may only keep a given Diskus[®] across visits during the run-in. They may not keep blinded scheduled Diskuses[®] across visits during the post-randomization treatment periods. ALL Diskuses[®] must be collected and logged at all post-randomization visits and new Diskuses[®] dispensed, even if a Diskus[®] is still in its original pouch. See the BARD Pharmacy MOP for further details on study drug dispensation and logging.

Compliance Assessments with Multiple Diskuses[®]

At most post-randomization visits participants will be dispensed two Diskuses[®] to use until the next visit. The Diskus[®] label will indicate when the first Diskus[®] should be used and the pouch of the second Diskus[®] will include dates of use for that inhaler. Participants should return both Diskuses[®] to the site at their next study visit. When calculating compliance with multiple Diskuses[®], do the following:

- a. Number of scheduled puffs: Calculate this value normally, following procedures outlined above. Exclude doses that should have been skipped to accommodate the 12-hour long-acting beta-agonist hold prior to the visit.
- b. Number of remaining puffs reflected on the counters: Total the values on the counters for all used and returned Diskuses[®]. If a Diskus[®] is still in its original pouch, it may be ignored for purposes of calculating compliance.
- c. Number of puffs taken: $60 * (\# \text{ opened Diskuses}^{\text{®}}) - (\text{Remaining puffs from step b})$. The calculation for two Diskuses[®] is 120-remaining puffs totaled from both counters.

Note: If the participant does not return all dispensed Diskuses[®] to the scheduled visit, compliance cannot be calculated with any degree of certainty. Do not calculate compliance from one returned Diskus[®] if the participant was dispensed more than one, even if the participant reports that the missing Diskus[®] was not opened. Q1040-Q1060 on P5_COMPLY should be left blank in this situation. A comment should be added in Q6000 indicating not all Diskuses[®] were returned. Entry errors related to the missing

values should be marked unresolvable with a similar comment. The participant should be encouraged to locate and return the missing Diskus(es)[®] as soon as possible. Submit a data correction to update the values in Q1040-Q1060 if the missing Diskus(es)[®] are subsequently returned.

Overcompliance

If a participant appears to have taken significantly more than 1 puff BID from his/her scheduled Diskus[®], it is important to determine why this has occurred. If a child has been in charge of his/her own dosing, the counter could have been advanced too frequently (through extra 'clicks') without the participant having really taken too much medication. Parents of pediatric participants should be supervising dosing in the AM and PM to avoid this problem. Another potential reason for apparent overcompliance includes misunderstanding the study procedures/dose such that a participant will take an increased dose consistently throughout the initial few weeks of the run-in. When evaluating the participant's dosing compliance, if he/she appears to have taken 150% (or more) of the prescribed dose, probe for the participant's understanding of the study procedures and retrain, as necessary. Ensure that the participant is following the appropriate order of procedures at home: e-diary completion followed by scheduled peak flow measurement followed by AM or PM dose (1 puff). If the participant has taken more than 4 puffs per day consistently (or more than 200% of the study dose), contact the DCC for assistance in determining the appropriate course of action for processing the participant through the trial. Taking too much medication can interfere with decision-making at certain points in the run-in.

2.15 Drop-out Status (Treatment Period)

These procedures are applicable for all three BARD age tracks.

Definition and Treatment

During the post-randomization portion of the study, if the study physician determines that continuation on the current blinded treatment regimen is not in the best interest of the participant for any reason other than poor asthma control, but that termination from the study is not warranted, the participant will be assigned treatment period drop-out status. For example, a participant may be dropped from a treatment period and achieve treatment period drop-out status due to intolerable side effects of the blinded study regimen. Once this status is assigned, the participant should be seen immediately at the performance site for adjustment of his/her study medications. He/she will stop taking doses from his/her blinded study Diskus[®] and will be given open-label 1xICS Flovent[®] as follows:

- Age 5-11 Track: 50 mcg BID
- Age 12-17 Track: 100 mcg BID
- Age 18+ Track: 100 mcg BID

Participants who are deemed treatment period drop-outs should be scheduled to complete the next cross-over visit (i.e., 4, 7, 10) to start the upcoming treatment period as soon as possible. If the participant is deemed a treatment period drop-out during the fourth treatment period, he/she will be terminated from the study following normal study termination procedures. See the discussion of Withdrawals in this section.

Documentation

When a participant has been deemed a treatment period drop-out, the following forms should be completed:

- BARD Treatment Period Drop-out Form (P5_TRT_DROPOUT)

If a participant is stopping his/her blinded scheduled Diskus[®] regimen on the advice of the study physician and has been deemed a treatment period drop-out, the P5_TRT_DROP-OUT form should be completed. This is a single form that is only submitted if the participant meets the treatment period drop-out criterion.

Note: If the participant is discontinuing his/her scheduled blinded Diskus[®] due to achieving treatment failure status, drop-out status does not apply. In that case, complete a Significant Asthma Exacerbation form (P5_SIGEX) to document the treatment failure event. See the discussion of Treatment (Arm) Failure in this section for further details.

- Clinical Adverse Events form (AECLIN)

Document the event using ICD-9 code 000.99 (protocol-defined treatment period drop-out).

- Concomitant Medications for Asthma/Allergy and Adverse Events (CMED)

Document the open-label Flovent[®] prescribed in lieu of the blinded scheduled Diskus[®] on the CMED form. Link the Flovent[®] entry to the drop-out adverse event.

- Change in Scheduled Diskus[®] form (P5_CHANGE_DISKUS)

A P5_CHANGE_DISKUS form should be submitted to document the date when the participant stops dosing from his/her scheduled Diskus[®]. Q1000 should be answered 'Adverse Event' and the code from AECLIN corresponding to the drop-out event should be listed in Q1010. When the participant enters the next treatment period and resumes dosing from a scheduled blinded Diskus[®], another P5_CHANGE_DISKUS form should be submitted to document the date blinded study drug was resumed. On that form Q1000 should be answered 'Started New Treatment Period.'

Spirotel[®] and Compliance Assessments

Please refer to the Treatment (Arm) Failure discussion in this section for information on managing the Spirotel[®] data and reports and assessing compliance when a participant is deemed a treatment period drop-out.

2.16 Eligibility Criteria (Screening)

These procedures and criteria are applicable for all three BARD age tracks.

Visit 0A

Complete Eligibility Checklist 1 (P5_ELIG1)

Complete Eligibility Checklist 2 (P5_ELIG2)

Complete Eligibility Checklist 3 (P5_ELIG3)

General Summary

Near the beginning of Screen Visit A (Visit 0A) coordinators will complete Eligibility Checklist 1 (P5_ELIG1). This checklist covers very basic eligibility criteria that the participant or his/her guardian can provide information to address. Examples include plans to move in the next 16 months (the study duration), use of corticosteroids or a respiratory tract infection in the past 4 weeks, etc. Participants or their parents/guardians should review the data recorded on P5_ELIG1 and initial/date the source documentation box on page 2 of the form.

Participants who pass all of the eligibility checks on P5_ELIG1 will have a thorough medical history taken and will undergo a comprehensive physical examination at Visit 0A. Findings from these procedures can affect the participant's continued study eligibility. Eligibility criteria related to the participant's medical condition and medical history are recorded on Eligibility Checklist 2 (P5_ELIG2). Participants or their parents/guardians should review the data recorded on P5_ELIG2 and initial/date the source documentation box on page 3 of the form.

If the participant remains eligible at Visit 0A following his/her exam and medical history assessment, he/she will perform spirometry with reversibility testing (post 4 puffs albuterol). Eligibility criteria related to baseline FEV₁ and reversal are documented on Eligibility Checklist 3 (P5_ELIG3). This checklist also documents the participant's ability to use the study inhalers and spirotel[®] correctly.

Note that individuals who do not have source documentation confirming that they have asthma and do not show an improvement of at least 12% in FEV₁ in response to 4 puffs of albuterol at Visit 0A remain eligible to continue in the trial, provided they perform a methacholine challenge at Visit 0B. PC₂₀ results from the challenge will determine if these individuals are eligible to continue beyond Visit 0B.

Participants who pass all the eligibility checks on P5_ELIG1, P5_ELIG2 and P5_ELIG3 are formally enrolled in the BARD study and will enter the study run-in. Data for these participants should be entered into the BARD database and forwarded to the DCC.

Participants who do not meet all of the eligibility checks on P5_ELIG1, P5_ELIG2 and P5_ELIG3 are not eligible for study enrollment. Forms that were completed at Visit 0A should not be entered into the study database or forwarded to the DCC; they should be filed in the participant's study folder at the performance site. These individuals are considered screen failures.

Visit 0A1

Complete ICS Step-Down Assessment form (P5_STEPDOWN_ASSESS)

Participants who are in the 2-step step-down group begin the study on 2-2.5xICS Flovent[®] for the first 2 weeks. These individuals are assessed at Visit 0A1 to determine if they meet criteria to step their dose down to 1xICS. Part of the assessment involves checking their asthma control for study eligibility. These criteria are documented on the ICS Step-Down Assessment form (P5_STEPDOWN_ASSESS). See the discussion of Inhaled Corticosteroid (ICS) Step-Down Groups and Assessment in this section for further details.

Visit 0B

Complete Eligibility Checklist 4 (P5_ELIG4)

Eligibility criteria that are assessed at Visit 0B are recorded on Eligibility Checklist 4 (P5_ELIG4). All participants who return for Visit 0B and are eligible for the procedure will undergo spirometry and methacholine challenge at the visit. Participants who require a PC₂₀ to confirm their asthma diagnosis will be evaluated for eligibility. If their PC₂₀ does not meet study criteria, they are ineligible to continue.

Inclusion/exclusion criteria assessed at each of visits 0A, 0A1, and 0B are outlined in detail below. Criteria assessed for eligibility for randomization are covered in the Eligibility Criteria (Randomization) section.

Nightshift workers and others with altered schedules

BARD has no specific exclusion for nightshift workers and individuals with other altered day/night schedules. Individuals working the 11 PM to 7 AM shift or the 12 AM to 8 AM shift may be screened and enrolled at the local investigator's discretion. These participants should follow normal AM and PM daily procedures, dosing from the study Diskus[®] during the AM hours (5 AM until 10 AM ideal timeframe) and PM hours (5 PM until 10 PM ideal timeframe) and completing the e-diary questions during the specified

AM and PM scheduled sessions. Depending on the participant's schedule, his/her AM and PM symptoms and peak flows may be reversed. A notation should be made to this effect in the clinic notes and on the SpiroTel[®] Participant Visit Report. See the Urine Cortisol:Creatinine Laboratory Test section for clarification on handling the overnight urine collection for shift workers.

Visit 0A - Inclusion Criteria

- For participants in the Age 18+ Track: Ability to provide informed consent, as evidenced by the signing of a copy of the BARD study consent form approved by the study institution's Committee on Human Subjects' Research (i.e., Institutional Review Board).

For participants in the Age 5-11 and Age 12-17 Tracks: Ability of parent or guardian to provide informed consent, as evidenced by signing a copy of the consent form approved by the study institution's Committee on Human Subjects' Research (i.e., Institutional Review Board). Verbal or written assent by the minor participant should be documented according to local institutional guidelines.

The informed consent (and assent, as applicable) documents must be signed on or before the Visit 0A date.

See the discussion of Informed Consent in this section for further details.

This criterion is documented in Q1000, Q1010, and Q1020 on P5_ELIG1.

- Male or female, age 5 and older (no upper limit).

This criterion is documented in Q1040 on P5_ELIG1.

- Participant self-report of Black/African American ancestry, defined as having at least one Black biological grandparent.

Having at least one Black or African American biological grandparent is a minimum requirement for enrollment in the study. If a participant self-identifies as Black or African American, but he/she does not know his/her grandparents (or parents in some cases), he/she will be allowed to enroll. The assumption is made that if someone self-identifies as Black, then he/she has at least one Black parent or grandparent and meets the inclusion criterion. Individuals who are adopted and do not know their biological relatives, but self-identify as Black or African American, may enroll. Individuals who do not know their biological relatives for

reasons other than adoption who self-identify as Black or African American may also enroll.

Hispanics with at least one Black biological grandparent may enroll. In general, individuals who do not self-identify as Black, but who confirm that they have at least one Black biological grandparent, may enroll.

This criterion is documented on P5_ELIG1 in Q1050. This question should be answered 'Yes' if any of the scenarios described above apply.

Note that no substantiation of the biological Black or African American grandparent is required. The grandparent will not need to be named or otherwise tracked. This criterion is confirmed solely on the basis of participant (or participant parent/guardian) self-report.

- Stable asthma controller therapy dose for at least 2 weeks prior to Visit 0A.

For purposes of this study, 'controller therapy' is defined as inhaled corticosteroids (ICS) and ICS combination therapy with long-acting beta-agonists (LABAs).

Use of LABAs alone does not qualify. If a screened participant is on LABA alone (not recommended under the current asthma therapy guidelines), he/she may be prescreened, consented, and started on low dose 1xICS (Flovent[®]) for 2 weeks. At that point Visit 0A may be scheduled for a full evaluation of his/her eligibility for the trial. Local IRB rules and guidelines must be followed.

To qualify on this criterion, a participant must have taken his/her controller medications within 3 days of Visit 0A. Stable dose is defined as use of the same medication on the same dosing schedule for a 2-week period. Individuals who dose every other day will qualify as long as they consistently dosed from the same medication in the 2-week window prior to Visit 0A.

In order to perform spirometry at Visit 0A, participants who are taking ICS/LABA combination drugs (Advair[®], Symbicort[®], Dulera[®]) will need to hold their medication for 24 hours prior to the visit (to meet the LABA washout). This criterion is satisfied as long as the participant was taking his/her medication regularly the full 2 weeks prior to the visit, with the exception of the 24-hour washout period.

This criterion is documented in Q1010 on P5_ELIG2.

-
- If intranasal steroids will be needed at any time during the study, willingness of the participant to use a single intranasal steroid at a stable dose continuously for the duration of the study, starting at or before Visit 0A.

Any intranasal steroid may be used, as long as it is used at a constant dose continuously throughout the participant's study participation. Constant dose for this study will be defined as use of the same nasal steroid on at least 4 days per week; PRN dosing is not allowed. The study physician should be consulted if the participant is not using an intranasal steroid at the time of screening (Visit 0A) and the need for one is unclear. Examples include: Nasonex, Flonase, Nasacort, Rhinocort, etc. Intranasal steroids are not provided by the BARD study.

Use of intranasal steroids must be recorded on the Concomitant Medications for Asthma/Allergy and Adverse Events form (CMED). It is important to the goals of the study to be able to account for all steroid dosing, including intranasal steroids.

This criterion is documented in Q1080 on P5_ELIG2.

- Inadequately controlled on low, medium, or high dose inhaled corticosteroid (ICS) monotherapy, or low or medium dose ICS/LABA combination therapy OR well-controlled on low, medium or high dose ICS monotherapy or low, medium, or high dose ICS/LABA combination therapy.

Individuals who are taking tiotropium (Spiriva), a long-acting anticholinergic medication not currently FDA approved for the treatment of asthma, should be classified in the same fashion as someone who is taking a long-acting beta-agonist (LABA).

For purposes of assessing this criterion, inadequate asthma control will be defined as an ACT/CACT score at Visit 0A <20; well-controlled asthma will be defined as an ACT/CACT score ≥20.

To score the ACT (for participants in the Age 12-17 and Age 18+ Tracks):

- Each response to the 5 ACT questions has a point value from 1 to 5 as shown on the form.
- To score the ACT, add up the point values for each response to all five questions.
- The score should range from 5 to 25.

To score the CACT (for participants in the Age 5-11 Track):

- Responses for the first four questions range from 0 to 3. Responses for the last three questions range from 0 to 5.
- To score the CACT, add up the point values for each response to all seven questions.
- The score should range from 0 to 27

To determine the participant's baseline ICS dose level (low-medium-high), perform the following steps. This information can be recorded in the Clinic Use Only box on page 1 of P5_ELIG2.

- Locate the participant's current ICS, nebulized steroid, or ICS/LABA dose information on the Prior Asthma/Allergy Treatment form (PRIOR_TRT). Be sure to reference the drug used just prior to entering the study.
- Record the ICS code from Q1470 (monotherapy), Q1535 (nebulized steroid) or Q1600 (combination therapy) in step a in the Clinic Use Only box.
- Note whether the participant is taking a combination medication with LABA (or tiotropium) or not. Record this information in step e in the Clinic Use Only box.
- Refer to the Prior Asthma/Allergy Treatment Form reference card (PRIOR_TRT_CARD) to find the generic drug name. Record it in step ai in the Clinic Use Only box.
- Record the # daily puffs/treatments taken from Q1480 (ICS monotherapy), Q1540 (nebulized steroid) or Q1610 (combination therapy) in step b in the Clinic Use Only box.
- Refer to PRIOR_TRT_CARD to find the mcg/puff or mg/treatment for the participant's medication. Record it in step c in the Clinic Use Only box. Note the following adjustments if the participant is using any of the following combination medications:

Advair MDI: Convert 45 mcg dose to 44
 Convert 115 mcg dose to 110
 Convert 230 mcg dose to 220

Dulera MDI: Convert 100 mcg dose to 110
 Convert 200 mcg dose to 220

Symbicort MDI: Convert 80 mcg dose to 90
 Convert 160 mcg dose to 180

- Calculate the daily dose in mcg/mg by multiplying the # daily puffs x mcg/puff or #daily treatments x mg/treatment. Record daily dose in step d in the Clinic Use Only box.
- Compare the participant's daily ICS dose in mcg/mg to the Inhaled Corticosteroid Daily Dosage Level table on the BARD ICS Dose and Step Determination reference card (P5_ICS_DOSE_STEP). Find the entry for the correct ICS and for the correct age group (5-11 or 12+). Determine if the participant's dose is classified as low, medium, or high. Note the adjustments for the following combination medications:

Advair MDI: Compare to fluticasone MDI
 Dulera MDI: Compare to mometasone DPI
 Symbicort MDI: Compare to budesonide DPI

Note that a more detailed version of the table presented on the P5_ICS_DOSE_STEP reference card is included in this manual in the Inhaled Corticosteroid (ICS) Step-Down Groups and Assessment section.

- Record the ICS dose level (low, medium, high) in Q1020 on P5_ELIG2.

The P5_ICS_DOSE_STEP reference card also includes a table to classify each participant's asthma guideline therapy step based on his/her ICS dose level and whether he/she is on monotherapy or combination therapy (with LABA or tiotropium/Spiriva). Using this reference, determine the participant's guideline step and record it in Q1030 on P5_ELIG2.

Use the following table to assess the participant's eligibility based on his/her asthma control level and guideline step.

Eligibility Based on Guideline Step and Asthma Control Status

Therapy Type	ICS Dose Level	Asthma Guideline Step	Inadequate Control (ACT/CACT<20)	Well-Controlled (ACT/CACT≥20)
ICS Monotherapy	Low	2	Eligible	Eligible
	Medium	3	Eligible	Eligible
	High	4	Eligible	Eligible
ICS/LABA Combination	Low	3	Eligible	Eligible
	Medium	4	Eligible	Eligible
	High	5	Ineligible	Eligible

Participants who are inadequately controlled on step 5 therapy are ineligible (asthma too severe). Participants who are well-controlled on step 2 therapy (analogous to the 1xICS dose used in the BARD run-in) were also ineligible when the BARD study began (asthma too mild). In July 2014, in an effort to aid recruitment of children in the age 5-11 range, the protocol was modified (version 24.0) to allow individuals well-controlled on low dose ICS monotherapy to enroll.

This criterion is documented in Q1040, Q1050 and Q1060 on P5_ELIG2. See the Inhaled Corticosteroid (ICS) Step-Down Groups and Assessment discussion in this section for further details.

- Able to perform reproducible spirometry according to ATS criteria.

Participants will perform baseline spirometry, followed by inhalation of 4 puffs of albuterol, followed by post-albuterol spirometry at Visit 0A. Participants must be able to perform at least 3 and no more than 8 acceptable maneuvers with FVC and FEV₁ reproducible volumes (according to ATS/ERS criteria) during both spirometry sessions (pre- and post-albuterol) to remain eligible for the study. See the AsthmaNet Spirometry Manual in Appendix 1 of the AsthmaNet General Manual of Operations for details on ATS/ERS criteria.

The AsthmaNet spirometry overreader will give feedback on each spirometry session to ensure that all necessary criteria are met. If a participant continues in the study beyond Visit 0A and the overreader scores his/her Visit 0A spirometry session(s) poorly, then he/she will be considered ineligible and will need to be terminated from the study. Spirometry is performed at all post-randomization visits. It is important to the goals of the trial because FEV₁ is part of the composite primary outcome variable.

This criterion is documented in Q1000 on P5_ELIG3 in section 1 of the form.

- Baseline FEV₁ ≥40% of predicted and/or post-bronchodilator FEV₁ ≥40% of predicted

Use the value from Q1040 from the participant's Spirometry Testing form (SPIRO) at Visit 0A to assess the baseline FEV₁ criterion. Record the information in Q1010 on P5_ELIG3.

Use the value from Q1040 from the participant's Post-Albuterol (4 puffs) Spirometry Testing form (PALB4_SPIRO) at Visit 0A to assess the post-bronchodilator FEV₁ criterion. Record the information in Q1020 on P5_ELIG3.

The participant is eligible if either the baseline FEV₁ ≥40% of predicted, or the post-albuterol FEV₁ ≥40% of predicted, or both. If neither FEV₁ is ≥40% of predicted, the participant is ineligible.

A copy of the pre- and post-albuterol spirometry reports generated through the MedGraphics system should be submitted with the Visit 0A packet.

This criterion is documented in Q1010 and Q1020 on P5_ELIG3 in section 1 of the form.

- Ability of the participant to use the spiroteI[®] e-diary/peak flow meter correctly.

This criterion will be evaluated objectively for all participants using the SpiroteI[®] Performance Checklist (SPIROTEL_PERF) (use Version 2.0 to coordinate with the SpiroteI II device) along with the BARD/SIENA demo device. Train the participant on the use of the spiroteI[®] device (configured for BARD), including the e-diary questions and peak flows for scheduled AM and PM sessions, as well as unscheduled peak flows. Observe the participant using the device to do an AM scheduled session and a PM scheduled session (no peak flows are required for the PM session for this evaluation). Complete a SPIROTEL_PERF checklist as you observe the participant go through each step. If the participant does not demonstrate satisfactory performance, retrain him/her and complete a new checklist until his/her understanding of the device and subsequent performance improve. Participants must achieve a score of 13 out of 13 to be considered proficient at using the spiroteI[®].

Checklists should be filed in the participant's study folder at the performance site; do not forward them to the DCC.

This criterion is documented in Q1040 on P5_ELIG3 in section 2 of the form.

- Ability of the participant to use a metered dose inhaler (MDI) properly.

This criterion will be evaluated objectively for all participants using the version of the MDI Inhalation Technique Checklist that corresponds to how they plan to use their MDI (either with or without a spacer). Participants who do not plan to use a spacer must achieve a perfect score of eleven (which evaluates two separate inhalations) to pass the performance check on the MDI Inhalation Technique Checklist (Without Spacer) (TECH_MDI_NOSP). Participants who plan to use a spacer must achieve a perfect score of twelve (which evaluates two separate inhalations) to pass the performance check on the MDI Inhalation Technique Checklist (With Spacer) (TECH_MDI_SP). Participants will dose from their albuterol rescue inhaler as part of the pre/post-bronchodilator spirometry session at Visit 0A for purposes of this assessment. See the Inhalation Technique Assessment discussion in this section for further details.

Checklist(s) should be filed in the participant's study folder at the performance site; do not forward them to the DCC.

This criterion is documented in Q1050 on P5_ELIG3 in section 2 of the form.

- Ability of the participant to use a Diskus[®] properly.

The Diskus[®] Inhalation Technique Checklist (TECH_DISKUS) will be used to evaluate the participant's ability to coordinate use of the Diskus[®] device. Participants must achieve a perfect score of ten to pass the performance check. They will use a Diskus[®] Demonstrator unit (contains no drug) to carry out the performance check. See the Inhalation Technique Assessment discussion in this section for further details.

Checklist(s) should be filed in the participant's study folder at the performance site; do not forward them to the DCC.

This criterion is documented in Q1060 on P5_ELIG3 in section 2 of the form.

Visits 0A and 0B: Asthma Verification Inclusion Criteria

All participants must have documentation of spirometry and/or methacholine challenge test results that confirm their asthma diagnosis to remain eligible for the study. The BARD protocol is very flexible in this regard, making allowances for use of source documentation of past tests, if available, as well as including relevant tests at Visits 0A and 0B as part of normal visit procedures. To remain eligible for the study, each participant must meet at least one of the following criteria by the time Visit 0B has been completed:

- Beta-agonist reversibility defined as $\geq 12\%$ improvement in FEV₁ in response to 4 puffs of albuterol at Visit 0A.

At Visit 0A all participants will undergo a bronchodilator reversibility test. During this test, participants perform baseline spirometry followed by the administration of 4 puffs of albuterol and another spirometry session 10-15 minutes later. See the Spirometry discussion in this section and the Spirometry Manual of Operations in appendix 1 of the AsthmaNet General Manual of Operations for further details on reversibility testing procedures.

For purposes of eligibility assessment, reversibility is calculated on the basis of the baseline spirometry results (recorded on the Spirometry Testing form (SPIRO)) and the post 4 albuterol puffs spirometry session (recorded on the Post-Albuterol (4 puffs) Spirometry Testing form (PALB4_SPIRO)). Reversal is the relative change in FEV₁ expressed as a percentage.

Sample reversal calculations:

- % reversal:

To calculate the participant's % reversal with 4 puffs of albuterol, take the difference in raw FEV₁ values (in liters) (post FEV₁ value – pre FEV₁ value) and divide by the pre FEV₁ value. Multiply the result by 100.

Example:

Pre-test FEV₁ (from Q1030 SPIRO form): 3.24 liters

Post-test FEV₁ (from Q1030 PALB4_SPIRO form): 3.80 liters

Reversal % = $(3.80 - 3.24) / 3.24 * 100 = 17.28\%$

If the participant's reversal % is $\geq 12\%$ (without rounding) at Visit 0A, he/she meets the criterion. The participant in the example meets the criterion.

This eligibility criterion is recorded in Q1080 on section 3 of P5_ELIG3.

Note that individuals who do not meet the reversal criterion at Visit 0A and do not have source documentation satisfying the asthma verification criteria may continue in the trial, provided they meet all other eligibility criteria at Visit 0A. These participants will need to undergo spirometry and methacholine challenge testing at Visit 0B to attempt to meet the PC₂₀ eligibility criterion. If they do not have a PC₂₀ ≤ 16 mg/ml or meet at least one of the comparisons of baseline FEV₁ percent predicted against values from pre- and post-albuterol spirometry at Visit 0A (see BARD Eligibility Checklist 4 (P5_ELIG4)), they will be ineligible to continue beyond Visit 0B.

Participants who meet the reversal criterion at Visit 0A will still undergo spirometry and methacholine challenge testing at Visit 0B for characterization purposes.

- Valid source documentation within the past 12 months for an acceptable overread albuterol reversibility test showing an improvement of $\geq 12\%$ in FEV₁ in response to albuterol.

Source documentation consists of a report for an AsthmaNet pre/post spirometry test (or maximum reversal test) performed using AsthmaNet equipment and procedures at an AsthmaNet site. The test must have been overread by the AsthmaNet spirometry overreader and have received acceptable scores. (Tests performed using the '98' prefix in the participant ID are not overread and are invalid for this purpose.) The test must have been done within 1 year of the Visit 0A date and may have been done in conjunction with another AsthmaNet study. The amount of albuterol administered during the test is undefined; therefore, results from a pre/post or maximum reversal test where 2, 4, 6, or 8 albuterol puffs are administered are acceptable.

See above for sample reversal calculations. This eligibility criterion is recorded in Q1090 on section 3 of P5_ELIG3. Information from source documentation must be completed on P5_ELIG3 for verification by the DCC. The spirometry report(s) must be submitted with the visit packet.

- Valid source documentation for two acceptable overread AsthmaNet spirometry reports collected over the previous 12 months that show an absolute relative change in %predicted FEV₁ of ≥12%.

Source documentation consists of two spirometry reports from sessions performed using AsthmaNet equipment and procedures at an AsthmaNet site. Sessions must both be for the same participant who is currently being screened, and they must have been overread by the AsthmaNet spirometry overreader and have received acceptable scores. Spirometry reports must have been done within 1 year of the Visit 0A date and may have been done as part of another AsthmaNet study. No constraints are imposed regarding conditions surrounding the two spirometry sessions. That is, it is not necessary to prove that both sessions were done under the same conditions with respect to medications or substances taken prior to the test, presence or absence of respiratory tract infection symptoms, etc. A relative change in %predicted FEV₁ of ≥12% is indicative of variable lung function which will be accepted as substantiation that the participant has asthma. Percent predicted values are used to adjust out the effect of growth in children and adolescents over the period of time elapsing between measurements.

Absolute relative change calculations:

- Absolute relative change %:

To calculate the absolute relative change between two %predicted FEV₁ values, take the difference in % predicted FEV₁ values and calculate the absolute value of the difference. Divide the difference by the smaller of the two %predicted FEV₁ values. Multiply the result by 100.

Example:

Spirometry reports show that on 1/31/14 Stacy's %predicted FEV₁ was only 63%. Her FEV₁ %predicted value is 87% on 6/1/14.

Absolute relative change % = $|63-87| / 63 * 100 = 38\%$

If the participant's % is ≥12% (without rounding), he/she meets the criterion. Stacy meets the criterion.

This eligibility criterion is recorded in Q1160 on section 3 of P5_ELIG3. Information from source documentation for both tests must be completed on P5_ELIG3 for verification by the DCC. Spirometry reports must be submitted with the visit packet.

-
- Valid source documentation from an AsthmaNet methacholine challenge performed within 12 months of the Visit 0A date reflecting a $PC_{20} \leq 16$ mg/ml if the participant was on inhaled corticosteroids (ICS) at the time of the challenge or a $PC_{20} \leq 8$ mg/ml if the participant was not on ICS at the time of the challenge.

To qualify, challenges must have been carried out by an AsthmaNet-certified technician using AsthmaNet equipment, procedures, and methacholine supplies. The challenge must also have been overread by the AsthmaNet grader and received an acceptable score. Tests that have a '98' prefix in the participant ID are not overread and, therefore, do not meet study source documentation criteria.

The PC_{20} cutoff for entry (8 mg/ml or 16 mg/ml) should be assessed based on the participant's ICS status *at the time the historical test was performed*. This status may or may not be the same as the participant's status on the day of Visit 0A.

This eligibility criterion is recorded in Q1250 on section 3 of P5_ELIG3. Information from source documentation for the challenge must be completed on P5_ELIG3 for verification by the DCC. The methacholine challenge report must be submitted with the visit packet.

- Asthma confirmed by bronchial hyper-responsiveness defined as a $PC_{20} \leq 16$ mg/ml at Visit 0B.

All participants who qualify to perform the methacholine challenge at Visit 0B will proceed with the challenge. See the Methacholine Challenge discussion in this section for further details. This eligibility criterion will be assessed at Visit 0B only for the subgroup of individuals who did not meet any of the asthma verification criteria at Visit 0A.

Individuals whose FEV_1 falls $\geq 20\%$ in response to the diluent will have a PC_{20} of 0 recorded on the Methacholine Challenge Testing form (METHA). These individuals may be considered eligible to continue in the study if they have a known history of asthma and the local investigator is confident that they have asthma.

A copy of the methacholine challenge report generated through the MedGraphics system should be submitted with the Visit 0B packet.

This criterion is documented in Q1020 on P5_ELIG4.

- Absolute relative change in %predicted FEV₁ of ≥12% when comparing the participant's baseline %predicted FEV₁ from Visit 0B to the participant's baseline %predicted FEV₁ from Visit 0A.

This eligibility criterion will be assessed at Visit 0B only for the subgroup of individuals who did not meet any of the asthma verification criteria at Visit 0A.

See the example above for calculating absolute relative change for two %predicted FEV₁ values.

This comparison is between the pre-albuterol baseline FEV₁ at Visit 0A (from Q1040 on SPIRO) and the pre-diluent baseline FEV₁ at Visit 0B (from Q1040 on SPIRO). Both spirometry sessions must meet ATS criteria and be technically acceptable to qualify.

This criterion is documented in Q1030 on P5_ELIG4.

- Absolute relative change in %predicted FEV₁ of ≥12% when comparing the participant's baseline %predicted FEV₁ from Visit 0B to the participant's post-albuterol %predicted FEV₁ from Visit 0A.

This eligibility criterion will be assessed at Visit 0B only for the subgroup of individuals who did not meet any of the asthma verification criteria at Visit 0A.

See the example above for calculating absolute relative change for two %predicted FEV₁ values.

This comparison is between the post-albuterol (4 puffs) FEV₁ at Visit 0A (from Q1040 on PALB4_SPIRO) and the pre-diluent baseline FEV₁ at Visit 0B (from Q1040 on SPIRO). Both spirometry sessions must meet ATS criteria and be technically acceptable to qualify.

This criterion is documented in Q1040 on P5_ELIG4.

Visit 0A – Exclusion Criteria

- Unwilling to provide a blood sample for DNA extraction and genetic analysis (part of co-primary aims of the study).

Genetic ancestry analysis is the basis for the co-primary hypothesis of the BARD trial. Therefore, individuals who are unwilling to consent to provide a blood sample for genetic analysis for this purpose are ineligible. When consenting the participant on or before Visit 0A, review the participant's (or his/her guardian's) response to the following question in the text of the genetics consent section:

“Do you agree to genetic testing and the sharing of your (or your child's) coded genetic samples with AsthmaNet and NIH/NHLBI research centers/investigators for the purposes of identifying genes and/or variations in genes related to asthma, allergies, and related diseases (to be performed only with the agreement of the AsthmaNet Steering Committee)? For this study, this agreement also includes the tests related to ancestry described above.”

If the participant or guardian answers this question ‘No’, the participant is ineligible to continue in the study.

The participant or guardian may answer the following question in the text of the genetics consent ‘No’ and the participant remains eligible for BARD:

“Do you agree to allow your clinical site to identify and get in touch with you in the future based on the results of genetic testing (to be performed only with the agreement of the AsthmaNet Steering Committee and the local Human Subjects' Protection Board)?”

Note that blood for genetic analysis is not drawn until the participant is randomized at Visit 1. See the discussion of Genetics Blood Draw in this section for details.

This criterion is documented on P5_ELIG1.

- Plans to move away from the clinical site in the upcoming 16 months such that a participant's ability to complete the study will be jeopardized.

If a participant is planning to move in the near future to a location that would preclude his/her completion of the study at the original performance site or at another AsthmaNet BARD performance site, then he/she should not be enrolled.

This concern should be discussed with college students who tend to relocate during the summer months to determine if they will be able to complete all study visits at the local site or make alternate arrangements. Only participants who have a high likelihood of completing the entire study (through Visit 13) should be screened and enrolled.

This criterion is documented on P5_ELIG1.

- Use of investigative drugs or enrollment in an intervention trial in the past 30 days, or plans to enroll in such a trial during the BARD study.

Good clinical practice dictates that an individual should not participate in multiple intervention trials at the same time, due to possible interactions of study interventions which pose a safety concern and confounding of the resulting data. When screening potential BARD participants, ensure that they are not currently participating in another intervention trial and, if they participated in one recently, that at least 30 days have elapsed since they terminated from the other study. Do not screen or enroll individuals who indicate that they are interested in participating in other intervention studies while they are still in the BARD trial.

Note: Participants who are completing the final visit for the STICS trial and are interested in enrolling in BARD must wait a minimum of 30 days before completing Visit 0A. The waiting period between studies applies even if the participant was on open-label medications at the end of the STICS trial.

While in the BARD trial, individuals may participate in non-intervention studies that do not interfere with the medications and procedures required for the BARD trial. Contact the BARD scientific coordinator at the DCC to discuss individual circumstances as they arise.

This criterion is documented on P5_ELIG1.

- Medical contraindication to long-acting beta-agonists (LABA) (salmeterol or formoterol) or a history of adverse reaction to inhaled corticosteroids (ICS) (fluticasone) or LABA preparations or any of their ingredients

This criterion is documented on P5_ELIG1.

- Systemic corticosteroid treatment for any condition within the past 4 weeks.

Participants who have received systemic corticosteroids for treatment of any condition (e.g., asthma and allergies, skin conditions, myositis, etc.) within 4 weeks of Visit 0A should not complete the visit until the full 4 week washout has been met. Coordinators should determine why corticosteroids were prescribed, as the underlying condition may be exclusionary.

Systemic corticosteroids include oral (e.g., prednisone), injectable (IM), and intravenous (IV) steroids.

This criterion is documented on P5_ELIG1.

- Asthma exacerbation requiring treatment with systemic corticosteroids in the past 4 weeks.

Participants who have experienced a significant asthma exacerbation within 4 weeks of Visit 0A should not complete the visit at this time. These individuals should defer Visit 0A until the full 4 weeks have passed and their asthma is stable.

Systemic corticosteroids include oral (e.g., prednisone), injectable (IM), and intravenous (IV) steroids.

This criterion is documented on P5_ELIG1.

- History of life-threatening asthma exacerbation requiring treatment with intubation and mechanical ventilation, or resulting in a hypoxic seizure within the past 2 years.

Individuals requiring non-invasive mechanical ventilation (e.g., positive pressure) may be eligible. The local investigator should review the details of the medical history and make a determination of the individual's suitability for the study.

This criterion is documented on P5_ELIG1.

- History of a respiratory tract infection in the past 4 weeks.

A respiratory tract infection is defined as a cough, runny nose plus or minus fever, or sore throat that is not related to allergen exposure. This criterion is evaluated by participant self-report; no specific medications need to have been taken to meet this criterion. The 4-week washout period should begin after the last day of cold symptoms and applies only at Visit 0A. At all subsequent visits,

the occurrence of a recent infection should be documented on the Clinical Adverse Events (AECLIN) form and the visit may proceed with spirometry testing and other study procedures as deemed appropriate by the study physician.

This criterion is documented on P5_ELIG1.

- Use of six or more courses of systemic corticosteroids for treatment of asthma in the past year.

Systemic corticosteroids include oral (e.g., prednisone), injectable (IM), and intravenous (IV) steroids. Individuals who are on chronic systemic corticosteroid therapy for asthma (or any condition, in general) are ineligible for the study.

This criterion is documented on P5_ELIG2.

- Allergen immunotherapy other than an established maintenance regimen implemented continuously for a minimum of 3 months.

Allergen immunotherapy (also referred to as hyposensitization therapy or allergy shots) is allowed during the BARD trial. Participants must be on consistent immunization therapy for at least 3 consecutive months prior to Visit 0A for the program to be considered an established maintenance regimen. Participants must be willing to continue on the same program, and new programs should not be initiated, for the duration of the individual's participation in the BARD trial.

Before screening a participant who is receiving allergen immunotherapy *other than allergy shots*, contact the BARD Scientific Coordinator at the DCC for an assessment of the participant's eligibility.

This criterion is documented on P5_ELIG2.

- Smoking of any substance (cigarettes, a pipe, cigar, marijuana, other illegal drugs, electronic cigarettes (e-cigs), etc.) in the past year (12 months).

Use of electronic cigarettes is also known as vaping. As there is thought to be a strong correlation between vaping and use of traditional tobacco products, and the effects of vaping are still largely unknown, anyone who has used an e-cigarette within one year of Visit 0A is ineligible to enroll.

Note that vaping of any substance, including non-nicotine preparations, is not allowed within 12 months of entering the study. The effect of other substances on

the airways is unknown and could affect the results of study tests and assessment of study drug effects.

Use of a hookah (water-pipe smoking device) with any substance in the past year is also exclusionary.

This criterion is documented on P5_ELIG2.

Note: Participants may use smokeless tobacco products (e.g., chew, snuff etc.) during the study. However, use of these substances should be discouraged. Participants should refrain from using these products on the day of a study visit, especially at Visit 1 when sputum induction will be performed. Use of smokeless tobacco products is no longer exclusionary for spirometry procedures, but it is documented on the BARD Pulmonary Procedure Checklist (P5_PULMONARYCHK) at each visit that includes spirometry.

- Age 5-11 and Age 12-17 Tracks: Lifetime smoking history ≥ 5 pack-years.
Age 18+ Track: Lifetime smoking history ≥ 10 pack-years.

The pack-year limit applies regardless of when an individual stopped smoking.

Definition of pack-year: A participant smoked for one pack-year if he/she smoked one pack of cigarettes (i.e., 20 cigarettes) a day for a period of one year. In general, the number of pack-years someone smoked is computed as:

$$\text{pack-years} = \# \text{packs/day} * \# \text{years smoked that quantity}$$

A participant with a 10-pack-year history could have smoked one pack of cigarettes per day over 10 years or two packs a day for 5 years, or many other combinations of packs/day and durations.

If a participant smoked an odd number of cigarettes per day, or had a history of smoking variable amounts of cigarettes per day over time, the resulting number of pack-years should be estimated to one decimal place for each part of the calculation.

For example, suppose a participant smoked an average of 8 cigarettes per day for 6 years, and 3 cigarettes per day for 3 years, eventually quitting. His/her pack-year history would be computed as:

$$(8/20) * 6 + (3/20) * 3 = 2.4 + .5 = 2.9 \text{ pack-years}$$

This criterion is documented on P5_ELIG2.

Note: Pack-year history is quantified on the Adult Asthma and Allergy History form (ASTHMA_HX_ADULT) completed at Visit 0A for participants in the Age 12-17 and Age 18+ Tracks. Coordinators should use this information to answer Q1110 and Q1120 on P5_ELIG2 for these participants. No pack-year history is captured for participants in the Age 5-11 Track. The Pediatric Asthma and Allergy History form (ASTHMA_HX_PED) is completed for these participants. This form collects only information on maternal smoking during pregnancy and exposure to smoking in the household. Input from the participant's parent/guardian should be used to answer Q1120 for participants in the Age 5-11 Track.

- Pregnancy or lactation at Visit 0A or plans to become pregnant in the next 16 months.

At Visit 0A this criterion is confirmed only by participant self-report. If the participant is eligible to continue in the trial and is a woman of child-bearing potential, she will undergo a urine pregnancy test at Visit 0B prior to the methacholine challenge at that visit. All women of childbearing potential will have a urine pregnancy test performed at Visit 1, prior to randomization in the trial. For additional details, see the Pregnancy Test discussion in this section.

Note that women who are post-pregnancy and lactating but are not breast feeding are eligible for BARD screening.

This criterion is documented on P5_ELIG2.

- If potentially able to bear children, not using an acceptable form of birth control.

Acceptable forms of birth control include:

- Birth control patches (Ortho Evra™)
- NuvaRing®
- Oral contraceptives
- Norplant®
- Depo-Provera®
- IUD
- IUS
- Single and double barrier methods (e.g., condom, spermicidal foam)
- Surgical sterilization (i.e., hysterectomy, tubal ligation, or vasectomy in monogamous partner)

- Post-menopausal (at least 1 year since last menses)
- Abstinence

This list is summarized on the Birth Control Methods reference card (BIRTH_CTRL).

A history of infertility may not be used as a substitute for appropriate birth control.

This criterion is documented on P5_ELIG2.

- Chronic diseases (other than asthma) that in the opinion of the local investigator would prevent participation in the trial or put the participant at risk by participating.

In particular, individuals with an established diagnosis of vocal cord dysfunction or chronic diseases of the lung (other than asthma; e.g., emphysema, chronic bronchitis, pulmonary embolism, malignancy, cystic fibrosis, etc.), kidney, heart, liver, endocrine or nervous system, or immunodeficiency will be excluded.

Note that the majority of the following conditions are exclusionary only if deemed clinically unstable or contraindicated for the protocol in the judgment of the local investigator and the principal investigator for the protocol. If a potential participant's eligibility is in question, contact the BARD scientific coordinator at the DCC for assistance.

This criterion is documented on P5_ELIG2.

At Visit 0A this criterion will be assessed by participant self-report and through information gathered during the medical history and physical exam.

Exclusionary conditions include, but are not limited to:

- Addison's disease
- AIDS
- Cardiac arrhythmias (clinically significant)
- Cardiac disorder (except hemodynamically insignificant ASD, VSD or heart murmur)
- Cataracts¹
- Chest surgery (call for exception, if warranted)

¹ Individuals who have undergone successful cataract surgery and have no evidence of current disease may be enrolled.

-
- Clotting disorders
 - Congenital anomalies of lung and chest, including growth abnormalities that affect predictability of expected lung function parameters
 - Congestive heart failure
 - Coronary artery disease (unstable or severe)
 - Cushing's disease
 - Diabetes mellitus (poorly controlled)
 - Dyspnea by any cause other than asthma
 - Eating disorder (e.g., anorexia or bulimia – active disease only)
 - Eczema, severe (if likely to require oral/systemic corticosteroid treatment)
 - Factor deficiency
 - Failure to thrive
 - Gastroesophageal reflux (GERD) (if not controlled by standard medical therapy)
 - G6PD deficiency
 - Glaucoma
 - Hematologic disease (unstable, e.g., severe anemia, sickle cell disease²)
 - Hepatic disease³
 - Hypertension (poorly controlled)
 - Hyperthyroidism⁴
 - Immunologic compromise⁵
 - Inflammatory bowel disease (IBD, including Crohn's disease and ulcerative colitis) (if likely to require oral/systemic corticosteroid treatment)
 - Lactation (if pregnant or breast feeding)
 - Lung disease other than asthma (e.g., COPD, emphysema, chronic bronchitis, pulmonary embolism, malignancy, cystic fibrosis, bronchiectasis, bronchopulmonary dysplasia, among others)
 - Lupus (active disease, requiring immunosuppressants)
 - Any malignancy other than basal cell skin cancers⁶
 - Mental illness (uncontrolled)⁷
 - Mental retardation
 - Myasthenia gravis

² Sickle cell trait is allowable.

³ Nonactive hepatitis B/C is allowable; active hepatitis (including antigen positivity or disease requiring treatment) is exclusionary.

⁴ Controlled hypothyroidism is allowable.

⁵ Resulting in prior infections and/or susceptibility to new infections.

⁶ History of cancer may be acceptable if the participant has been cancer-free for at least 5 years, interactions between maintenance medications and study medications have been considered, and the local investigator has reviewed the case. Send details to the DCC.

⁷ Anxiety, depression, or bipolar disease well-controlled on allowed medications are allowable conditions for the BARD trial.

-
- Neurologic disease (including epilepsy requiring treatment and febrile seizure in infancy)
 - Osteogenesis imperfecta
 - Peptic ulcer disease (active)
 - Phenylketonuria
 - Pregnancy
 - Renal disease (active disease requiring treatment with medications that affect study drugs)
 - Rheumatoid arthritis (if likely to require oral/systemic corticosteroid treatment)⁸
 - Schizophrenia
 - Skeletal disorders, including osteoporosis
 - Sleep apnea (untreated)⁹
 - Sleep disorder (history of)¹⁰
 - Substance abuse (including active drug or alcohol abuse)
 - Thyrotoxicosis
 - Tracheomalacia
 - Tuberculosis (active disease excluded; history of positive skin test with negative chest X-ray allowed)
 - Urinary retention (active symptoms within last 6 months)
 - Vocal cord dysfunction (diagnosis of)

These illnesses and conditions are listed on the BARD Exclusionary Medical Conditions reference card (P5_EXCLMED). This reference does not include an exhaustive list of exclusionary conditions. If a participant has a condition that the local physician deems unsafe for BARD participation, then he/she should not be allowed to screen for the study.

If a participant has a condition listed on the P5_EXCLMED reference card, but the local physician feels that study participation would be appropriate, contact the BARD scientific coordinator at the DCC with details. She will consult the BARD lead investigators and will document the final decision.

This criterion is documented on P5_ELIG2.

- Need for the use of any of the drugs listed in the table that follows; inability to go off these drugs for the required washout periods prior to Visit 0A and for the

⁸ Participants who have rheumatoid arthritis and are on excluded medications should not be screened; osteoarthritis is an allowable condition for the BARD trial

⁹ Individuals with an OSA diagnosis who are receiving treatment with CPAP, BiPAP, or APAP are eligible.

¹⁰ Occasional insomnia is allowable.

duration of the BARD study. The BARD Exclusionary Drugs reference card (P5_EXCLDRUG) contains a summary of this table.

It is important to note that any and all changes in a participant's medications must be approved by a study physician and documented in the participant's clinic notes.

This criterion is documented on P5_ELIG2.

Drugs to be withheld throughout the study (washout periods prior to Visit 0A)

Excluded Drug	Generic Names (may not be inclusive)	Trade Names (may not be inclusive)	Washout Prior to Visit 0A
Steroid Medications			
Oral or intravenous steroids (for any reason), except prednisone as provided in study	prednisone, prednisolone, dexamethasone	Decadron, Medrol, Orapred, Prednisone, Prelone, Pediapred	4 weeks
Inhaled steroids, except as provided in study	beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone, triamcinolone acetonide	Aerobid, Alvesco, Asmanex, Azmacort, Flovent, Pulmicort, QVAR	None
Intranasal steroids, except at stable drug and dose throughout the study	beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone, triamcinolone acetonide	Beconase AQ, Flonase, Nasacort AQ, Nasarel, Nasonex, Omnaris, Rhinocort	None
Nonsteroidal, Anti-inflammatory Medications			
Leukotriene modifiers	montelukast, zafirlukast, zileuton	Accolate, Singular, Zylflo	1 week
Cromolyn/Nedocromil for asthma	cromolyn, nedocromil	Intal, Tilade	1 week
Bronchodilators			
Oral β -agonists	albuterol, metaproterenol, terbutaline	Alupent, Brethine, Bricanyl, Metaprel, Proventil, Repetabs, Ventolin, Volmax	1 week
Short-acting inhaled β -agonists	epinephrine	Bronkaid Mist, Duo-Medihaler, Medihaler-Epi, Primatene Mist	6 hours
Intermediate-acting inhaled β -agonists (except study RESCUE drug)	albuterol, bitolterol, levalbuterol, metaproterenol, pirbuterol, terbutaline	Alupent, Brethaire, Brethine, Bronkometer, Maxair, Metaprel, Proventil, Tornalate, Ventolin, Xopenex	6 hours
Long-acting inhaled β -agonists, except as provided in study	formoterol, salmeterol	Advair, Dulera, Foradil, Serevent, Symbicort	24 hours
Short-acting anticholinergics	atropine, ipratropium bromide, pirenzepine, scopolamine	Atrohist, Atrovent, Bellatal, Combivent, Donnatal, Scopoderm, Transderm-	8 hours

Excluded Drug	Generic Names (may not be inclusive)	Trade Names (may not be inclusive)	Washout Prior to Visit 0A
		Scop	
Long-acting anticholinergics	tiotropium	Spiriva	24 hours
Xanthine Derivatives			
Short-acting theophylline	theophylline	Aminophylline, Slo-Phyllin	12 hours
Long-acting theophylline	theophylline	Slo-bid, Theo-Dur	24 hours
Ultra long-acting theophylline	theophylline	Theo-24, Uniphyll	48 hours
Biologic Therapy			
Anti-IgE therapy	omalizumab	Xolair	3 months
Anti-IL5 therapy	mepolizumab	Nucala	6 weeks
Drugs that Alter Steroid Metabolism			
Anticonvulsants	carbamazepine, phenobarbital, phenytoin	Carbatrol, Di-Phen, Dilantin, Epitol, Equetro, Luminal, Phenytek, Solfoton, Tegretol	2 weeks
Oral antifungal medications	clotrimazole, fluconazole, ketoconazole, miconazole, and others	Diflucan, Extina, Kuric, Nixoral, Xolegel, and others	2 weeks
Bactericidal Antibiotics	rifampin	Rifadin, Rifamate	2 weeks
Antibiotics			
Macrolide antibiotics, chronic use excluded	azithromycin, clarithromycin, dirithromycin, erythromycin, roxithromycin, troleandomycin	Biaxin, Dynabac, Rulid, Surlid, TAO, Zithromax, Zitromax	2 weeks
Cardiac Drugs			
Alpha-beta blockers	labetalol	Normodyne	2 weeks
Beta-blockers	acebutolol, atenolol, betaxolol, bisoprolol, carteolol, metoprolol, nadolol, penbutolol, pindolol, propranolol, timolol	Blocadren, Cartrol, Corgard, Inderal, Kerlone, Levatol, Lopressor, Sectral, Tenormin, Visken, Zebeta	2 weeks
Psych or CNS-Related Drugs			
Monoamine oxidase (MAO) inhibitors	harmaline, iproclozide, iproniazid, isocarboxazid, nialamide, phenelzine, selegiline, toloxatone, tranlycypromine	Nardil, Parnate	4 weeks

Note: Use of oral corticosteroids for conditions other than asthma prior to successful completion of Visit 0B is exclusionary. Assessment of asthma control on 1xICS and the ability to complete a valid methacholine challenge are both compromised in this situation; the participant should be terminated from the trial. He/she may re-enroll after meeting the 4-week prednisone washout requirement prior to Visit 0A. If a participant is prescribed oral or parenteral corticosteroids for a non-asthma condition later in the run-

in and prior to qualifying for randomization, contact the DCC for assessment of the situation. Participants should be asked to contact clinical staff if they are prescribed any non-study steroid medications during the run-in.

The following table contains drugs and substances that are allowed during the study, but must be withheld for specified periods of time prior to visits 0A, 0B, 1-13¹¹.

Drugs to be withheld prior to pulmonary function visits 0A, 0B, 1-13

Drug/substance	Trade Names	Washout Prior to Visits
Albuterol (study RESCUE inhaler)	Ventolin [®]	6 hours
Salmeterol (blinded study Diskus [®]) ¹²	Advair [®] or Flovent [®]	12 hours
Methylxanthine-containing food or beverages (caffeinated colas, coffee, tea)	Coke, Pepsi, Mountain Dew, Barq's Rootbeer, Red Bull	4 hours
Methylxanthine-containing medications	Anacin, Darvon, Esgic, Excedrin, No-Doz, Norgesic, Vivarin	4 hours
Alcohol-containing foods or beverages		4 hours

- Use of any prescription or over-the-counter medication other than those listed on the BARD Allowed Medications reference card (P5_MEDALLOW)

Chronic use of any medications other than beta-agonists or inhaled corticosteroids (ICS), except:

- acetaminophen
- analgesics for acute/chronic pain management (with MD discretion)
- antianxiety agents/anxiolytics (e.g., diazepam, chlordiazepoxide, alprazolam, lorazepam, gabapentin, buspirone) at a chronic, stable dose
- antibiotics (oral) (e.g., tetracycline, penicillin, cephalosporin, quinolones, monobactam, sulfonamides, minocycline, nitroimidazoles (Flagyl), macrolides (for intermittent use to treat acute adverse events only))
- antibiotics for acne (topical/oral) (macrolides allowed for intermittent use only)
- anticholesterol medications (e.g., Lopid, statin medications)
- specific antidepressants at stable, chronic dose
 - Selective Serotonin Reuptake Inhibitors (SSRI) (e.g., alaproclate, etoperidone, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, zimelidine)
 - Selective Serotonin Norepinephrine Reuptake Inhibitors (SSNRI) (e.g. desvenlafaxine, duloxetine, venlafaxine)

¹¹ These drugs/substances are allowed between visits, but not prior to pulmonary function testing. See Spirometry discussion.

¹² Hold is applicable after randomization at Visit 1; applies to visits 2-13.

- Non-SSRI/SSNRI antidepressants (except MAOI class drugs) (e.g., amitriptyline, amoxapine, bupropion, mirtazapine, nefazodone, trazodone, and others)
- Antifungal medications (topical preparations only) (e.g., clotrimazole, ketoconazole, miconazole, and others)
- antihistamines (oral and nasal) (e.g., chlorpheniramine (Chlor-Trimeton), desloratadine (Clarinex), diphenhydramine (Benadryl), fexofenadine (Allegra, Allegra-D), loratadine (Claritin), azelastine (Astelin, Astepro), olopatadine (Patanase) and others)
- specific antihypertensive medications- stable dose for well-controlled hypertension
 - alpha blockers (e.g., doxazosin, prazosin, terazosin)
 - angiotensin converting enzyme (ACE) inhibitors (e.g., benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril, ramipril)
 - angiotensin receptor blockers (Sartans) (e.g., candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan)
 - calcium channel blockers (e.g., amlodipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine, verapamil)
 - diuretics (e.g., amiloride, bumetanide, chlorothiazide, chlorthalidone, furosemide, hydrochlorothiazide, indapamide, methyclothiazide, metolazone, spironolactone, triameterene)
 - mineralocorticoid receptor antagonists (e.g., eplerenone)
 - sympathetic nerve inhibitors (e.g., clonidine, guanabenz, guanfacine, methyl dopa)
- antitussives (over-the-counter) (e.g., dextromethorphan)
- birth control patches (e.g., Ortho Evra™)
- bisphosphonates (e.g. alendronate (Fosamax), ibandronate (Boniva), zoledronic acid (Zometa))
- calcium-based antacids (e.g., TUMS)
- calcium supplements
- CNS stimulants/appetite suppressants/ADHD medications (e.g., amphetamine preps, lisdexamfetamine, methylphenidate hydrochloride (Ritalin), sibutramine, dextroamphetamine/amphetamine (Adderall))
- Cox-2 drugs (e.g., celecoxib (Celebrex), rofecoxib (Vioxx), valdecoxib (Bextra))
- decongestants (nasal) (e.g., oxymetazoline (Afrin) and others)
- decongestants (oral) (e.g., pseudoephedrine (Sudafed) and others)
- Depo-Provera®
- oral diabetes medications (for treatment of stable, controlled diabetes)
- erectile dysfunction medications (e.g. sildenafil, tadalafil, vardenafil)
- estrogen/progesterone replacement therapy for postmenopausal women
- expectorants (over-the-counter) (e.g., guaifenesin)

-
- eye preparations for allergic eye symptoms (topical) (e.g., antihistamines, NSAIDS, antiallergic compounds)
 - H₂ blockers (e.g., ranitidine, cimetidine, famotidine, nizatidine) for GERD
 - hair growth preparations (e.g., finasteride (Propecia))
 - hemorrhoid treatments
 - herpes medications (e.g., acyclovir (Zovirax), valacyclovir (Valtrex))
 - insulin (for treatment of stable, controlled diabetes)
 - intranasal steroids (any drug) at a stable dose throughout the entire study
 - laxatives
 - Librax
 - Lipase inhibitors (Alli[®], Xenical[®])
 - lithium
 - migraine analgesics/preventatives (e.g., butalbital, Midrin, triptan drugs, topiramate (Topamax))
 - nasal antiallergic spray (Cromolyn/Atrovent)
 - nasal saline spray
 - non-steroidal anti-inflammatory medications (e.g., aspirin, ibuprofen, naproxen, ketoprofen)
 - Norplant[®]
 - NuvaRing[®]
 - oral contraceptives
 - pimecrolimus for atopic dermatitis – avoid daily use
 - proton pump inhibitors (e.g., omeprazole (Prilosec), lansoprazole (Prevacid), esomeprazole (Nexium)) for GERD
 - psyllium
 - sleep aids (prescription or over-the-counter) used PRN
 - stool softeners
 - study medications (Flovent[®] (various strengths), RESCUE Ventolin[®], RESCUE prednisone (only for use as directed by a study physician), blinded Diskus[®])
 - tacrolimus for atopic dermatitis – avoid daily use
 - thyroid replacement medication (e.g., Levothroid, Levoxyl, Synthroid)
 - tretinoin for acne (Retin-A, Atralin, Renova, Avita, Altinac)
 - vitamins, minerals
 - low-potency topical corticosteroids (BID) (e.g., aciometasone dipropionate, desonide, dexamethasone, dexamethasone sodium phosphate, fluocinolone acetonide, hydrocortisone, hydrocortisone acetate)
 - medium-potency topical corticosteroids (BID) (e.g., betamethasone benzoate, betamethasone dipropionate, betamethasone valerate, clocortolone pivalate, desoximetasone, diflorasone 0.05%, fluocinolone acetonide, fluocinonide 0.05%, flurandrenolide, fluticasone propionate,

hydrocortisone butyrate, hydrocortisone valerate, mometasone furoate, triamcinolone acetonide)

This list is summarized on the BARD Allowed Medications reference card (P5_MEDALLOW).

In general, a participant is ineligible if he/she chronically uses any medication other than rescue beta-agonist, study drug, and the medications in the preceding list. If a participant's use of a specific allowed medication is chronic, a complete clinical assessment should be performed to ensure the participant's safety and his/her ability to complete the entire study. Care should be taken to evaluate any underlying conditions the participant may be treating with these medications, in the event that he/she may have an exclusionary medical condition.

If a participant is taking a medication that does not appear in the above list, but also does not appear on the BARD Exclusionary Drugs reference card (P5_EXCLDRUG), first consult the local investigator. If the local investigator feels the participant should be considered eligible, then contact the BARD scientific coordinator at the DCC with the details. She will contact the lead study investigators and will document the final decision on the participant's suitability for the study.

This criterion is documented on P5_ELIG2

- Participant's identical sibling is enrolled in BARD.

Genetically-related individuals (e.g., mother-child pairs and non-identical siblings) may enroll and become randomized in the BARD trial if they meet all eligibility criteria. Family relationships will be tracked on the BARD Biological Relative Tracking Form (P5_RELATIVE). This form tracks links among biological first-degree relatives (parent-child relationships, full siblings, half siblings, and identical siblings). All relationships are allowed without limit, with the exception of identical siblings. If a participant has an identical sibling already enrolled in the BARD trial, he/she is ineligible to enroll. If the enrolled sibling does not achieve randomization and is terminated from the trial (and will not be re-enrolled), then the participant may enroll in BARD and exception will be tracked. Contact the DCC for approval of the exception if this situation arises. Identical siblings are excluded due to the genetic ancestry analysis that is part of the co-primary aims of the study. Relationships are being tracked so that adjustments can be made to the statistical analyses, as needed.

This criterion is documented in Q1320 on P5_ELIG3.

2.17 Eligibility Criteria (Randomization)

These procedures are applicable for participants in all three BARD age tracks.

Randomization Eligibility Evaluation at Visits 0B, 0C, 0D

Participants are evaluated for randomization eligibility criteria at Visits 0B, 0C, and 0D while on low dose inhaled corticosteroids (1xICS). A final confirmation check is done at the time of Visit 1. If a participant meets all inclusion criteria and does not meet any of the exclusion criteria for randomization at Visit 0B, 0C or 0D, he/she can complete Visit 1 and become randomized. Visit 1 is the randomization visit. If the participant is qualified for randomization at the time of Visit 0B, he/she should be scheduled to return to the performance site as soon as the next day, or up to 2 weeks later, to complete Visit 1. He/she should remain on 1xICS in the interim. If the participant is deemed eligible for randomization at Visit 0C or 0D, he/she may complete Visit 1 and become randomized the same day, or he/she may be scheduled to return for Visit 1 as soon as the next day, or up to 2 weeks later at his/her convenience. If Visit 1 will be completed the same day as Visit 0C or 0D, special data management procedures apply for carrying out the visit and assembling and submitting the data. See section 4 of this manual for details on combining Visit 0C or 0D with Visit 1. Note that if a performance site intends to combine Visit 0C/0D with Visit 1 if the participant is deemed eligible for randomization at Visit 0C/0D, additional asthma and stress questionnaires must be completed at the beginning of the visit (prior to determining eligibility). Additional procedures are included in the gray box at the top of Visit Procedure Checklist 0C/0D (P5_VISIT0CD_A, P5_VISIT0CD_P). If the participant is not deemed eligible for randomization and will not complete Visit 1 the same day, the 'extra' questionnaires should be filed in the participant's study folder or shredded; they will not be data entered or submitted to the DCC.

If a participant appears to have met randomization eligibility criteria on the basis of information he/she provides during scheduled phone contacts between visits 0B/0C and 0C/0D, he/she should be seen as soon as possible for formal evaluation to confirm eligibility and achieve randomization. The Visit 0C/D Checklist should be followed, including the additional questionnaires in the gray box at the top if Visit 1 will be performed the same day if the participant's eligibility is confirmed. If the participant is deemed eligible, but he/she will not complete Visit 1 the same day, the coordinator should enter and submit the Visit 0C or 0D packet and schedule him/her for Visit 1 as soon as possible. Ensure that appropriate prednisone washouts will be met before scheduling Visit 1. If the participant is not deemed eligible for randomization at the impromptu visit, do not complete or enter the Visit 0C/D packet. The participant should

return to the performance site for the next regularly scheduled visit (0C or 0D) for further evaluation.

If a participant is seen for a scheduled Visit 0D and does not qualify for randomization, his/her study participation is complete. A Termination of Study Participation form (P5_TERM) should be completed and termination procedures followed.

Visits 0B, 0C, 0D, 1

Complete Randomization Eligibility Checklist (P5_RAND_ELIG)

Inclusion Criteria for Randomization

- Lack of acceptable asthma control on 1xICS

Lack of acceptable asthma control during the run-in period is defined as:

1. On more than 2 days per week for any 1-week period during the run-in, the participant experienced one or more of the following indicators of poor asthma control:

- Asthma symptoms rated at the following severity levels:

Symptom	Mild	Moderate	Severe
Shortness of breath	X	X	X
Wheezing	X	X	X
Chest Tightness	X	X	X
Phlegm/mucus	X	X	X
Cough		X	X

This criterion is evaluated from the symptom scores entered into the spirotel[®] e-diary by the participant on a daily basis. Specifically, Q4-8 and Q11-15 from the Spirotel[®] Coordinator Reference Card (P5_SPIROTEL_CREF) are evaluated. Mild symptoms qualify with the exception of cough, which must be graded moderate or severe (for consistency with the definition used in the CARE BADGER trial).

- Use of inhaled bronchodilator for symptom rescue (≥ 1 puff).

Preventative puffs taken prior to exercise or allergen exposure do not count towards this criterion.

This criterion is evaluated from information the participant enters into his/her spirote[®] e-diary for Q17 on P5_SPIROTEL_CREF.

- Peak flows (PEF) in the red or yellow zone (<80% of the current PEF reference).

PEF reference values are updated over the course of the run-in period. See the Reference Peak Flow (PEF) discussion in this section for details on defining and updating the PEF reference value for each participant.

This criterion evaluates scheduled AM and PM PEFs present in the participant's e-diary to determine if he/she experienced a PEF in the yellow zone (between 50 and 80% of the current PEF reference value) or red zone (<50% of the current PEF reference value) on a given day. Note that this criterion only evaluates PEF values from scheduled AM and PM sessions (trial types 1 and 2), not unscheduled PEFs. Scheduled sessions require three blows and save the best of three.

This part of the 'lack of acceptable asthma control' criterion is evaluated using rolling 1 week (7 day) periods across the entire run-in. If the participant has at least one of the indicators of lack of asthma control defined above for a given day, that day is flagged as an 'out of control' day. Each 7 day period is evaluated to determine if the participant had three or more 'out of control' days in that block of time. If the participant experienced any 7 day period with three or more 'out of control' days, then he/she meets the 'lack of acceptable asthma control' requirement for randomization. This criterion is evaluated across visits such that a given 7 day period may encompass data collected before and after a given visit date.

This criterion is evaluated and displayed for clinic personnel on the BARD Spirote[®] Eligibility Assessment Report (P5_ELIG_RPT). This report shows all data collected/downloaded for a given participant starting at Visit 0A1 (if applicable) through the current visit. All calendar days are represented even if the participant did not perform any e-diary tasks on a given day. The report shows visit number, download date, and calendar date (in chronological order). The next column (entitled

'Symptom/PEF/Rescue Flag') identifies with an 'X' the days that have been evaluated as 'out of control' days based on the above definition. If a given 7 day period has three or more 'X's, then that week meets the 'lack of acceptable asthma control' definition for randomization. The last column of the report table (entitled 'Lack of Asthma Control Criteria Met') shows an 'X' for every calendar day where the previous 7 day block of time (including that day) has at least three days flagged as 'out of control'. If a participant has at least one 'X' in the last column for the data corresponding to the current visit, then he/she qualifies on the 'lack of acceptable asthma control' criterion for the current visit. This holds even if the week that qualifies the participant includes data downloaded at the previous visit (i.e., the qualifying week crosses the previous visit date).

2. More than 1 night with awakening(s) due to asthma in a 2-week period.

This criterion is evaluated from the nighttime awakening information entered into the spirote[®] e-diary by the participant on a daily basis. Specifically, Q1 from P5_SPIROTEL_CREF is evaluated. Any day on which the participant entered 1 or more awakenings is flagged as an 'awakening' day. Each 2-week (14 day) period is evaluated to determine if the participant had two or more 'awakening' days in that block of time. If the participant experienced any 14 day period with two or more 'awakening' days, then he/she meets the 'lack of acceptable asthma control' requirement for randomization. This criterion is evaluated across visits such that a given 14 day period may encompass data collected before and after a given visit date.

This criterion is evaluated and displayed for clinic personnel on the BARD Spirote[®] Eligibility Assessment Report (P5_ELIG_RPT). The column entitled 'Awakening Flag' identifies with an 'X' the days that have been evaluated as 'awakening' days based on the above definition. If a given 14 day period has two or more 'X's, then that 2-week block meets the 'lack of acceptable asthma control' definition for randomization. The last column of the report table (entitled 'Lack of Asthma Control Criteria Met') shows an 'X' for every calendar day where the previous 14 day block of time (including that day) has at least two days flagged as 'awakening' days. If a participant has at least one 'X' in the last column for the data corresponding to the current visit, then he/she qualifies on the 'lack of acceptable asthma control' criterion for the current visit. This holds even if the 2 weeks that qualify the participant includes data downloaded at the previous visit (i.e., the qualifying 2 weeks cross the previous visit date).

Information on generating the BARD Spirotel[®] reports can be found in the Spirotel[®] discussion in this section of the BARD MOP. Also see the Spirotel[®] MOP in appendix 6 of the AsthmaNet General MOP.

Note: All Spirotel[®] downloads for a given participant must be performed on the same MedGraphics laptop for the Spirotel[®] Eligibility Assessment Report to generate properly.

This criterion is documented on P5_RAND_ELIG in Q1035.

- Ability to complete at least 75% of the Spirotel[®] e-diary and peak flow (PEF) sessions.

This criterion requires the participant to complete at least 75% of his/her AM and PM Spirotel[®] sessions to qualify for randomization. A complete session is one where all e-diary questions were answered and at least one peak flow maneuver was performed. Full days between visits are considered (i.e., visit dates are not included). The number of complete AM and PM sessions are counted. The compliance percentage is calculated as:

Comp. % = (#Complete AM sessions + # Complete PM sessions)/(2 x #full days)

This eligibility criterion is evaluated and presented for clinic personnel on the Spirotel[®] Eligibility Assessment Report (P5_ELIG_RPT). The report shows the number of full days since the last visit, number of complete AM sessions, and number of complete PM sessions, as well as the compliance percentage used for evaluation of the participant's eligibility. If the compliance percentage is less than 75%, the participant is ineligible for randomization.

This criterion is documented on P5_RAND_ELIG in Q1040.

Note: This e-diary and PEF compliance calculation differs from that presented on the BARD Spirotel[®] Participant Compliance Report (P5_COMPLY). The calculation on the P5_COMPLY report requires both AM and PM e-diary and PEF sessions to be complete and computes the percentage of days when the participant carried out all Spirotel[®] activities (a stricter definition of compliance). P5_COMPLY will be generated at each visit and data entered throughout the study to track overall e-diary and PEF compliance and to provide feedback to participants. P5_ELIG_RPT will be generated only during the run-in for purposes of establishing participant eligibility for randomization.

Note: If Visit 1 occurs one day following a screen visit (0B, 0C, or 0D), there will be no full days on which to make compliance calculations. In that case the report will show 0 full days and blanks for the number of complete AM and PM sessions and compliance percent. When completing P5_RAND_ELIG in this case, answer Q1040 'N/A'.

- Ability to take at least 75% of the scheduled doses from the study Diskus[®].

Participants are instructed to take 1 puff from their open-label Flovent[®] Diskus[®] in the AM and 1 puff in the PM. In order to assess the participant's level of asthma control on 1xICS and his/her study eligibility, he/she must follow dosing procedures at least 75% of the time. Compliance with Diskus[®] dosing during the run-in is captured on P5_RAND_ELIG. This criterion is documented in Q1090. See the Dosing Compliance discussion in this section for details on performing the compliance calculations.

If the participant has not taken at least 75% of the required doses from his/her Diskus[®], he/she is considered to be non-compliant and ineligible for randomization.

This criterion is documented in Q1090 on P5_RAND_ELIG.

General Non-compliance Note: If the participant is seen for Visit 0B and does not meet e-diary/PEF compliance (and/or Diskus[®] compliance) criteria and does not meet any of the exclusionary criteria (see below), he/she may be rescheduled to repeat the visit in 2 weeks in an effort to retrain and increase compliance. In that case, information collected at the initial visit should be recorded on P5_RAND_ELIG and the form should be entered as a single form. P5_ELIG_RPT should be submitted with the form. When the participant returns in 2 weeks for re-evaluation, P5_ELIG_RPT should be regenerated to determine the participant's e-diary/PEF compliance since the last visit. Only at Visit 0B (and Visit 0A1 for ICS step-down assessment) are the compliance calculations on this report performed on a download-specific basis; at Visits 0C, 0D, and 1 the calculations use all data associated with the visit number (combining data across all available downloads). At the repeat Visit 0B, the calculations will be completed only for new data entered in the Spirotek[®] by the participant since his/her original Visit 0B. At the repeat visit a new P5_RAND_ELIG form is completed and entered with the 0B visit packet. Diskus[®] compliance calculations should be based only on the interval (approximately 2 weeks) since the original visit. If the participant does not meet both compliance criteria (e-diary/PEF and Diskus[®] dosing) the second time he/she is evaluated at Visit 0B, he/she is ineligible to continue in the study. A BARD Termination of Study Participation form (P5_TERM) should be completed and study termination procedures followed. Participants are allowed one instance of non-compliance during

the run-in. If a participant is non-compliant for two evaluations, he/she should be terminated from the trial. Re-enrollment starting at Visit 0A can be considered at the discretion of clinical personnel.

In order to be eligible for randomization, the participant must meet lack of acceptable asthma control criteria, e-diary/PEF compliance requirements, and Diskus[®] compliance requirements during the same visit interval (0B, 0C, 0D). If Visit 0B is reattempted due to lack of compliance on the first assessment, and all criteria are met on the second attempt, the participant is considered eligible for randomization. At the second visit attempt, to determine if lack of acceptable asthma control criteria have been met, examine only days after the previous download/visit attempt. If there are any Xs in the last column in the Asthma Control Assessment portion of the report for any days after the previous download/visit attempt, then lack of acceptable asthma control criteria have been met. Note that this assessment may include information from days prior to the previous visit/download in establishing lack of asthma control, but the BARD Protocol Writing Committee determined that this is acceptable.

All three criteria (lack of asthma control, e-diary/PEF compliance and Diskus[®] compliance) are required for randomization to ensure that the study is including a population of asthmatics who are symptomatic/unstable on low dose ICS (1xICS). If lack of acceptable asthma control is evident, but the participant is not taking his/her ICS a large percentage of the time, the suboptimal control could be attributed to lack of treatment. If lack of acceptable asthma control is evident, but the participant is not completing his/her e-diary a large percentage of time, then it could be argued that he/she is not attentive to symptoms and PEF measurements to implement his/her asthma action plan appropriately. If he/she had treated symptoms and low PEFs as laid out in the action plan, then he/she may not have met the lack of acceptable asthma control conditions.

At Visit 1, if the participant was fully qualified for randomization at a previous screen visit (i.e., 0B, 0C or 0D), this information is captured on P5_RAND_ELIG in Q1025 and Q1030. In that case, the participant does not need to have met 'lack of acceptable asthma control' criteria since the qualification visit. Information is captured in Q1040 and Q1090 on the participant's compliance since the qualification visit, but randomization can proceed at Visit 1 at the discretion of clinical personnel even if the participant does not meet the 75% minimum requirements. If compliance with e-diary/PEF procedures or Diskus[®] dosing has decreased, the participant should be retrained and counseled.

Exclusion Criteria for Randomization - Exacerbations

Occurrence of an asthma exacerbation during the run-in while on 1xICS is not exclusionary and may, in fact, qualify the participant for randomization after he/she meets the required 14 day washout from prednisone/systemic steroids. The participant must meet all inclusion criteria for randomization, including lack of acceptable asthma control and compliance requirements as outlined above. If an exacerbation occurs and the participant does not meet compliance criteria for randomization, then he/she must be terminated from the trial. If an exacerbation occurs and the participant meets compliance criteria but does not meet lack of acceptable asthma control requirements for randomization, then he/she may still be eligible for randomization at the discretion of the BARD investigators. Contact the DCC with details to seek approval prior to randomizing the participant. See the Significant Asthma Exacerbation discussion in this section for further details on the definition and handling of exacerbations for the BARD study.

Exclusionary criteria related to asthma exacerbations follow. These should be evaluated at all screen visits (0B, 0C, 0D, 1). If the participant meets any of these criteria, he/she must be terminated from the study. In that case, submit a BARD Termination of Study Participation form (P5_TERM) and follow study termination procedures.

- Asthma exacerbation requiring hospitalization during the run-in.

If the participant experiences a severe exacerbation requiring in-patient hospitalization while on 1xICS during the run-in, he/she is ineligible to continue in the study due to safety concerns. In addition to completing a P5_TERM form, a Serious Adverse Event Reporting Form (SERIOUS) should be submitted.

This criterion is documented in Q1120 on P5_RAND_ELIG.

- Three significant asthma exacerbations on low dose inhaled corticosteroids during the run-in.

If a participant experiences multiple exacerbations requiring treatment with systemic corticosteroids during the run-in on 1xICS, he/she is ineligible to continue in the study due to safety concerns.

This criterion is documented in Q1130 on P5_RAND_ELIG.

- Asthma exacerbation during the run-in that may have been a result of the participant's lack of compliance with ICS dosing and/or e-diary/PEF procedures.

If a participant experiences an exacerbation during the run-in and he/she was non-compliant with taking his/her ICS or completing e-diary/PEF procedures, he/she must be terminated from the study.

This criterion is documented in Q1140 on P5_RAND_ELIG.

Exclusion Criteria for Randomization – Visit 1

Complete Eligibility Checklist 5 (P5_ELIG5)

Visit 1 is only completed for participants who meet all criteria for randomization as laid out on the BARD Randomization Eligibility Checklist (P5_RAND_ELIG). Eligibility Checklist 5 (P5_ELIG5) is a final opportunity prior to randomization to evaluate the participant for general eligibility criteria that may cause him/her to be ineligible for the study and would not be identified on the P5_RAND_ELIG form. BARD is an intention-to-treat study, which means that once a participant is randomized, he/she will be retained in the trial unless a safety issue is uncovered.

- Use of any of the excluded drugs listed in the BARD Exclusionary Drug Table (see the discussion of Eligibility Criteria (Screening)) during the run-in period. The BARD Exclusionary Drugs reference card (P5_EXCLDRUG) contains a summary of this table.

Use of oral corticosteroids does not exclude the participant as long as he/she meets all criteria on the P5_RAND_ELIG form, including the 14 day prednisone washout prior to Visit 1. If the prednisone was taken for a non-asthma-related adverse event after the participant met all randomization eligibility criteria, the participant is not excluded unless the adverse event itself poses a problem for study participation (i.e., is exclusionary). See the BARD Exclusionary Medical Conditions reference card (P5_EXCLMED) for details.

This criterion is documented in Q1000 and Q1000D on P5_ELIG5.

- Participant wishes to withdraw consent.

This is a final opportunity to ensure that the participant understands fully what study participation entails and is willing to continue. If the participant decides to withdraw consent, a BARD Termination of Study Participation form (P5_TERM) should be completed and submitted and the participant should not be randomized.

This criterion is documented in Q1010 on P5_ELIG5.

- Any new information that makes the participant ineligible.

If any new exclusionary criteria are uncovered prior to randomization, the participant must not be randomized. Document the reason the participant is now ineligible in Q1020D on P5_ELIG5. Complete and submit a BARD Termination of Study Participation form (P5_TERM) in this case.

This criterion is documented in Q1020 and Q1020D on P5_ELIG5.

2.18 Genetics Blood Draw

The genetics blood draw is applicable for all three BARD age tracks.

Visit 1

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

Genetics Consent

Before drawing blood for genetic analysis, verify that the participant or his/her guardian has given consent to participate in the genetic analysis component of the BARD study. Unlike most AsthmaNet studies, the genetics blood draw is required for the BARD trial due to the importance of the ancestral analysis to the goals of the study. Participants must agree to provide blood for genetic testing and the sharing of his/her coded genetic samples for the purposes of identifying genes and/or variations in genes related to asthma, allergies, and related diseases and for tests related to ancestry. The first statement in the genetics portion of the consent where the participant provides initials covers this. To participate in the BARD trial, the participant does not need to provide consent for future contact based on the results of genetic testing. This is generally the second statement in the genetics portion of the consent where the participant provides initials.

Blood Draw

Genetics blood is drawn in conjunction with the blood draws for ImmunoCAP, total IgE, cotinine, and complete blood count (CBC) at Visit 1. The order of blood draws outlined in the Blood Samples and Tests discussion in this section must be observed. Blood should be drawn at Visit 1 only for randomized participants.

As outlined in the AsthmaNet Genetics MOP, the amount of blood drawn for genetic analysis is dependent on the participant's BARD age track as follows:

- Age 5-11 Track: One 10 mL purple top vacutainer
- Age 12-17 Track: Three 10 mL purple top vacutainers
- Age 18+ Track: Three 10 mL purple top vacutainers

Make certain that all tubes are as full as possible to ensure sufficient DNA for ancestry analysis and future genetic analyses. If a participant cannot provide full purple-top

vacutainers of blood as listed above, collect as much blood as possible and submit it to the Arizona Genetics Lab in Tucson for DNA extraction and storage.

If a genetics blood sample cannot be obtained at Visit 1 (due to a hard stick, dehydration or another problem), the blood draw should be attempted again at a subsequent visit, preferably Visit 2, if the participant or his/her guardian concurs.

Blood draws must be attempted at Visit 1 for all randomized participants; however, if the draw is unsuccessful, the participant may continue in the trial. This will be considered an exception and it should not occur frequently. Genetics blood availability will be summarized by partnership and performance site on the BARD Accrual Report.

Genetics Sample Tracking

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.

Information regarding the genetics blood drawn for a given participant must be entered onto the AsthmaNet Genetics Sample Log (GEN_SAMP_LOG) just prior to refrigerating the samples. This log tracks the collection date and time, refrigeration date and time and the volume of blood collected in each tube. The log collects information needed for BioLINCC purposes.

GABLOOD Form

Complete the Genetic Analysis Blood Draw form (GABLOOD) for all randomized participants. 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 and section 4 of the BARD MOP for specific information on completing the GABLOOD form. Note that the participant/guardian must review the form and complete the source documentation information (initials and date), even if the blood draw was unsuccessful.

Note: If a participant consents to provide a genetic blood sample, but the sample is not obtained at Visit 1 (due to a hard stick, dehydration or another problem), the blood draw may be attempted again at a subsequent protocol visit if the participant concurs. If the genetics blood draw will be attempted at a future visit, then the Visit 1 packet GABLOOD form should be marked missing. 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 2). If the blood draw is attempted a second time 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 a single form with the current visit's packet. In that case, Q1000 and Q1010 should be completed, indicating that a blood sample was not obtained, and the participant or his/her guardian should provide source documentation. All randomized individuals must have a GABLOOD form present in the database before a Termination of Study Participation form (P5_TERM) is entered for them. Only one GABLOOD form should be entered per randomized participant.

Shipping Charges

Costs related to shipping BARD genetics samples to the Genetics Lab in Tucson have been included in the clinical site's BARD budget. The local site's FedEx account should be used for these shipments.

2.19 Geographic Information Systems (GIS) Add-on Study

The GIS add-on project is applicable to all three BARD age tracks.

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

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

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

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

Visit 1 (for randomized participants only)

Administer GIS consent; document assent as appropriate
Complete GIS Consent Tracking Form (GIS)

After the participant has been randomized at Visit 1, introduce the GIS Add-On Study to him/her (and his/her guardian, if under 18). Explain that participation is optional and what it entails. Document the participant's decision regarding participation on the GIS Consent Tracking Form (GIS). One form should be completed for each randomized participant to allow the DCC to monitor participation and to provide input to the GIS

researchers on which addresses they should have received. A form should be completed for randomized participants who do not consent to participate so that their status can be tracked.

Visit 1 (for randomized participants who consent to participate in the GIS Add-On Study only)

Complete the GIS Address Tracking Form (GIS_ADDRESS) with all addresses where the participant has resided since enrolling in BARD at Visit 0A

Add the participant's address(es) to the GIS BARD spreadsheet

Upload the updated spreadsheet to Pitt (see GIS MOP)

If the participant agrees to participate in the GIS Add-On Study, then further documentation is required. Complete an administrative GIS Address Tracking Form (GIS_ADDRESS) including all addresses where the participant has lived since enrolling in the BARD trial at Visit 0A. Provide approximate dates of residence.

All addresses recorded on GIS_ADDRESS should be added to the bottom of the GIS BARD address spreadsheet for the performance site. Ensure that addresses are being added to the correct spreadsheet. Each site should maintain a separate spreadsheet for BARD, SIENA, and STICS; IDs for participants from the various studies should not be combined into one spreadsheet.

The updated spreadsheet should be uploaded to the University of Pittsburgh each time an addition or update is made.

Visits 4, 7, 10, and 13 (for randomized participants who consent to participate in the GIS Add-On Study only)

Ask the participant for updated home address information (GIS_ADDRESS)

Add the participant's new address to the GIS BARD spreadsheet, if applicable

Upload the updated spreadsheet to Pitt (see GIS MOP), if applicable

At each cross-over visit and at the final BARD visit, participants who consented for the GIS Add-On Study should be asked to verify their current home address. If they have changed addresses, the updated address should be recorded on the GIS_ADDRESS form.

If a new address has been added to the GIS_ADDRESS form, the address should also be added to the bottom of the GIS BARD address spreadsheet for the performance site. Ensure that addresses are being added to the correct spreadsheet. Each site should maintain a separate spreadsheet for BARD, SIENA, and STICS; IDs for participants from the various studies should not be combined into one spreadsheet.

The BARD spreadsheet should be uploaded to the University of Pittsburgh each time an addition or update is made.

2.20 Home Environment Questionnaire

This questionnaire is applicable for all three BARD age tracks.

Visit 2

Administer Home Environment Questionnaire (HEQ)

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

This questionnaire is completed by participant or guardian interview. The coordinator should provide assistance for any questions when requested. If the participant/guardian would rather not answer certain questions, they may be left blank. The participant/guardian should initial and date the source documentation box on the last page of the form when the questionnaire is finished.

Note: It is possible that a participant may achieve treatment period drop-out or treatment failure status during treatment period 1, prior to Visit 2. In that case, the coordinator should administer the questionnaire at the next contact visit with the participant. If it is completed after Visit 1 and prior to Visit 4, the form should be entered as a single form with visit number 1 on it. Alternatively, the questionnaire can be administered and completed at Visit 4 and entered as a single form at that visit.

2.21 Household Socio-Economic Information Form

This questionnaire is applicable for all three BARD age tracks.

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 form (HOUSEHOLD_SEI). 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 participant or his/her parent/guardian. The respondent can decline to answer any question he/she wishes.

2.22 Informed Consent

Informed consent procedures apply for all three BARD age tracks.

Visit 0A

Acquire signed BARD informed consent (acquire parent/legal guardian signature for ages 5-17)

Acquire signed (if applicable) or verbal BARD assent

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

The BARD consent template explains the procedures and time commitment necessary to participate in the BARD trial, should the potential participant be deemed eligible. The AsthmaNet Data and Safety Monitoring Board reviewed and approved the template language which was prepared and submitted to each performance site's Institutional Review Board (IRB) for consideration. Some IRBs require or request changes to the template language which are reviewed by the DCC for consistency with the intent of the original document and completeness in terms of included information. A copy of the IRB approval memo and an IRB-stamped version of the consent document must be forwarded to the DCC prior to the start of recruitment at a given performance site. Each performance site must use its most recent IRB-approved version of the consent document in obtaining consent. The potential study participant must be given the opportunity to read, understand, and sign the consent document before any study-related activities take place. If the participant is a minor, his/her parent or guardian must read and sign the consent, and the participant must provide either written or verbal assent (according to local guidelines) before any study-related activities take place.

Guidelines for obtaining consent:

- At the beginning of Visit 0A or prior to scheduling the visit, provide the potential participant or his/her parent or guardian a copy of the informed consent document and ask him/her to read it thoroughly. The participant should not sign the form until after you have discussed its contents with him/her. A copy of the study assent form should accompany the consent if the potential participant is a minor. Follow local IRB guidelines on assenting participants.
- Allow ample time for the potential participant and/or the parent/guardian to read the informed consent form thoroughly. This will take some time, as the

documents are often lengthy and include very detailed information for full disclosure.

- If the potential participant or parent/guardian is unable to read the informed consent form or seems to be struggling, offer to read it to him/her or to help him/her with the more difficult sections.
- Be prepared to answer any questions the potential participant may have. If the person does not appear to understand the study or what participation entails, or if he/she has any other doubts about enrolling or enrolling his/her child, do not ask him/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 the first visit or during the run-in for a reason that can be remedied (recent respiratory tract infection, recent prednisone burst, non-compliance, etc.), he/she may be re-enrolled starting at Visit 0A at a later date. During the new Visit 0A, the participant should be given a clean copy of the performance site's most current, IRB-approved BARD consent document to review and sign. See the Re-Enrollment discussion in this section for further details.

If modifications are made to the BARD consent document and approved by the local IRB while a participant is in the study, he/she must be re-consented following local IRB rules. All versions of the BARD consent document the participant signed must be retained in his/her BARD study folder and are subject to audit.

Local IRB rules and regulations regarding the consenting and assenting process should be followed at all times.

Note: The BARD consent template contains language for the BARD main study and genetic analysis participation, which is not optional for this study. Some IRBs required the language for the genetics component to be in its own consent document, despite the fact that participation is mandatory to enroll in BARD. At Visit 0A, consent should be sought for genetic analysis participation, regardless of how the consents are packaged at a given performance site. All signed documents must be retained in the participant's study folder.

The date the participant signed the BARD study consent is recorded and tracked on BARD Eligibility Checklist 1 (P5_ELIG1). Genetic analysis participation is tracked on the

Genetic Analysis Blood Draw form (GABLOOD) which is completed at the blood draw visit (Visit 1 for most participants). See the Genetics Blood Draw discussion in this section for further details.

Visit 0A

Administer BioLINCC consent; document assent, as appropriate
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 BARD study (potentially including sputum supernatant and pellets, plasma, serum, DNA, and urine) will be transferred to BioLINCC and made available to other researchers. A participant or his/her parent or guardian must be asked to give 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 0A, after a participant or his/her parent or guardian provides consent to be in the BARD trial, he/she must be given the IRB-approved BARD BioLINCC consent document to review. If he/she agrees to allow leftover BARD 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 participant should indicate his/her preference in the consent document, prior to signing it. If the participant or his/her parent or guardian consents to participate in BioLINCC, then his/her consent document must be retained with the BARD study consent document in the participant's BARD study folder at the performance site. This consent document is subject to audit during an AsthmaNet data quality site visit.

Minor participants should be given an opportunity to provide assent for BioLINCC participation (either written or verbal, per local guidelines). The concept of the biobank should be explained to them in simple terms and they should be asked if they agree to participate, or not. Assent should be documented accordingly.

Every BARD participant must have a BioLINCC Consent Tracking Form (BIOLINCC) completed at Visit 0A. This form tracks whether or not the participant agreed to donate his/her leftover BARD 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.

Visit 1

Administer GIS consent; document assent, as appropriate

After the participant is randomized at Visit 1, introduce the Geographic Information Systems add-on study to him/her (and his/her guardian, if under 18). Explain that participation is optional and requires the transmission of the participant's street address to the University of Pittsburgh so that its geographic coordinates can be mapped and stored for analysis. See the discussion of the Geographic Information Systems (GIS) Add-On Study in this section for further details. Follow the GIS Add-On Study MOP for information on storage of consent documentation and general procedures related to this study. There are no data forms to complete for the BARD database related to this project. There is no compensation to the participant or his/her parent/guardian for participation in this add-on study.

Note: Only individuals who become randomized at Visit 1 are eligible to participate in this add-on study.

2.23 Inhalation Technique Assessment

Inhalation technique assessments are applicable for all three BARD age tracks.

Metered Dose Inhaler (MDI) Technique

Visit 0A

Instruct participant on use of Ventolin[®] (RESCUE) inhaler (HTMDI)
Assess inhalation technique using the MDI Inhalation Technique Checklist
(TECH_MDI_NOSP or TECH_MDI_SP)

Because proper rescue medication (i.e., Ventolin[®]) dosing is crucial for the success of the BARD study, each participant must demonstrate that he/she can accurately use a metered-dose inhaler (MDI). Proper MDI technique is an eligibility requirement that is assessed at Visit 0A on BARD Eligibility Checklist 3 (P5_ELIG3).

A participant handout titled “How to Use Your Metered Dose Inhaler (MDI)” has been developed as a quick reference for the participant to ensure that he/she is using correct MDI technique at home. The coordinator should review this handout with the participant at the visit and answer any questions that arise.

To assure that each participant has met the AsthmaNet standards for MDI use, an MDI Inhalation Technique Checklist (Without Spacer) (TECH_MDI_NOSP) and an alternate version with spacer (TECH_MDI_SP) have been developed. Each participant should be evaluated using the checklist that applies to the way in which he/she plans to use his rescue MDI at home (i.e., with or without a spacer/AeroChamber). Participants are considered eligible at Visit 0A only after they are able to carry out each of the steps listed on the applicable technique checklist.

Due to our inability to secure a supply of placebo MDIs to be used for technique assessment, participants' MDI inhalation technique will be observed while they are inhaling the first two puffs of (active) albuterol in preparation for the post-albuterol spirometry session. Coach and correct the participant, as needed. He/she may be assessed for up to four total acceptable puffs that are needed prior to the post-albuterol spirometry session.

Assessment without Spacer

During the technique assessment, ten separate criteria are assessed for participants not using a spacer using the TECH_MDI_NOSP checklist. The participant is given one point for each of the following steps that is completed correctly:

1. Removes cap of inhaler.
2. Shakes inhaler up and down.
3. Breathes OUT fully.
4. When breathing out fully, does so away from MDI.
5. Puts mouthpiece in mouth, closes lips around mouthpiece.
6. Activates inhaler by pressing down on canister one time.
7. Breathes IN SLOWLY, filling lungs with medicine.
8. Holds breath for at least 5 seconds (with or without mouthpiece in mouth).
9. Removes mouthpiece from mouth before breathing normally.
10. Breathes normally for at least 30-60 seconds.

After successfully completing one puff/inhalation, the participant must repeat the sequence correctly for a second puff to earn the 11th point and pass the technique assessment.

Results of the technique assessment are recorded on the TECH_MDI_NOSP checklist and stored in the participant's study folder; do not submit these forms to the DCC.

Assessment with Spacer

During the technique assessment, eleven separate criteria are assessed for participants using a spacer using the TECH_MDI_SP checklist. The participant is given one point for each of the following steps that is completed correctly:

1. Removes cap of inhaler and spacer.
2. Shakes inhaler up and down.
3. Attaches inhaler to back of spacer.
4. Breathes OUT fully.
5. When breathing out fully, does so away from spacer/MDI.
6. Puts spacer mouthpiece in mouth, closes lips around mouthpiece.
7. Activates inhaler by pressing down on canister one time.
8. Breathes IN SLOWLY, filling lungs with medicine. No whistle should be heard.
9. Holds breath for at least 5 seconds (with or without spacer in mouth).
10. Removes spacer from mouth before breathing normally.
11. Breathes normally for at least 30-60 seconds.

After successfully completing one puff/inhalation, the participant must repeat the sequence correctly for a second puff to earn the 12th point and pass the technique assessment.

Results of the technique assessment are recorded on the TECH_MDI_SP checklist and stored in the participant's study folder; do not submit these forms to the DCC.

Note: It is important to remind participants that exactly one actuation from the inhaler is allowed for each inspiration (i.e., no double, triple, etc. actuations for a single inspiration).

Diskus[®] Technique

Visit 0A

Assign participant a Diskus[®] Demonstrator. Affix yellow label to back of device and complete ID number and initials.

Proper study medication dosing is critical for the success of the BARD study. Because all study drugs (blinded and open-label, with the exception of rescue Ventolin[®]) are delivered via a Diskus[®] device, each participant must demonstrate that he/she can accurately use a Diskus[®]. Proper Diskus[®] technique is an eligibility requirement that is assessed at Visit 0A on BARD Eligibility Checklist 3 (P5_ELIG3). Diskus[®] technique will be reinforced and reassessed at all BARD visits, with the exception of the termination visit.

The DCC will supply each performance site clinical Diskus[®] Demonstrator units for use in training and assessing participants on Diskus[®] technique. These units do not contain any ingredients (not even placebo) and can be used multiple times on a given occasion for purposes of training. Sites will be sent yellow "BARD Diskus[®] Demonstrator" labels to adhere to the demonstration units so that they can be assigned to a given participant for reuse at subsequent visits. Coordinators should affix a label to the back of the assigned demo device and complete the participant's BARD ID number and initials in the fields provided.

Visits 0A-12

Instruct participant on use of Diskus[®] (HTDISKUS)
Assess Diskus[®] inhalation technique using Diskus[®] Demonstrator (TECH_DISKUS). Complete as many forms as necessary and store in participant's folder

A participant handout titled “How to Use Your Diskus[®]” has been developed as a quick reference for the participant to ensure that he/she is using correct technique at home. The coordinator should review this handout with the participant at the visit and answer any questions that arise.

To assure that each participant has met the AsthmaNet standards for Diskus[®] use, a Diskus[®] Inhalation Technique Checklist (TECH_DISKUS) has been developed. Participants are considered eligible at Visit 0A only after they are able to carry out each of the steps listed on the technique checklist. Diskus[®] technique will be reinforced and reassessed at all BARD visits, with the exception of the termination visit.

During the technique assessment, ten separate criteria are assessed. The participant is given one point for each of the following steps that is completed correctly:

1. Uses thumb or finger in thumb grip to open device until the mouthpiece appears.
2. Keeps Diskus[®] horizontal prior to step #3 and until step #7 is completed.
3. Slides lever once until it clicks.
4. Breathes OUT fully.
5. When breathing out fully (step #4), does so away from Diskus[®].
6. Puts lips tightly above and below mouthpiece opening.
7. Breathes IN QUICKLY, filling lungs with medicine.
8. Holds breath for at least 5 seconds (with or without Diskus[®] in mouth).
9. Removes Diskus[®] before breathing normally.
10. Closes Diskus[®] by placing thumb or finger in the thumb grip and sliding it closed.

The participant must score 10 out of 10 to pass the technique assessment. Retrain and reassess as many times as needed. Results are recorded on the TECH_DISKUS checklist and stored in the participant’s study folder; do not submit these forms to the DCC.

Visits 0A-11

Store participant’s Diskus[®] Demonstrator for use at future visits

Each participant will be assigned his/her own Diskus[®] Demonstrator for use at every visit. After the participant has demonstrated adequate technique at a visit, the Diskus[®] should be disinfected and stored in its own Ziploc bag. Clean the mouthpiece with an alcohol wipe and allow it to dry completely before closing the device and inserting it into the Ziploc bag.

2.24 Inhaled Corticosteroid (ICS) Step-Down Groups and Assessment

These procedures are applicable for all three BARD age tracks.

Visit 0A and Visit 0A1

At Visit 0A participants enter the study on their own asthma controller medications (e.g., inhaled corticosteroid (ICS) monotherapy, nebulized steroids, or ICS/long-acting beta-agonist (LABA) combination therapy). To complete Visit 0A, they must have washed out from leukotriene modifiers for 1 week and oral corticosteroids for at least 4 weeks. Individuals on combination therapy must wash out from the LABA component for 24 hours prior to the visit. Participants who are taking tiotropium (Spiriva) must wash out from this medication for 24 hours and should be treated in the same fashion as those taking a LABA when making decisions related to entry asthma guideline step and initial run-in ICS dose.

During Visit 0A the participant is assessed for study eligibility in terms of his/her asthma control (assessed by the Asthma Control Test (ACT or CACT, as age appropriate)) and current asthma guideline therapy step. See the discussion of Eligibility Criteria (Screening) in this section for further details.

In order to determine eligibility, the participant's current medications and dose levels must be reviewed to classify his/her asthma guideline therapy step. If the participant is eligible, then his/her current step determines the ICS level on which he/she enters the study run-in. Some individuals will require a 2-step step-down process to get to low dose run-in ICS (i.e., 1xICS). These individuals will require an extra 2 weeks in the run-in and an extra visit (Visit 0A1) during which they will be assessed to determine if they can decrease their run-in ICS to 1xICS. Some individuals will require only a 1-step step-down process and will start the study on 1xICS. Other individuals will enter the study already on the equivalent of 1xICS and will also start the study on 1xICS. These participants are considered step-neutral.

This section discusses classification of the participant's current asthma guideline step, assignment of the participant's step-down group, and the assessment process for determining if a 2-step step-down participant can decrease his/her run-in ICS to 1xICS.

Classification of Asthma Guideline Step

At Visit 0A a complete medical history is taken for each participant. This includes completion of the Prior Asthma/Allergy Treatment form (PRIOR_TRT). Q1470 on this form records the most recent ICS monotherapy the participant has used, Q1535 records the most recent nebulized steroid the participant has used, and Q1600 records the most recent ICS/LABA combination therapy the participant has used, referencing codes from the Prior Asthma/Allergy Treatment Form Reference Card (PRIOR_TRT_CARD). PRIOR_TRT_CARD has unique codes for each formulation of ICS and ICS/LABA and includes mcg/mg dosing for the ICS component per puff/nebulized treatment. Number of daily puffs of medication for ICS monotherapy and ICS/LABA combination therapy is recorded in Q1480 and Q1610, respectively. Number of daily treatments for nebulized steroid is recorded in Q1540. Using the information from the fields corresponding to the participant's current asthma medications, his/her daily ICS dose (in mcg or mg) can be calculated by multiplying # daily puffs/treatments by mcg/mg dose per puff/treatment. Once the participant's daily ICS dose has been calculated, its level can be classified as low, medium, or high by referencing the table on the next page (abstracted from the Guidelines from the National Asthma Education and Prevention Program Expert Panel Report 3 (revised September 2012)). This table includes recommended dosing guidelines in terms of the timing of the doses over the course of a day. An abbreviated table is represented on the BARD ICS Dose and Step Determination reference card (P5_ICD_DOSE_STEP). Steps for determining and recording the participant's current ICS dose level are outlined in the Clinic Use Only box on page 1 of BARD Eligibility Checklist 2 (P5_ELIG2).

Example:

Tom is 31 years old. He is taking Advair Diskus[®] 250/50 1 puff BID. When completing the Clinic Use Only box on P5_ELIG2, the following should be recorded:

- a. ICS code: 1101
 - ai. fluticasone propionate DPI
- b. ICS daily puffs: 2
- c. ICS mcg/puff: 250
- d. ICS daily dose: $2 \times 250 = 500$ mcg
- e. Currently using LABA or tiotropium/Spiriva? Yes.

Comparing Tom's daily dose of 500 mcg to the Fluticasone propionate DPI row of the ICS Daily Dosage Level table on P5_ICD_DOSE_STEP, his dose would be considered "Medium". The 'Ages 12+' column should be used to assess his dose. This information should be recorded in Q1020 on P5_ELIG2.

Comparative Daily ICS Dosages Table¹³

Drug	Low Daily Dose (mcg or mg)		Medium Daily Dose (mcg or mg)		High Daily Dose (mcg or mg)	
	Ages 5-11	Ages 12+	Ages 5-11	Ages 12+	Ages 5-11	Ages 12+
Beclomethasone MDI	80-160	80-240	>160-320	>240-480	>320	>480
40 mcg/puff	1-2 puffs BID	1-3 puffs BID	3-4 puffs BID	4-6 puffs BID		
80 mcg/puff	1 puff BID	1 puff AM, 2 puffs PM	2 puffs BID	2-3 puffs BID	≥3 puffs BID	≥4 puffs BID
100 mcg/puff (Canadian)						
Budesonide DPI	180-360	180-540	>360-720	>540-1,080	>720	>1,080
90 mcg/inhalation	1-2 inhs BID	1-3 inhs BID	3-4 inhs BID			
180 mcg/inhalation		1 inhs AM, 2 inhs PM	2 inhs BID	2-3 inhs BID	≥3 inhs BID	≥4 inhs BID
Budesonide Nebules	0.5	N/A	1.0	N/A	2.0	N/A
0.25 mg/nebulization	1 neb 2x/day					
0.50 mg/nebulization	1 neb/day		1 neb 2x/day			
1.00 mg/nebulization			1 neb/day		1 neb 2x/day	
Ciclesonide MDI	80-160	160-320	>160-320	>320-640	>320	>640
80 mcg/puff	1-2 puffs/day	1-2 puffs BID	1 puff AM, 2 puffs PM or 2 puffs BID	3-4 puffs BID	≥3 puffs BID	
160 mcg/puff	1 puff/day		1 puff BID	2 puffs BID	≥2 puffs BID	≥3 puffs BID
Flunisolide MDI	160	320	320-480	>320-640	>480	>640
(80 mcg/puff)	1 puff BID	2 puffs BID	2-3 puffs BID	3-4 puffs BID	≥4 puffs BID	≥5 puffs BID

¹³ Table taken from Guidelines from the National Asthma Education and Prevention Program Expert Panel Report 3 (revised September 2012)

Drug	Low Daily Dose (mcg or mg)		Medium Daily Dose (mcg or mg)		High Daily Dose (mcg or mg)	
	Ages 5-11	Ages 12+	Ages 5-11	Ages 12+	Ages 5-11	Ages 12+
Fluticasone MDI	88-176	88-264	>176-352	>264-440	>352	>440
44 mcg/puff	1-2 puffs BID	1-3 puffs BID	3-4 puffs BID			
110 mcg/puff			1 puff BID	2 puffs BID	≥2 puffs BID	3 puffs BID
220 mcg/puff				1 puff BID		≥2 puffs BID
Fluticasone furoate DPI¹⁴				100	≥100	200
100 mcg/puff				1 puff/day	1 puff/day	
200 mcg/puff					1 puff/day	1 puff/day
Fluticasone propionate DPI	100-200	100-300	>200-400	>300-500	>400	>500
50 mcg/inhalation	1-2 inhs BID	1-3 inhs BID	3-4 inhs BID			
100 mcg/inhalation	1 inhs BID		2 inhs BID	2 inhs BID	>2 inhs BID	≥3 inhs BID
250 mcg/inhalation				1 inhs BID	1 inhs BID	≥2 inhs BID
500 mcg/inhalation ¹⁵						
Mometasone DPI	110	110-220	220-440	>220-440	>440	>440
110 mcg/puff	1 inhs/day	1-2 inhs PM	1-2 inhs BID	3-4 inhs PM or 2 inhs BID	≥3 inhs BID	≥3 inhs BID
220 mcg/puff		1 inhs PM	1-2 inhs/day	1 inh BID or 2 inhs PM	≥3 inhs divided in 2 doses	≥3 inhs divided in 2 doses

¹⁴ Fluticasone furoate (e.g., Breo Ellipta combination therapy and Arnuity Ellipta monotherapy) has not been included in the NAEPP Guidelines to date. The BARD PWC decided to categorize its dose level conservatively based on limited information provided by GSK.

¹⁵ This formulation was not included in the NAEPP Guidelines. Dosing is normally 1 inhalation BID which would be classified as high dose.

Example (continued):

Once a participant's daily ICS dose has been classified as low, medium, or high, the Asthma Guideline Step Determination table on P5_ICD_DOSE_STEP should be used to determine his/her asthma step. This information is recorded in Q1030 on P5_ELIG2.

Tom's daily ICS dose was classified as 'Medium'. He is taking a combination medication that contains LABA. Using the Asthma Guideline Step Determination table on P5_ICD_DOSE_STEP, he is currently being treated at Step 4.

Assignment of Step-Down Group

In order to be eligible for randomization, participants in the BARD trial must be on low dose (1xICS) open-label Flovent[®] in the run-in. This dose corresponds to:

- Age 5-11 Track: 50 mcg 1 puff BID (daily dose 100 mcg)
- Age 12-17 Track: 100 mcg 1 puff BID (daily dose 200 mcg)
- Age 18+ Track: 100 mcg 1 puff BID (daily dose 200 mcg)

Low dose ICS monotherapy in the run-in corresponds to asthma guideline step 2.

Participants entering the BARD trial on step 2 therapy are considered step-neutral. They will begin the run-in on age-appropriate 1xICS outlined above. Participants entering the study on step 3 therapy require 1 step down. They will also enter the run-in on age-appropriate 1xICS.

Participants entering the study on step 4 or 5 therapy are classified in the 2-step step-down group. Participants in the Age 5-11 Track will begin the study on 2xICS (100 mcg 1 puff BID). Participants in the Age 12-17 and Age 18+ Tracks will begin the study on 2.5xICS (250 mcg 1 puff BID). Participants in the 2-step step-down group will take the intermediate run-in dose for 2 weeks, then they will return to the performance site for an extra visit, Visit 0A1. At Visit 0A1, they will perform spirometry and be evaluated for asthma control using the Asthma Control Questionnaire (ACQ), and a determination will be made as to whether or not their run-in ICS dose can be stepped down further to 1xICS. The step-down assessment is described in the following section.

The BARD Flovent[®] Dose Determination Reference Card (P5_FLOVENT_DOSE) was created as a quick reference for Flovent[®] doses applicable to each BARD Age Track under different circumstances, including the requirement for 2-step ICS step-down.

The following table summarizes the step-down groups and the dose of ICS on which they will begin the run-in.

Asthma Guideline Step at Visit 0A	Step-Down Group	Initial Run-In ICS Dose	Visit 0A1 Needed?
Step 2	Neutral	1xICS	No
Step 3	1 Step	1xICS	No
Step 4	2 Step	2-2.5xICS	Yes
Step 5	2 Step	2-2.5xICS	Yes

Note: Children using nebulized medications prior to study entry may be switched to inhalers at the time of Visit 0A. They will need to demonstrate appropriate MDI and DPI technique to enter the run-in. Only inhaled study medications (Diskus[®] and MDI Ventolin[®]) may be used during the trial.

Example (continued):

Tom is 31 years old and is currently being treated at Step 4. He is in the 2-step step-down group. He will start the run-in on 2.5xICS (250 mcg Flovent[®] Diskus[®] 1 puff BID). After 2 weeks, he will return for Visit 0A1 to be assessed for step-down to 1xICS (100 mcg Flovent[®] Diskus[®] 1 puff BID).

Assessment for Run-In ICS Step-Down to 1xICS

Visit 0A1

Administer Asthma Control Questionnaire (ACQ7)

Complete Pulmonary Procedure Checklist (P5_PULMONARYCHK)

Perform Spirometry Testing (SPIRO)

Complete ICS Step-down Assessment (P5_STEPDOWN_ASSESS)

Participants who begin the run-in on 2-2.5xICS must be seen for a short visit after 2 weeks on the intermediate ICS dose. This visit is referred to as Visit 0A1. At this visit the participant will complete the Asthma Control Questionnaire (ACQ7) as the first visit procedure before any other data are collected or discussed. Parents should help younger children complete the questionnaire. Adverse events and concomitant medications will be recorded/updated. The participant's spirote[®] reports will be generated, printed and reviewed as follows:

-
- Spirotel[®] Participant Visit Report (P5_SPIROTEL_RPT): This report summarizes all data the participant has saved in the spirotel[®] since he/she left the clinic at Visit 0A.
 - Spirotel[®] Participant Compliance Report (P5_COMPLY): This report summarizes generic compliance (defined as the proportion of full days between visits that the participant completed all e-diary and PEF procedures). This report will be generated at all BARD visits through Visit 13.
 - Spirotel[®] Eligibility Assessment Report (P5_ELIG_RPT): This report is generated only during the run-in at Visits 0A1, 0B, 0C, 0D, and 1. This report summarizes all of the days between 0A and the current visit and indicates which days the participant had symptoms/low peak flow/rescue albuterol use or had a nighttime awakening. An 'X' is present in the applicable column on any day when these events occurred. The last column indicates days when 'lack of acceptable asthma control' criteria have been met. These criteria require the participant to have symptoms or low peak flow or rescue albuterol use more than 2 days in any one-week period, or to have 2 or more night-time awakenings in any two-week period. See the Spirotel[®] and Eligibility Criteria (Randomization) discussions in this section for further details. This report also summarizes spirotel[®] compliance for eligibility purposes using a different definition than that used for P5_COMPLY. For eligibility assessment purposes, participants will be required to complete at least 75% of the spirotel[®] sessions (e-diary and PEF), counting the AM procedures as one session and the PM procedures as a separate session. Compliance information reflected on the Visit 0A1 report is download-specific (it does not include all data from Visit 0A if the participant has had multiple downloads between the two visits).

Spirometry testing will be performed after verifying that all necessary drug and substance holds have been met. Following completion of spirometry, the study coordinator should complete Question 7 on the ACQ7 form by categorizing the participant's % predicted FEV₁ value.

After spirometry has been completed, the BARD ICS Step-Down Assessment form (P5_STEPDOWN_ASSESS) is completed to evaluate the participant's eligibility to continue in the study. The following criteria are assessed:

Exclusion Criteria:

- Participant experienced an asthma exacerbation requiring treatment with systemic corticosteroids.

If the participant required prednisone or other systemic corticosteroids for an asthma exacerbation while on 2-2.5xICS, he/she is ineligible to continue in the trial, as he/she is not a candidate to have his/her ICS dose reduced to the 1xICS level.

This criterion is documented in Q1000 on P5_STEPDOWN_ASSESS.

- Participant has an ACQ score ≥ 1.50 at Visit 0A1.

Before scoring the ACQ, ensure that all questions have been answered with only one response per question. If the participant skipped a question or provided more than one answer for one or more questions, ask him/her to make the necessary corrections. The participant should not have answered Question 7. This question should be completed by the study coordinator after spirometry is performed.

A 'Clinic Use Only' box has been provided on P5_STEPDOWN_ASSESS to assist in computing the ACQ score. Write the number (ranging from 0-6) corresponding to the response provided for each question in the blank line above each question number. Sum the responses across all seven questions and complete the 'Total' line. Divide the total by 7 and round to the second decimal place. Record the score on the lines provided.

If the participant's score is less than 1.50, he/she is eligible to step down his/her ICS to the 1xICS level. The dose reduction can take place even if the participant has not met the 75% level with compliance for study dosing and/or spirotel[®] procedures. Additional training and counseling should be done if the participant's compliance level does not meet study requirements.

If the participant's score is greater than or equal to 1.50, he/she is ineligible to step down his/her ICS to the 1xICS level. In this case the participant is ineligible to continue in the study.

This criterion is documented in Q1015 on P5_STEPDOWN_ASSESS.

If either criterion is met, the participant is ineligible to continue in the study. A Termination of Study Participation form (P5_TERM) should be completed.

Note: Under the original protocol, participants were ineligible to continue in the trial if they met the 'lack of acceptable asthma control' criteria during the 2-week period on 2-2.5xICS. A few months into trial recruitment, it was realized that many participants in the 2-step step-down group were unable to continue in the trial due to this criterion, even

though they only experienced mild symptoms or a few peak flows in the yellow zone, and usually only for the first week after decreasing their asthma therapy. Clinically they would have been considered eligible for the dose reduction. A protocol modification was made to remove the 'lack of acceptable asthma control' exclusion criterion and replace it with the ACQ criterion above.

Compliance Assessment

The P5_STEPDOWN_ASSESSMENT form records spirotel[®] and Diskus[®] dosing compliance information. Under the original protocol, spirotel[®] compliance of at least 75% was required to continue with ICS step-down to 1xICS because data from the spirotel[®] were being used to assess for 'lack of acceptable asthma control.' When the protocol was modified to employ the ACQ as a means of determining acceptable asthma control for ICS step down, spirotel[®] compliance was no longer an issue in the decision-making process and this requirement was dropped. Compliance data continue to be recorded on P5_STEPDOWN_ASSESS as a means of tracking adherence, documenting problems, and providing coordinators the opportunity to review and reinforce study procedures and requirements.

E-diary and Peak Flow Compliance:

Refer to the Eligibility Criteria (Randomization) discussion in this section of the BARD MOP for details on recording and interpreting spirotel[®] compliance from the Spirotel[®] Eligibility Assessment Report (P5_ELIG_RPT).

Dosing Compliance:

Refer to the Dosing Compliance discussion in this section of the BARD MOP for details on computing Diskus[®] compliance values.

2.25 Medical History

The medical history is applicable for all three BARD age tracks with differences in forms and procedures noted below.

Visit 0A

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

A comprehensive medical history is taken at Screen Visit A (Visit 0A). The medical history is broken into three parts:

1. Asthma and Allergy History form (ASTHMA_HX_ADULT, ASTHMA_HX_PED)

Age 12-17 and Age 18+ Tracks: Complete ASTHMA_HX_ADULT

The Adult Asthma and Allergy History form (ASTHMA_HX_ADULT) collects information regarding the onset of asthma and family history, recent asthma symptoms and acute episodes of asthma, asthma triggers, allergies, and basic smoking history.

Note that smoking history is quantified in pack-years. One pack-year is defined as a one-year period when the participant smoked one pack (20 cigarettes per pack) per day. Participants whose smoking history changed over time will have their pack-year history calculated in pieces and summed over the entire history. For example:

Sam smoked ½ a pack of cigarettes per day (10 cigs per day) while in his last 2 years of college. Following college, he smoked a pack per day (20 cigs per day) for five years, until his employer no longer allowed smoking in the building. At that point he cut back to 5 cigarettes per day (0.25 packs per day) for 6 months while trying to quit. He has been a non-smoker ever since.

Sam's pack-year history is calculated as follows:

$$(2 \times .5) + (5 \times 1.0) + (.50 \times .25) = 6.125 \text{ pack-years}$$

Sam may be eligible for BARD, depending on his age. Note that pack-year history is assessed for eligibility at Visit 0A on Eligibility Checklist 2 (P5_ELIG2).

Age 5-11 Track: Complete ASTHMA_HX_PED

The Pediatric Asthma and Allergy History form (ASTHMA_HX_PED) collects information regarding the onset of asthma and family history, recent asthma symptoms and acute episodes of asthma, asthma triggers, allergies, and the participant's exposure to smoking, both in utero and living in his/her current household. This history does not collect information on the participant's smoking history to apply the concept of 'pack-years.' The participant's parent/guardian will need to address the participant's smoking history when responding to questions on Eligibility Checklist 2 (P5_ELIG2).

2. The Prior Conditions for All Participants (PRIOR_COND_ALL) and Prior Conditions for Adult Participants (PRIOR_COND_ADULT) forms collect detailed information on prior diseases, illnesses, conditions and surgeries the participant has had.

Age 5-11 and 12-17 Tracks: Complete only PRIOR_COND_ALL

Age 18+ Track: Complete PRIOR_COND_ALL and PRIOR_COND_ADULT

3. The Prior Asthma/Allergy Treatment form (PRIOR_TRT) collects detailed information about the medications the participant used to treat asthma and allergies in the past 12 months. This form also collects non-asthma/allergy use of oral and injectable steroids. Information on this form will be used to determine if the participant meets necessary washouts for spirometry at Visit 0A and for entry into the study according to the eligibility criteria.

This form is completed for all three BARD age tracks.

The medical history is administered early in the visit so that eligibility criteria that are relatively easy to confirm can be checked quickly. All portions of the medical history are obtained by participant interview. Read each question to the participant 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 participant reporting. If the 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.

See Section 10 of the AsthmaNet General Manual of Operations for further details regarding the completion of the medical history forms.

2.26 Methacholine Challenge

Methacholine challenge procedures are applicable for all three BARD age tracks.

General Instructions

Methacholine challenges are used in the BARD trial to establish a participant's study eligibility (through the PC₂₀ criterion evaluated at Visit 0B) and to characterize methacholine responsiveness in the study population.

Individuals performing methacholine challenges must be AsthmaNet-certified in this procedure or, at minimum, supervised by AsthmaNet-certified personnel. There are no special certifications required to perform methacholine challenges for participants in the Age 5-11 track other than that technicians must possess pediatric spirometry certification.

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

Participants must pass all of the checks on the BARD Pulmonary Procedure Checklist (P5_PULMONARYCHK) to proceed with spirometry and methacholine challenge at the visit. They must also pass all of the checks on the version of the Methacholine Challenge Testing Checklist that is applicable for their age track as follows:

- Age 5-11 Track: Pediatric Methacholine Challenge Testing Checklist (METHACHK_PED)
- Age 12-17 Track: METHACHK_PED
- Age 18+ Track: Adult Methacholine Challenge Testing Checklist (METHACHK_ADULT)

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

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

Post-Methacholine Challenge Procedures

After a methacholine challenge has been completed, the participant should be reversed with albuterol back to at least 90% of baseline (pre-challenge) lung function. Baseline lung function (FEV₁) is obtained from Q1030 on the participant's Spirometry Testing form (SPIRO) completed at the visit.

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

Puffs of albuterol given to reverse the participant from a methacholine challenge should not be counted in the RESCUE Ventolin[®] puffs the participant enters into his/her spirotel[®] device the evening of the visit.

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

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

Visit 0B

Complete Methacholine Challenge Testing Checklist (METHACHK_ADULT or METHACHK_PED)

Perform Methacholine Challenge Testing (METHA)

Complete Additional Treatment Post Methacholine Challenge form (METHA_ADD_TRT), if needed

Methacholine challenge testing is required at Visit 0B for all participants who qualify by the criteria on the appropriate METHACHK form to carry out the procedure. This is true even for individuals who provided source documentation for a previous AsthmaNet PC₂₀ to meet eligibility criteria at Visit 0A. At Visit 0B all participants have been on 1xICS Flovent[®] for at least 2 weeks, allowing for a standardized reference PC₂₀ for characterization purposes. In addition, the PC₂₀ from this visit can be used to qualify the participant for asthma verification criteria if he/she did not reverse adequately at Visit 0A and did not have source documentation to support his/her eligibility.

Note: All participants who meet the compliance criteria at Visit 0B (spirotel[®] e-diary and peak flow criteria and Diskus[®] dosing criteria) should proceed with the Visit 0B procedures, including the methacholine challenge (if eligible for the procedure). Participants do not have to meet the 'lack of acceptable asthma control criteria' and qualify for randomization at the time of 0B to continue with the methacholine challenge.

Results of the challenge are recorded on the Methacholine Challenge Testing form (METHA) and are referenced on BARD Eligibility Checklist 4 (P5_ELIG4). The methacholine challenge report generated through the MedGraphics system must be printed and submitted with the data forms.

If an individual does not meet all the criteria on the appropriate Methacholine Challenge Testing Checklist (METHACHK_ADULT or METHACHK_PED) at Visit 0B, he/she cannot proceed with the challenge at the visit. If the participant has met asthma verification eligibility criteria, he/she can complete Visit 0B (without the challenge) and continue in the study normally. If he/she has not met asthma verification eligibility criteria at this point in the study and cannot perform the procedure to produce a PC_{20} value for eligibility assessment due to not meeting a required washout period, then Visit 0B may be delayed in order to meet all necessary washouts (from cold symptoms, exacerbations, etc.) *at the discretion of the local investigator*. Individuals will continue on low dose ICS (1xICS) during the washout period. Note that this scenario applies to individuals who experience an exacerbation during the run-in on 1xICS and may otherwise have qualified for randomization.

Eligible individuals who do not qualify to perform the methacholine challenge due to low FEV_1 at the time of the visit may make one additional attempt to complete the challenge prior to the randomization visit (Visit 1) if clinically stable. The challenge can be attempted at Visit 0C or 0D, if the participant requires these visits during the run-in. Methacholine challenge and spirometry forms have been included at these visits as single forms for this purpose. If a participant comes to the clinic between run-in visits and is willing to attempt the challenge, use the visit number of the next run-in visit when completing the single forms. For example, if the participant returns following Visit 0B and prior to Visit 0C and completes the challenge, use Visit ID 0C on the single forms. Forms should only be data entered and submitted to the DCC if the challenge was completed successfully.

Participants who qualify for the methacholine challenge but do not meet the PC_{20} criterion for eligibility and have not otherwise met the asthma verification eligibility criteria are ineligible to continue in the BARD study. In this case, data collected at Visit 0B should be data entered and submitted to the DCC and a P5_TERM form should be completed. Study termination procedures should be followed.

Note: Methacholine challenge forms have been added to Visit 1 as single forms for use only in special circumstances. If a participant is ineligible to perform the methacholine challenge at Visit 0B, but he/she is eligible to remain in the study and to schedule the randomization visit (Visit 1) right away, then the challenge can be attempted at the time of Visit 1 if the participant is able to meet all of the safety criteria at that time. If the

participant is in the Age 12-17 Track or Age 18+ Track and will be completing sputum induction at Visit 1, then he/she should complete procedures in the following order: baseline spirometry (SPIRO) → methacholine challenge (if eligible) (METHACHK_PED or METHACHK_ADULT, METHA, METHA_ADD_TRT) → sputum induction (SPUTUMCHK, SPUTUM, SPUTUM_ADD_TRT). The participant should be reversed following the methacholine challenge with 4 puffs of albuterol in order to qualify him/her for sputum induction. With this sequence of procedures, no Post-Albuterol (4 puffs) Spirometry Testing form (PALB4_SPIRO) will be present in the visit packet.

Another circumstance that may necessitate a methacholine challenge being performed at Visit 1 occurs when the challenge performed at Visit 0B is deemed unacceptable by the AsthmaNet spirometry overreader prior to Visit 1's completion. When this happens, it would be ideal for a technically acceptable challenge to be performed at the time of Visit 1 for characterization purposes. If the participant needs the PC₂₀ in order to qualify on the asthma verification criteria, then he/she must complete a new challenge and have the results overread prior to completion of Visit 1.

2.27 Missed Visits

Missed visit procedures are applicable for all three BARD age tracks.

A missed visit is defined as one for which the participant is unavailable to undergo any clinic procedures for purposes of obtaining important outcome data for analysis. If spirometry is attempted during a visit, the visit is not considered missed, even if not all visit procedures are completed. If the Pulmonary Procedure Checklist (P5_PULMONARYCHK) is completed, the visit is not considered missed, even if the participant does not qualify to perform spirometry at the visit.

Spirometry is important to the BARD study because it represents the third tier comparison between treatments for the primary composite outcome variable. Visits for which only administrative procedures, such as drug collection/dispensation, spirotel[®] download and quality control, and compliance assessments are carried out are considered missed visits as reflected on the BARD Accrual Report.

Ideally all visits for a participant should occur at the same time of day (+/- 3 hours) as measured by the time that baseline spirometry takes place during a visit. When this is not possible, it is desirable for all visits to fall within a 4-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 be seen within the 3-hour time window, contact the BARD Scientific Coordinator at the DCC to discuss the allowance of an exception. Visits that take place outside the 3-hour window from the time of baseline spirometry at Visit 1 without a pre-approved exception will be assigned protocol deviations.

If it is not possible to schedule a visit within the regular visit window, schedule it in the extended window, if possible. If a participant cannot be seen within the extended windows, contact the BARD Scientific Coordinator at the DCC to discuss alternate arrangements. See the Visit Windows discussion in this section for further details.

If a participant cannot come to the clinic at all within the regular or extended windows and no suitable alternate arrangements can be made, the visit will be considered missed. Arrangements should be made to send new study medications to the participant and to provide him/her a new spirotel[®] device and Asthma Monitoring Log (P5_ASTHMA_LOG). If at all possible the participant's spirotel[®] device should be returned to the performance site for downloading and quality control. Note that in the BARD trial, due to its design, most visits cannot be missed. See below for visit-specific information.

Visits 0A, 0B, 1

These visits are mandatory; they cannot be missed due to the procedures that take place at the visits which could compromise the study if not carried out completely. More specifically, eligibility assessments take place at visits 0A and 0B, and randomization takes place at visit 1.

Contact the BARD Scientific Coordinator at the DCC if scheduling issues arise for these visits. If the participant cannot accommodate the screening visit schedule, then he/she may need to be terminated from the study and re-enrolled at a later date as his/her schedule permits.

Visits 0A1, 0C, 0D

These visits are not needed for all participants and can, therefore, be missed. Visit 0A1 is only needed for participants who require two steps to step down to 1xICS. See the discussion of Inhaled Corticosteroid (ICS) Step-Down Groups and Assessment for further details. Visits 0C and 0D are needed only for participants who have been deemed eligible for the study but who have not yet met 'lack of acceptable asthma control' criteria to be eligible for randomization.

Visits 2, 5, 8, 11

These visits serve as the 2-week baseline visits for each of the four treatment periods. They are mandatory for any participant who is continuing to progress through the treatment period normally. Individuals who meet treatment failure or treatment arm drop-out criteria during the first few weeks of the treatment period will skip the 2-week baseline visit of the treatment period. Those are the only cases where missing the 2-week baseline visit is acceptable.

In truly extenuating circumstances, only for participants who have been very compliant to date, a baseline visit may be completed via phone call in lieu of a clinic visit in an effort to gather partial data. Contact the BARD Scientific Coordinator at the DCC to receive and document approval and to discuss related procedures. This is considered an exception.

Visits 3, 6, 9, 12

These visits occur in the middle of each of the four treatment periods. While it is not ideal for these visits to be missed, these visits may be skipped if absolutely necessary. Contact the BARD Scientific Coordinator at the DCC to discuss possible options to prevent missed data for these visits.

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

be made to get a new supply of study drugs to the participant before he/she runs out of double-blind medication or Ventolin[®]. New Diskus[®] number(s) should be generated through the BARD Randomization Module using the number of the missed visit, and a BARD Scheduled Diskus[®] form (P5_MED) should be completed and data entered.

Visits 4, 7, 10

These visits are the treatment period cross-over visits at which the participant begins a new treatment regimen. For this reason, by design, they cannot be missed.

Visit 13

Visit 13 is the termination visit for those who complete the trial. For this reason, it cannot be missed.

2.28 Participant Assignment Log and Protocol Enrollment

These procedures are applicable for all three BARD age tracks.

Visit 0A

Assign participant ID number (P5_LOG)

A Participant Assignment Log (P5_LOG) has been developed for BARD for each performance site. This log includes columns for unique participant ID numbers, participant initials, participant's name, and randomization status.

Participant ID numbers are preprinted on P5_LOG and are comprised of 7 digits:

- The first digit is the number of the AsthmaNet protocol. For the BARD protocol the first digit is 5.
- The next 3 digits are the AsthmaNet performance site identifier
- 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 for the BARD protocol at Visit 0A at a given site.

To assign an individual a participant ID number, select the next available blank entry on the BARD Participant Assignment Log. This number will be the primary participant identifier used during the BARD study; it should be used in all communications with the DCC. The participant ID number also should be used to label the participant's BARD 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 0A, 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 (P5_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.

Protocol Enrollment at Visit 0A

Immediately following assignment of the participant's ID number on the BARD Participant Assignment Log (P5_LOG), the protocol enrollment module should be accessed to enroll the participant formally in the BARD 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.

When assigning the participant's BARD ID number in the Protocol Enrollment module, coordinators should select the appropriate age track from a pull-down menu under the 'Track' heading. The system will provide a warning if the participant's current age does not fall into the ranges defined for each of the tracks. If an error is made in track assignment, the DCC should be contacted as soon as possible (prior to entering any participant data).

Visit 1

Randomize participant (check box on P5_LOG)

After accessing the randomization module at Visit 1 to randomize the participant, check the box in the 'Randomized' column on P5_LOG.

2.29 Participant Identification Card

These procedures are applicable for all three BARD age tracks.

The BARD Participant Identification (ID) Card (P5_ID_A, P5_ID_P) provides a quick reference for the participant or his/her guardian to use to monitor his/her asthma. It includes the participant's reference peak flow and 50% and 80% 'stop light' values for determining when an individual may be experiencing an asthma exacerbation. The ID card also contains instructions for treatment of asthma exacerbations by physicians and emergency department personnel who may not be familiar with the BARD study. The ID card should be carried by the participant at all times in a wallet or purse that is readily accessible.

Two versions of the ID card have been created due to the differences in study treatments between the pediatric (age 5-11) and adolescent/adult (ages 12+) groups. Each participant should be given the ID card applicable to his/her age track as follows:

- Age 5-11 Track: P5_ID_P (pediatric version)
- Age 12-17 and Age 18+ Tracks: P5_ID_A (adolescent/adult version)

Visit 0A

Complete and distribute Participant ID Card (P5_ID_A, P5_ID_P)

Print the appropriate BARD Participant Identification (ID) Card (P5_ID_A or P5_ID_P) for the participant's age track. Write the participant's name, BARD protocol ID number, and the names and phone numbers of study personnel on the card. The participant may enter the name and number of his/her primary physician, if applicable. All information should be written in dark ink.

Fill in the participant's reference PEF value (in liters/minute) on the front of the card. This value is obtained from Q1000 on the BARD Spirotek[®] Reference Peak Flow Report (P5_PEF_REF) at Visit 0A.

Calculate 80% and 50% of the participant's reference PEF value (round to the nearest liter/minute). Enter the resulting values in the denoted blank fields on the back of the participant's ID card. These values aid the participant in recognizing when he/she may be having an asthma exacerbation.

Review the contents of the ID card with the participant or his/her guardian and explain the use of the card. Stress to the participant that the Ventolin[®] (RESCUE) inhaler is the

first-line treatment for asthma symptoms. If no relief is achieved, the participant should contact performance site personnel to determine whether he/she should come to the clinical site or go to the nearest emergency department for care. Review when and where emergency care should be sought. Remind the participant that he/she should seek care from study personnel, if possible. However, participants should never delay seeking care if study personnel cannot be reached.

Treatment procedures have been developed with the utmost regard for participant safety. Instruct the participant to contact study personnel if he/she receives emergency treatment outside the study. Document medications, procedures, and other treatments the participant received.

Visits 0A1-12

Update study card with new reference peak flow, if needed (P5_ID_A, P5_ID_P)

Ask the participant to present his/her BARD Participant ID Card (P5_ID_A, P5_ID_P).

Check the reference peak flow value in Q1000 on the BARD SpiroteI[®] Reference Peak Flow Report (P5_PEF_REF) generated at the current visit. If the reference value has changed, the participant will need a new ID card. In that case:

- Print a new copy of the appropriate ID card (P5_ID_A or P5_ID_P)
- Complete the participant's ID number, name, site personnel contact information and primary physician contact information.
- Fill in the participant's new reference PEF value (in liters/minute) on the front of the card.
- Calculate 80% and 50% of the participant's new reference PEF value (round to the nearest liter/minute). Enter the resulting values in the denoted blank fields on the back of the participant's ID card.

See the Reference Peak Flow (PEF) discussion in this section for further details on the calculation of reference peak flow values.

Note: Individuals who are over the age of 21 will not have their reference peak flow values updated after randomization at Visit 1. Individuals under the age of 21 will have their reference peak flow adjusted after Visit 1 only due to increases in predicted peak flow that impact the reference value.

2.30 Participant Status Report

This report is applicable for all three BARD age tracks.

A BARD Participant Status Report has been developed to communicate important information from the BARD database to the performance sites on a participant-specific basis. The report shows, in numeric order of participant ID number, all participants enrolled in the BARD trial at a specific performance site *for whom Visit 0A data have been entered*, along with the columns of information defined below.

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

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

Age Track: This is a categorical variable that shows the participant's age track at study entry based on his/her calculated age at the time of Visit 0A. This column is coded 'Age 5-11 Track', 'Age 12-17 Track', 'Age18+ Track'. Coordinators should check the participant's BARD Age Track Assignment form (P5_AGE_TRACK) to ensure that he/she has been enrolled in the correct track. See the Protocol Age Tracks discussion in this section for further details.

Step-Down Group: This is a categorical variable indicating the participant's asthma therapy step status upon entry into the run-in. This column is coded 'step-neutral', '1-step step-down', or '2-step step-down' based on the participant's guideline step recorded on P5_ELIG2 in Q1030 at Visit 0A.

Pre-Rand Term: Indicator of whether or not the participant was terminated from BARD prior to randomization at Visit 1. Sets to 'No' when P5_ELIG1 is entered; updates to 'Yes' if P5_TERM indicates that the participant terminated prior to randomization.

-
- Randomized:** Participant's randomization status. Updates to 'Yes' when the participant is randomized at Visit 1.
- Visit 1-12 Diskuses:** Sets to Diskus code numbers assigned to a participant at each of the referenced visits (through randomization module). If a backup Diskus is assigned for a particular visit, its number will show under the original Diskus number(s) assigned for that visit.
- Post-Rand Term:** Indicator of whether or not the participant terminated from BARD after randomization and before completion of Visit 13. Sets to 'Yes' if participant terminates early (when P5_TERM is entered); sets to 'No' when a randomized participant completes the trial.
- Completed Study:** Indicator of whether or not the participant completed the BARD trial through Visit 13. Sets to 'Yes' when a participant's P5_TERM form is entered indicating study completion. Sets to 'No' for participants with Post-Rand Term status of 'Yes.'
- # Gablood Forms Entered:** This column remains blank until Visit 1 is completed (blood draw visit). At that point the column will show the number of GABLOOD forms present in the database. Each randomized participant should have exactly one form present by the time he/she completes the trial or terminates prematurely.
- GIS Consent:** This column remains blank until a randomized participant has been approached for participation in the Geographic Information Systems Add-On Study for BARD. Once the GIS Consent Tracking form (GIS) has been entered for a given person, the column will be updated to 'Yes' if he/she consents to participate in GIS or 'No' if he/she refuses to participate. All individuals who have a 'Yes' in this column should have their addresses uploaded to the University of Pittsburgh.
- Small Molecule Sub-Study Consent:** This column remains blank until a participant has been approached for participation in the Small Molecule Sub-Study. Most often consent is sought at the end of Visit 0B; however, because the sub-study began after the BARD study was well into recruitment, some individuals will be consented late, at their next regular visit following the site's acquisition of IRB approval. Once a BARD Small Molecule Sub-Study form (P5_SMALL_MOLECULE) with visit ID 0B has been entered for a given participant, the column will be updated to 'Yes' if he/she consents to participate or 'No' if

he/she refuses to participate. Sites that are not participating in the Small Molecule Sub-Study should complete a form indicating 'N/A' for consent status.

Current Status: The participant's current study status is summarized in the following categories:

1. Enrolled in run-in (individuals who have Visit 0A data entered, no P5_TERM form, and have not yet been randomized at Visit 1)
2. Run-In term (individuals who have a P5_TERM form indicating termination prior to randomization)
3. Randomized and currently active (randomized at Visit 1 and no P5_TERM form entered)
4. Post-randomization drop-out (randomized and P5_TERM is entered and Q1000=0)
5. Completed BARD (completed study through Visit 13; P5_TERM Q1000=1)

The bottom of the Participant Status Report gives a frequency table for the 'current status' variable for all participants at a given performance site.

2.31 Perceived Stress Scale

This questionnaire is applicable only for the BARD Age 12-17 and Age 18+ Tracks.

The following information was taken from Dr. Sheldon Cohen's write-up on the following website: <http://www.mindgarden.com/products/pss.htm>:

"The Perceived Stress Scale (PSS) is the most widely used psychological instrument for measuring the perception of stress. It is a measure of the degree to which situations in one's life are appraised as stressful. Items were designed to tap how unpredictable, uncontrollable, and overloaded respondents find their lives. The scale also includes a number of direct queries about current levels of experienced stress. Moreover, the questions are of a general nature and hence are relatively free of content specific to any sub-population group. The questions in the PSS ask about feelings and thoughts during the last month. In each case, respondents are asked how often they felt a certain way.

Higher PSS scores have been associated with: failure to quit smoking, failure among diabetics to control blood sugar levels, greater vulnerability to stressful life-event-elicited depressive symptoms, and more colds."

The 10-item PSS¹⁶ (PSS-10) will be used in the BARD study in conjunction with planned Geographic Information Systems (GIS) analyses for participants who consent to participate in the GIS study. The PSS-10 has been incorporated into an AsthmaNet-formatted form, the Perceived Stress Scale (PSS_10) form. AsthmaNet received approval for use of the formatted form from Dr. Sheldon Cohen, one of the scale's original authors.

Visit 1

Administer Perceived Stress Scale (PSS_10)

The administration of the PSS-10 is one of the first procedures performed at Visit 1. This timing in the visit structure is intentional so that a participant's responses are not affected by other study procedures, such as spirometry and e-diary/peak flow review. Study coordinators should observe the order of procedures as they are laid out on the visit procedure checklists to ensure that PSS results are not biased by other study activities.

The PSS-10 is completed by the participant. When administering the questionnaire, request that the participant complete the entire 10-question form and provide answers

¹⁶ Cohen, S and Williamson, G. Perceived Stress in a Probability Sample of the United States. Spacapan, S. and Oskamp, S. (Eds.) *The Social Psychology of Health*. Newbury Park, CA: Sage, 1988.

as completely and as accurately as possible. No stated or implied time limit should be set. If the participant requests help with or clarification of any question, the study coordinator should instruct the participant to reread the instructions and to give the best answer possible to each question. The study coordinator should not provide an answer to any question. Providing guidance may bias the participant's responses.

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

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

The participant should provide source documentation on the PSS-10 form by providing his/her initials and the date/time in the source documentation box. Review the source documentation provided by the participant to ensure that the date and time are accurate before collecting the form.

2.32 Phone Contacts and BARD Contact Information Form

Phone contacts and contact information are applicable for all three BARD age tracks.

Run-In Phone Contacts

Visit 0B (week -6), 0C (week -2)

The BARD protocol designates 4 weeks between Visits 0B and 0C and 4 weeks between Visits 0C and 0D. To determine whether the participant might have met randomization eligibility criteria between visits (specifically, lack of acceptable asthma control criteria), and to address the participant's concerns regarding his/her asthma control, formal phone contacts should be scheduled between these visits. Phone contacts should be scheduled approximately 2 weeks following Visit 0B and Visit 0C. In addition to picking up eligibility for randomization earlier, these phone contacts also afford the coordinator an opportunity to ensure that the participant is carrying out his/her home procedures correctly, including taking study medications and completing e-diary questions and peak flows. In order for a participant to be eligible for randomization, he/she must maintain a high level of compliance with dosing from his/her study Diskus[®] and performing e-diary and peak flow procedures.

Run-in phone contacts are documented on the BARD Run-In Phone Contact Form (P5_CONTACT_RUNIN). This is an administrative form; data are not entered into the database. Completed forms should be stored in the participant's study folder at the performance site; do not forward these forms to the DCC. Phone contact documentation is subject to audit during an AsthmaNet site visit.

Phone contacts should be scheduled according to the dates provided on the participant's Visit Scheduler Report generated at Visit 0A or 0A1. If multiple attempts are made to contact the participant within the range of dates given on the report and no contact is made, the coordinator should continue to try to get in touch with the participant until his/her next scheduled visit. Document all contact attempts on P5_CONTACT_RUNIN.

Post-Randomization Phone Contacts

Visit 2 (week 5), 3 (week 11), 5 (week 19), 6(week 25), 8(week 33), 9(week 39), 11 (week 47), 12 (week 53)

The BARD protocol designates 6 weeks between Visits 2 and 3 and 6 weeks between Visits 3 and 4 during treatment period 1, 6 weeks between Visits 5 and 6 and 6 weeks

between Visits 6 and 7 during treatment period 2, 6 weeks between Visits 8 and 9 and 6 weeks between Visits 9 and 10 during treatment period 3, and 6 weeks between Visits 11 and 12 and 6 weeks between Visits 12 and 13 during treatment period 4. Because of the lack of clinic contact during these periods of the study, formal phone contacts should be scheduled between these visits. Phone contacts allow the coordinator to address the participant's concerns regarding his/her asthma control and to schedule an extra clinic visit, if needed. These phone contacts also afford the coordinator an opportunity to ensure that the participant is carrying out his/her home procedures correctly, including taking study medications and completing e-diary questions and peak flows. Further, they serve as a reminder for collection of overnight urine samples that are required at the end of each treatment period.

Phone contacts should be scheduled around the 3-week point in the visit intervals described above (i.e., mid-way through the 6-week interval). Ideal contact dates are listed on the Visit Scheduler Reports run at Visits 2, 5, 8, and 11. If multiple attempts are made to contact the participant within the range of dates given on the report and no contact is made, the coordinator should continue to try to get in touch with the participant until his/her next scheduled visit. Document all contact attempts on the BARD Contact Form (P5_CONTACT).

P5_CONTACT is a data collection form that captures important asthma outcomes data while it guides the coordinator through the normal phone contact process. Completed phone contact forms should be entered into the BARD database as single forms using the visit number from the last completed clinic visit in the header. The visit date on the form should be the date the phone contact occurs. If the participant provides information on adverse events experienced since the last clinic visit and/or new concomitant medications that were taken, this information should be recorded on the AECLIN/CMED forms for the last visit. In other words, any adverse event or concomitant medication information should be completed on the forms associated with the same visit number as the one on the P5_CONTACT form.

BARD Contact Information Form Visits 1-13

In addition to its completion at post-randomization phone contacts, the BARD Contact Form (P5_CONTACT) will be completed at Visit 1 and at each post-randomization visit. This form collects important general information on asthma outcomes, such as hospital stays, visits to emergency departments/urgent care facilities, visits to a primary care physician, and missed days of work/housework/school due to asthma. Data collected on this form as part of a study visit will be entered into the database as part of the visit packet.

2.33 Physical Exams

Physical exams are applicable for all three BARD age tracks. Specific procedures and forms differ by BARD age track, as outlined below.

See Section 3 of the AsthmaNet General Manual of Operations for information regarding the physical exam clinical procedures. BARD-specific procedures follow.

Adult Procedures

The following procedures apply to individuals enrolled in the BARD Age 18+ Track only.

Adult physical exams are documented on administrative forms that are not entered into the study database. Comprehensive exams are documented on the Adult Long Physical Exam form (LEXAM_ADULT) and brief exams are documented on the Adult Short Physical Exam form (SEXAM_ADULT). These forms should be completed at the applicable visits and stored in the participant's study folder at the performance site. These forms are subject to audit during an AsthmaNet site visit.

The short physical exam includes measures of resting blood pressure, pulse rate, and body temperature, as well as results of pulmonary auscultation. Short exams can be performed by study coordinators, registered nurses, physician assistants, and other individuals who are appropriately trained in these procedures and certified in the BARD protocol.

The long physical exam includes the measurements made during a short physical exam, as well as documentation of the presence/absence of oral candidiasis and physical findings. A licensed medical practitioner (LMP) must complete the physical findings and pulmonary auscultation portions of the long exam. A LMP is defined as a physician (MD/DO), physician assistant (PA), or nurse practitioner; a registered nurse does not qualify as a LMP. If a non-physician LMP completes a required long exam at the beginning or end of a study, the participant still must have interaction with a physician during the visit. The individual performing the long exam should be certified in the BARD protocol unless he/she is filling in temporarily for personnel who usually conduct these exams. Individuals who will provide these exams on a regular basis should possess BARD certification (physician or coordinator exam).

In addition to regular physical exams, additional physical measurements including height and weight, and waist, hip and neck circumference, are taken for adults at various points during each study. These measurements are documented on the Adult Body Measurements form (BODYMEAS_ADULT) and entered into the AsthmaNet

database. Body measurements can be made by study coordinators, registered nurses, physician assistants, and other individuals who are appropriately trained in these procedures and certified in the BARD protocol.

Note that height will be measured at all visits for adult participants who are between the ages of 18 and 21, until the participant reaches age 21. For visits with spirometry where no BODYMEAS_ADULT form is completed, the height measurement will be recorded on the BARD Pulmonary Procedure Checklist (P5_PULMONARYCHK). At Visits 0C and 0D, no P5_PULMONARYCHK form is completed. At those visits height will be measured and recorded in the clinic notes. Height updates are required for adults in this age range because they may still be growing and height impacts predicted lung function estimates. For the BARD trial, this can also affect an individual's peak flow reference value that defines his/her green/yellow/red zones and corresponding Asthma Action Plan.

Visits 0A, 13

Perform long physical exam (LEXAM_ADULT)

A long physical exam is required at Visit 0A in order to ensure that it is safe and appropriate for each participant to enroll in the BARD study. A long exam is required at Visit 13 to ensure that the participant leaves the study in good health with plans for follow-up care, as needed.

For the BARD trial, participants must have interaction with a physician at Visits 0A and 13, even if the physician is not performing the long exam.

The LMP conducting the long physical exam should sign, date and note the time in the gray box on the LEXAM_ADULT form as source documentation.

Visit 1

Perform short physical exam (SEXAM_ADULT)

A brief physical exam is conducted at Visit 1, prior to randomization at the visit.

The person conducting the physical exam should sign, date and note the time in the gray box on the SEXAM_ADULT form as source documentation.

Visits 0A, 13

Complete Adult Body Measurements form (BODYMEAS_ADULT)

Follow the instructions on the form for making the various measurements. Body mass index (BMI) should be calculated and written in the gray box under Q1010. This value is

not entered into the study database but it should be available for reference during the trial.

Note that height is captured on the BODYMEAS_ADULT form for adults at Visit 0A and Visit 13. Individuals who are less than 21 years of age will have their heights updated at every visit until the point when they turn 21. Updated heights are recorded on the BARD Pulmonary Procedure Checklist (P5_PULMONARYCHK) at most visits for these individuals.

Pediatric Procedures

The following procedures apply to individuals enrolled in the BARD Age 5-11 and Age 12-17 Tracks only.

Pediatric physical exams are documented on data collection forms that are entered into the study database. Comprehensive exams are documented on the Pediatric Long Physical Exam form (LEXAM_PED) and brief exams are documented on the Pediatric Short Physical Exam form (SEXAM_PED). These forms should be completed at the applicable visits and entered with the data packet.

The pediatric short physical exam includes measures of height and weight and assessment for oral candidiasis. Physical findings are also assessed (but are not data entered). Short exams can be performed by study coordinators, registered nurses, physician assistants, and other individuals who are appropriately trained in these procedures and certified in the BARD protocol.

The pediatric long physical exam includes the measurements made during a short physical exam, as well as documentation of a more extensive list of physical findings. A licensed medical practitioner (LMP) must complete the physical findings and pulmonary auscultation portions of the long exam. A LMP is defined as a physician (MD/DO), physician assistant (PA), or nurse practitioner; a registered nurse does not qualify as a LMP. If a non-physician LMP completes a required long exam at the beginning or end of a study, the participant still must have interaction with a physician during the visit. In most cases the professional who performs the long physical exam should be certified in the BARD protocol. If a LMP does physical exams for BARD only infrequently, as a short-term replacement for the usual LMP staff, then it is not required that he/she pass the protocol exam.

Note that height will be measured at all visits for pediatric participants in an effort to update their predicted lung function values as their height and age increase. Predicted peak flow may affect the reference peak flow value set for the participant, which defines his/her green/yellow/red zones and corresponding Asthma Action Plan. Height is also

monitored closely to examine the impact of the various steroid formulations on growth. Although short physical exams are not listed in the protocol for all visits where height is measured, the SEXAM_PED form will be used to gather height data for purposes of entering it into the database. The entire form should be completed and data entered following normal procedures.

Note that plotting of height and weight on age-appropriate growth charts is not required for the BARD trial. This study does not include a growth failure protocol. We will use the collected heights to analyze growth trends with respect to study treatments at the end of the trial.

Visits 0A, 13

Perform long physical exam (LEXAM_PED)

A long physical exam is required at Visit 0A in order to ensure that it is safe and appropriate for each participant to enroll in the BARD study. A long exam is required at Visit 13 to ensure that the participant leaves the study in good health with plans for follow-up care, as needed.

For the BARD trial, participants must have interaction with a physician at Visits 0A and 13, even if the physician is not performing the long exam.

The LMP conducting the long physical exam should sign, date and note the time in the gray box on the LEXAM_PED form as source documentation.

Visits 0A1, 0B, 0C, 0D, 1-12

Perform short physical exam (SEXAM_PED)

A brief physical exam is conducted at most visits to the clinical site due to the need to collect updated height information each time.

The person conducting the physical exam should sign, date and note the time in the gray box on the SEXAM_PED form as source documentation.

2.34 Prednisone Washout Requirements

Prednisone washout requirements are applicable for all three BARD age tracks.

Visit 0A

At study entry, the participant must have washed out for at least 4 weeks from any oral or injectable (systemic) corticosteroids taken for any reason. This requirement is documented on the Exclusionary Drugs for BARD reference card (P5_EXCLDRUG). It is evaluated during the eligibility assessment process on BARD Eligibility Checklist 1 (P5_ELIG1). Individuals who have not met the minimum washout of 4 weeks will need to be rescheduled for Visit 0A at a later date.

Visit 1 and Cross-Over Visits (4, 7, 10)

At these visits the participant is starting a new double-blind treatment period. The BARD trial does not include true washout periods prior to entry into a given treatment period. Instead, the first 2 weeks of each treatment period are used as a pseudo-washout and are ignored for purposes of the primary outcome analysis. In order to achieve a minimum washout from systemic corticosteroids of 4 weeks before collecting baseline data for a given treatment period (at visits 2, 5, 8, and 11), a 2-week (14 day) washout from the final dose of prednisone is required prior to entry into each treatment period. If a participant has been treated with prednisone or another systemic corticosteroid for an asthma exacerbation or for any other reason leading up to Visit 1 or one of the cross-over visits, he/she must delay the visit until the minimum 2-week washout is met. See the discussions of Treatment (Arm) Failures and Significant Asthma Exacerbations in this section for details on appropriate treatments during the required washout periods.

At Visit 1 the required washout is assessed and documented on the BARD Randomization Eligibility Checklist (P5_RANDOM_ELIG). At the cross-over visits (4, 7, 10), the required washout is documented on the BARD Prednisone Washout Form (P5_WASHOUT_PRED).

Baseline Visits (2, 5, 8, 11)

These visits serve as the 2-week 'baseline' visits in each of the four treatment periods. The participant has been on his/her new double-blind treatment regimen for 2 weeks prior to the visit. These visits serve as the starting point for comparisons made during the applicable treatment period. If the participant has received prednisone or another systemic corticosteroid for any reason during the 2-week baseline interval, the baseline visit must be delayed for a minimum of 1 week (7 days) and a maximum of 2 weeks (14

days). The baseline measurement needs to reflect a minimal washout from the effects of the prednisone while not being delayed so long that it will reflect any treatment effects associated with the new double-blind regimen. Participants remain on their double-blind regimen during the washout period.

At the baseline visits, the required washout is documented on the BARD Prednisone Washout Form (P5_WASHOUT_PRED).

Note that if the participant experiences two exacerbations, or requires 10 or more days of prednisone treatment for an exacerbation during the beginning of a treatment period, he/she should be considered as having experienced a treatment failure. Treatment failure procedures should be followed. See the discussion of Treatment (Arm) Failures in this section for further details.

2.35 Pregnancy Test

Pregnancy tests are applicable for all three BARD age tracks.

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

Visits 0B, 1, 4, 7, 10, 13

Complete Urine Pregnancy Test form (PREG_TEST) for female participants ages 6 and older

Administer urine pregnancy test, if necessary

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

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

Although the participant will be returning an overnight urine sample at Visits 1, 4, 7, 10, 13, a fresh urine sample must be collected at the time of the visit for use in performing the pregnancy test; do not take a sample from the overnight urine sample for this purpose.

Participants who are post-menopausal (defined as at least one year since last menses) or have undergone a hysterectomy or tubal ligation do not need to be tested. Juvenile participants who are pre-menarche also do not need to be tested. The parent/guardian should provide source documentation for pre-menarche individuals. This information is documented on the PREG_TEST form.

Note that a history of infertility does not constitute a valid reason to skip the pregnancy test at a visit, nor does a participant's insistence that she does not have heterosexual intercourse.

Note that individuals who are transgendered or are transitioning to the opposite gender should be tested for pregnancy in accordance with their biological sex. Biologically female participants who are of child-bearing potential must use birth control and provide urine for pregnancy tests as required by the protocol.

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

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

Visit 0B

If a participant is considered able to bear children, results of the pregnancy test must be known before she proceeds with the diluent stage of the methacholine challenge at Visit 0B. Pregnant women should not perform methacholine challenges. In addition, pregnant or nursing participants are ineligible for the BARD protocol, in general.

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

Pregnancies Discovered during Study Participation

If a woman is found to be pregnant at any time during the study, either through a pregnancy test performed at a study visit or through another means, she is ineligible for continued participation. Pregnant women should be seen at the performance site and terminated from further study participation immediately. Participants who become pregnant during the study should have a BARD Termination of Study Participation (P5_TERM) form submitted to the DCC as soon as possible recording pregnancy as the primary reason for study termination (Q1030 should be answered 'Yes' and Q1240 should be answered 'a'). Pregnancy should not be reported as an adverse event or as a serious adverse event in the BARD database.

GlaxoSmithKline (GSK), provider of the asthma drugs for the BARD trial, requires notification and follow-up information for any pregnancies that are discovered while a

female participant is in the study. This applies to randomized participants, as well as non-randomized participants who are in the run-in, as all are receiving GSK drugs. AsthmaNet is not required to report or follow up pregnancies for partners of male participants for the BARD study.

GSK has provided two forms that should be completed and submitted to the DCC for each on-study pregnancy. These forms have been posted on the AsthmaNet secure website in the Protocols:BARD:Documents folder. The participant's signed BARD consent document should include language giving the participant's consent to provide this information to GSK.

- Pregnancy Notification Form

This form must be completed and submitted to the DCC as soon as possible, and within 2 weeks of first becoming aware of the pregnancy.

- Pregnancy Follow-Up Form

This form should be completed and submitted to the DCC when the outcome of the pregnancy is known (including any premature termination of the pregnancy). This form should be submitted to the DCC no longer than 6-8 weeks following the estimated delivery date.

Completed forms should be scanned and e-mailed to Susan Kunselman (smj1@psu.edu) and Ron Zimmerman (rzimmerm@phs.psu.edu). If no forms are forthcoming following the termination of a study participant due to pregnancy, queries will be sent.

2.36 Protocol Age Tracks

These procedures are applicable for all three BARD age tracks.

Visit 0A

Complete Age Track Assignment Form (P5_AGE_TRACK)

Three enrollment age tracks have been defined in the BARD database:

- Age 5-11
- Age 12-17
- Age 18+

A participant's age track is defined on the basis of his/her chronological age at the time of Screen Visit A (Visit 0A). Ages should not be rounded up when making a track assignment, even if a participant is very close to his/her 12th or 18th birthday. Once a participant is enrolled in a given age track, he/she remains in that track for the duration of the time he/she is in the study, even if a birthday causes an age category to be bridged.

Three age tracks have been defined for this study because there are significant differences in study procedures between young children (ages 5-11) and adolescents (ages 12-17) and adults (ages 18+). Consenting/assenting procedures, qualification criteria for certain procedures (e.g., methacholine challenge and sputum induction), study medications, and appropriate questionnaires are just a few examples of areas where the three age groups differ. Establishing three tracks for the database allows for track-specific form packets and data entry screens and ensures that the correct forms are completed for each participant at each visit. Visit procedure checklists have been created specifically for the age 5-11 track. Visit checklists have been combined for the age 12-17 and age 18+ tracks with specific differences noted.

At Visit 0A the BARD Age Track Assignment Form (P5_AGE_TRACK) should be completed. This form records the participant's age at enrollment and his/her track assignment. If the participant is assigned to the Age 5-11 track, the appropriate age-based quality of life form is chosen (PedsQL or PAQLQ(S)). Pediatric participants in this age range should complete the quality of life questionnaire designated on this form for the duration of their study participation. The completed P5_AGE_TRACK form should be stored in the front of the participant's BARD study binder for quick reference.

When assigning the participant's BARD ID number in the Protocol Enrollment module, coordinators should select the appropriate age track from a pull-down menu under the

'Track' heading. The system will provide a warning if the participant's current age does not fall into the ranges defined for each of the tracks. Coordinators can override the warning and proceed, if appropriate. An alarm e-mail will auto-generate and be sent to the lead coordinator if it appears that a participant was enrolled in the wrong age track. If an error is made in track assignment, the DCC should be contacted as soon as possible (prior to entering any participant data).

2.37 Quality of Life Questionnaires

Quality of life questionnaires are applicable for all BARD age tracks. However, the choice of questionnaire(s) depends on the participant's age and age track. This section describes the four quality of life questionnaires used in the BARD study and outlines the appropriate ages of individuals to complete each.

All quality of life questionnaires are administered at Visits 0A, 1, 4, 7, 10, 13

General Instructions

Asthma questionnaires, including quality of life assessments, are generally the first procedures completed at a visit. Visits have been structured in this fashion so that participant responses will not be affected (biased) by other study procedures, such as spirometry, physical exam, and diary review. Questionnaire administration must not be moved to a different place in a study visit; it must be performed where indicated on the specific visit procedure checklist, relative to other procedures. The order of the questionnaires within a visit also should not be altered.

If a visit is partially completed and then rescheduled, and questionnaires were already completed, they must be completed anew at the beginning of the rescheduled visit. Do not allow the respondent to refer to or update his/her previously completed questionnaires. Old copies of the questionnaires should be filed in the participant's study folder or shredded; they should not be entered into the study database or forwarded to the DCC.

Basic guidelines for the administration of quality of life questionnaires follow.

- Administer the questionnaire in a relaxed environment where the respondent can concentrate on the questions without distraction.
- Provide the respondent a black pen and a writing surface.
- Be available for assistance; however, be careful not to lead the respondent or influence his/her responses.
- If a respondent is unclear on what a question means, it is best simply to repeat it exactly as it is worded. If the respondent asks for an explanation, say "Whatever it means to you." Never try to interpret or reword a question. This may introduce bias in his/her responses. Instruct the respondent to answer the question(s) to the best of his/her ability.

-
- Do not help a participant (or respondent) select an answer. For example, if a participant asks, "Well, my shortness of breath has been pretty bad recently. Does that mean I should choose 2?" Instead of saying "Yes," say, "There is no *right* answer. Select the number that best indicates how your shortness of breath, as a result of your asthma, has been in the last X weeks." X refers to the recall window for the particular questionnaire.
 - Be neutral when hearing any potential responses. Be sure that your words or manner do not imply surprise, sympathy, approval, or disapproval. For example, if a participant expresses frustration with his/her asthma while completing the questionnaire, do not express concern or sympathy at this time. This may require you to ignore your instincts and training. Wait until after the questionnaire is complete to offer advice, encouragement or suggestions.

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

Note: The *informed administration* approach will not be used in AsthmaNet studies; the participant/respondent should not look at past responses to the questionnaire when completing the form at a given visit.

Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ_12)

This questionnaire is applicable for participants in the BARD Age 12-17 and Age 18+ tracks.

The Asthma Quality of Life Questionnaire with standardized activities (AQLQ(S)) is a disease-specific questionnaire developed by Juniper et al. (Chest 1999;115,5:1265-1270) that measures how patients feel and function in their day-to-day lives as a result of their asthma. It was developed to measure the functional impairments experienced by adults 17 years of age and older. The Pediatric Asthma Quality of Life Questionnaire (PAQLQ) (Qual Life Res 1996; 5:35-46) was developed to measure the problems that children 7-17 years of age experience. In the BARD trial, adolescents (ages 12 and up) are included in the same treatment groups as adults. Therefore, it is ideal to analyze them with respect to quality of life using the same tool that is applied to the adults. The AQLQ+12 (Health and Quality of Life Outcomes 2005, 3:58) is a modification of the AQLQ(S) to make it suitable for both adolescents and adults. The aim of the adaptation was to ensure that the problems that are most troublesome to adolescents were

included while making as few alterations to the original AQLQ(S) questionnaire as possible. The AQLQ+12 questionnaire is valid for patients ages 12 and up.

This questionnaire has a 2-week recall period and 32 items. It should take the participant approximately five to ten minutes to complete the entire questionnaire.

This questionnaire has been rigorously tested to ensure that it is reproducible (i.e., repetition in stable subjects produces more or less the same results), valid (i.e., it is really measuring quality of life in asthma), and that it is responsive to change (i.e., it is able to detect important changes in quality of life, regardless of how small they are). Systematic errors by the person administering the questionnaire can greatly affect these measurement properties, so it is important to follow study guidelines.

AsthmaNet studies utilize the self-administered form of the AQLQ+12 questionnaire. This approach reduces the potential for interviewer bias and is also less tedious for both the participant and clinical personnel.

Paediatric Asthma Quality of Life Questionnaire (PAQLQS)

This questionnaire is applicable for participants in the BARD Age 5-11 Track who were between the ages of 7 and 11 (inclusive) at enrollment.

The Paediatric (Pediatric) Asthma Quality of Life Questionnaire with standardized activities (PAQLQ(S)) (Qual Life Res 1996; 5:35-46) was developed by Liz Juniper et al. to measure the functional problems (physical, emotional and social) that are most troublesome to children with asthma. It was developed and is valid for children between the ages of 7 and 17 years (inclusive). It will be used in the BARD protocol only for participants who are ages 7-11 (inclusive) at enrollment.

This questionnaire has a 1-week recall period and 23 items. It takes approximately five to ten minutes to administer and complete.

The measurement properties and validity of the PAQLQ have been evaluated in several studies in different countries. It has strong measurement properties and good validity. Studies have shown that children as young as 7 have no difficulties understanding the questions or the response choices and are able to give very accurate responses.

As recommended by Liz Juniper, we will use the interviewer administration method for this questionnaire. Coordinators should review her instruction manual for administering the PAQLQ(S) which is available on the secure AsthmaNet website in the Protocols:

BARD: Documents folder. At a minimum, coordinators should review pages 13-20 of this document.

When administering the interviewer version of the PAQLQ(S), green and blue response cards are used. The DCC purchased sets of these cards from Liz Juniper and distributed one set to each participating BARD site. Use only the official response cards while interviewing a child. Contact the DCC if the site's response cards cannot be located.

Note that the child participant must respond to the questions, not the parent or caregiver. Parents should be asked to wait in another room while the child completes the questionnaire. This prevents the child from looking to the parent for guidance and possibly biasing his/her responses. It also prevents the parent or caregiver from challenging the child's responses.

Before interviewing the child, ensure that he/she understands the 1-week timeframe of 'during the last week.' If in doubt, ask the child (or parent) to identify an event that occurred a week previously (such as a ball game or a movie he/she attended) and then ask the child to think about he he/she has been since that event.

Pediatric Quality of Life Inventory (PedsQL™)

This questionnaire is applicable for participants in the BARD Age 5-11 Track who are between the ages of 5 and 6 (inclusive) at enrollment.

The PedsQL™ (Pediatric Quality of Life Inventory) is a modular instrument developed to measure health-related quality of life in children and adolescents ages 2 to 18 (Varni et al. Med Care 2001; 39(8):800-812). In the BARD trial we will use it only for participants who are between the ages of 5 and 6 (inclusive) at Screen Visit A (Visit 0A). Children ages 7 through 11 at enrollment (inclusive) will complete the Paediatric Asthma Quality of Life Questionnaire (PAQLQ) described above. The appropriate questionnaire for participants in the Age 5-11 Track will be recorded at Visit 0A on the BARD Age Track Assignment Form (P5_AGE_TRACK), to be referenced throughout the participant's study tenure. Participants should complete the same quality of life questionnaire for the duration of their study participation, even if a child turns 7 while he/she is in the study.

The PedsQL generic core scales are multidimensional child self-report and parent proxy-report scales that measure general health-related quality of life. The generic instrument consists of 23 items applicable for healthy school and community populations, as well as pediatric populations with acute and chronic health conditions. It has been shown to be highly reliable and valid. Note that this tool does not measure asthma-specific quality of life. The Protocol Writing Committee considered using the

PedsQL Asthma Module but found that the verbiage used in some of the questions seemed too complex.

We will use the Parent Proxy Report version of the PedsQL™. Parents or guardians will supply the answers regarding their child's health. This questionnaire takes less than 4 minutes to complete.

RAND Impact of Asthma on Quality of Life SF-12 (RAND_IAQL_12)

This questionnaire is applicable for participants in the BARD Age 12-17 and Age 18+ Tracks.

Given how pervasive and impairing asthma is, there has been increased attention to the development and use of asthma outcome measures, particularly patient-reported outcomes that may be more meaningful to patients than traditional clinical markers of asthma severity. One key outcome is disease-specific quality of life (QOL), the patient's subjective perception of the impact of a disease and its treatment on his/her life (in contrast to general QOL, a broader measure of well-being). Asthma-specific QOL can be distinguished from asthma symptoms—for example, how often one experiences wheezing—in that asthma-specific QOL is a gauge of how much symptoms bother or matter to a patient in different areas of life.

According to the expert panel report (EPR-3) released by the National Heart, Lung, and Blood Institute's (NHLBI) National Asthma Education and Prevention Program, the goals of asthma treatment include improving the QOL for people who have asthma, controlling symptoms, reducing the risk of exacerbations, and preventing asthma-related death. Because these targeted aspects of asthma may respond differently to treatment, they should be monitored separately. Yet available instruments often confound QOL with asthma control, defined as the extent to which manifestations of asthma (symptoms, functional impairments, and risks of negative events) are minimized and goals for treatment are met. QOL items are commonly combined with items measuring asthma symptoms and functional impairment (e.g., limitations in daily activities, such as housework and walking up hills) in creating total scores. Thus, no existing instrument is able to provide separate and distinct information on the impact of asthma on QOL. This key limitation of asthma-specific QOL measures was emphasized by leaders in asthma research and practice at the Asthma Outcomes Workshop convened by the NHLBI in March 2010. At this workshop, the Asthma Related Quality of Life Subcommittee declined to recommend any existing instrument as a core outcome measure of asthma-specific QOL, and instead strongly recommended that new instruments be developed that measure the impact of asthma on QOL as a construct distinct from asthma control.

To address this need, Cathy Sherbourne, Maria Orlando Edelen, Nicole Eberhart, Brian Stucky, and Marielena Lara were funded by NHLBI to develop a freely available new system for measuring the impact of asthma on QOL that avoids confounding QOL with asthma symptomatology and functional impairment. The system, referred to as The RAND Impact of Asthma on Quality of Life item bank (RAND-IAQL), contains 65 items that focus on the patient's perception of the impact or bother of asthma on his/her QOL, and includes content ranging across many domains of life important to people with asthma. They also created freely available 4-item and 12-item short forms. Their developmental process began with formative work including literature review and expert recommendations, but the majority of the item content was generated based on feedback from adults with asthma who participated in focus groups. Salient themes generated from focus group discussions included both general (e.g., enjoyment of life) and specific (e.g., sleep difficulty, affect, medication dependence and side effects, physical activity limitations, social relations, health concerns) areas of impact. From these sources they arrived at a set of items representing a wide range of content regarding the impact of asthma on QOL. These items were then field-tested in a web-based sample of 2032 ethnically diverse adults who reported that they had asthma. Using data from a large national field test of adults with asthma, they evaluated the pool of candidate items using modern psychometric methods, including item response theory (IRT) and computerized adaptive tests (CAT). When conducting an IRT analysis items are "calibrated" (or characterized) to indicate the strength of the relationship between the item and the construct being measured (here the impact of asthma on QOL) and the location on the construct's scale where the item is most informative. The collection of calibrated items is referred to as an "item bank." The item bank provides a flexible and potentially sustainable assessment environment that minimizes respondent burden without sacrificing precision. A psychometric evaluation of the RAND-IAQL item bank suggested that though the concept of asthma impact on QOL is multi-faceted, it may be measured as a single underlying construct. Subsets of items from the bank can be administered either adaptively (i.e., with computer adaptive testing), or through carefully selected fixed-length instruments (i.e., short forms) that can be tailored to achieve various measurement goals. From the final set of 65 items two short forms were developed: 1) A brief 4-item short form comprised of items measuring general aspects of the impact of asthma on QOL (reliability = .86) and 2) a 12-item short form which contains the 4 general items along with 8 additional items that measure content-specific aspects of QOL (e.g., physical activity limitations, social concerns, health concerns, and sleep (reliability = .93)). Compared to the full item bank the RAND-IAQL-4 and RAND-IAQL-12 sacrifice very little measurement precision, despite drastically reducing respondent burden.

Validity results from their field data indicate that the RAND-IAQL measures distinguish between levels of asthma control. The impact of asthma on QOL was greater in persons

with indicators of more severe asthma, and in persons with comorbid medical and mental conditions and greater health care utilization.

Additional evidence is needed from clinical samples, as the initial field test was conducted in an online convenience sample of individuals with asthma. Use of a clinical sample would ensure appropriateness of the measure for clinical use, and would enable the researchers to conduct validity analyses not only in relation to patient-reported outcomes, but also using objective physiologic measures (spirometry, methacholine challenge, sputum eosinophils, and other physiologic measures). Furthermore, it is important to examine the responsiveness of the RAND-IAQL to established and experimental treatment, and to determine a minimal clinically important difference for the outcome measure. An efficient method for gathering this important additional validity and responsiveness information is to piggy-back the new questionnaire on ongoing clinical trials, including the BARD study.

The RAND IAQL-12 (12-item short form) has been incorporated in the BARD study at visits when the other QOL questionnaires are administered. It will be self-administered and completed by the participant. This questionnaire has a 4-week recall window.

Note that this questionnaire includes a source documentation box. After reviewing the completed form for accuracy and completeness, the participant should initial, date and record the time in the source documentation box on page 2.

2.38 Randomization

Randomization procedures are applicable for all three BARD age tracks.

Visit 1 Procedures

Randomize participant (Check box on P5_LOG)
Log/dispense Scheduled Diskus[®] (P5_DRG_SCH)
Confirm Diskus[®] dispensation (P5_MED)

BARD is a four-period cross-over trial during which each participant receives treatment with four different regimens over the course of his/her study participation. Each treatment period is 14 weeks long. The four treatment regimens employed during the study depend on the participant's age at enrollment at Screen Visit A (Visit 0A). All dosing is one inhalation BID.

Pediatric Regimens (age 5-11 track):

- 2xICS (Flovent 100)
- 2xICS+LABA (Advair 100/50)
- 5xICS-Ped dose (Flovent 250)
- 5xICS+LABA (Advair 250/50)

Adolescent/Adult Regimens (age 12-17 and age 18+ tracks):

- 1xICS+LABA (Advair 100/50)
- 2.5xICS (Flovent 250)
- 2.5xICS+LABA (Advair 250/50)
- 5xICS-Adult dose (Flovent 500)

Each participant will be randomized to a specific order of regimens to be received during the four treatment periods. The order of treatment administration is referred to as the treatment 'sequence.' For example, one sequence for a pediatric participant would be: 2xICS during period 1, followed by 2xICS+LABA during period 2, followed by 5xICS during period 3, followed by 5xICS+LABA during period 4.

Target sample sizes are 258 randomized pediatric participants and 236 randomized adolescent/adult participants Network-wide. No limits will be set on the number of participants in either age group that a given partnership can randomize.

Randomization balances treatment sequence assignments within the nine partnerships (i.e., Boston, Chicago, Denver, Madison, Pittsburgh, St. Louis, San Francisco,

Tucson/Durham, Winston-Salem/Emory), not within a given performance site. Randomization within each partnership is stratified on age group (age 5-11 versus 12+) based on the participant's age at enrollment at Visit 0A (and consistent with his/her assigned BARD age track).

At the end of Visit 1, if the participant meets all of the eligibility requirements documented on the BARD Randomization Eligibility Checklist (P5_RAND_ELIG) and Eligibility Checklist 5 (P5_ELIG5), he/she is eligible to be randomized.

At the time of Visit 1 the study coordinator should access the BARD Randomization Module on the secure AsthmaNet website and enter the appropriate visit number (i.e., 1), the participant's BARD ID number, and the performance site at which the participant is being randomized. At this point, the system is assigning the participant's treatment sequence and allocating a Diskus[®] located at the designated performance site that corresponds to his/her assigned regimen for treatment period 1. At Visit 1 the module will display one assigned Diskus[®] number whose format depends on the participant's age group: Pediatric Diskuses[®] are labeled P10000-P49999 and adolescent/adult Diskuses[®] are labeled A50000-A89999. Pediatric Diskuses[®] have light green labels and adolescent/adult Diskuses[®] have light blue labels.

After the participant is randomized successfully, the 'randomized' box should be checked on the BARD Participant Assignment Log (P5_LOG). The assigned Diskus[®] number should be logged on the Participant-Specific Drug Accountability Log for Post-Randomization Diskus[®] (P5_DRG_SCH). Information on the participant's assigned Diskus[®] number(s) at each visit will be included on the BARD Participant Status Report.

In order to validate the assigned Diskus[®] through the BARD database, the BARD Scheduled Diskus[®] form (P5_MED) should be completed any time a Diskus[®] number is generated through the randomization module to be dispensed to a participant. Remove the label from the assigned Diskus[®] pouch and attach it to Q2 on the P5_MED form. This form will be data entered as part of the Visit 1 packet.

It should be noted that participants can be randomized in the BARD randomization module at Visit 1 only if all of the following criteria are met:

- 1) The participant's BARD ID number is enrolled in the BARD protocol.
- 2) The participant's Visit 0A packet, including Visit 0A eligibility data, has been entered at the performance site (only first entry required). The Visit 0A eligibility forms (P5_ELIG1, P5_ELIG2, P5_ELIG3) must indicate that the participant is eligible.

- 3) The participant's Visit 0A1 packet must be entered for participants in the 2-step step-down group (only first entry required). The Visit 0A1 eligibility form (P5_STEPDOWN_ASSESS) must indicate that the participant is eligible for ICS dose taper and to continue in the study
- 4) No BARD Termination of Study Participation (P5_TERM) form has been entered for the participant.
- 5) At least 14 days have elapsed since Visit 0A or Visit 0A1 (2-step step-down group only). Participants must be evaluated on the 1xICS run-in Flovent[®] dose for at least 2 weeks before randomization eligibility can be determined and randomization can take place.
- 6) If any Randomization Eligibility Checklists (P5_RAND_ELIG) have been entered, they must support the participant's eligibility to continue to randomization on the basis of the participant's exacerbation history.

See Section 3 of this manual for details on accessing and interacting with the BARD randomization module.

Note that treatment sequence and regimen assignments in the BARD study are double-blind. That is, neither the participant, nor performance site personnel, will be aware of the status of the participant's Diskus[®] dispensed from Visit 1 through Visit 12. The majority of DCC personnel are also blinded to the treatment assignments while the study is ongoing.

Note: No pre-randomization of participants in advance of Visit 1 is allowed. Eligibility must be confirmed on the day of Visit 1, before accessing the BARD Randomization Module to generate a Diskus[®] number for a given participant.

Visits 2-12 Procedures

Generate new Diskus[®] number(s) via the randomization module
Log/dispense Scheduled Diskus(es)[®] (P5_DRG_SCH)
Confirm Diskus[®] dispensation(s) (P5_MED)

At Visits 2-12, clinical personnel must utilize the BARD Randomization Module to generate number(s) for new Diskus(es)[®] from which the participant will take his/her daily doses until the next regularly scheduled visit. To prepare for an upcoming visit and to provide lead time for the investigational pharmacists, the Diskus[®] number(s) may be generated up to one business day ahead of a visit.

The study coordinator should access the BARD Randomization Module on the secure AsthmaNet website and enter the applicable visit number from a dropdown menu, the participant's BARD ID number, and the performance site at which he/she is being seen for the visit. The randomization module will display the participant's new Diskus[®] number(s). At Visits 4, 7, and 10 the module will return one Diskus[®] number. At Visits 2, 3, 5, 6, 8, 9, 11, and 12 the module will return two Diskus[®] numbers. The assigned Diskus[®] number(s) should be logged on the Participant-Specific Drug Accountability Log for Post-Randomization Diskus[®] (P5_DRG_SCH) for the applicable visit number. Information on the participant's assigned Diskus[®] number(s) at each visit will also be included on the BARD Participant Status Report.

A BARD Scheduled Diskus[®] form (P5_MED) should be completed and data entered when Diskuses[®] are assigned. Affix labels from the pouches of all dispensed Diskuses[®] to the form.

It should be noted that the following criteria must be met at Visits 2-12 before Diskus[®] number(s) will be displayed:

- 1) The participant must have been randomized via the BARD Randomization Module at Visit 1.
- 2) The participant must not have been terminated from the study (i.e., no P5_TERM form has been entered).
- 3) At Visits 2, 5, 8 and 11: A minimal amount of time must have passed since the preceding visit.
- 4) The cross-over visit (i.e., visits 4, 7, 10) must have been completed and had Diskuses[®] assigned before the module will return Diskus[®] numbers for subsequent visits during the same treatment period. For example, Visit 4 randomization must have taken place before Visit 5 or Visit 6 Diskuses[®] will be assigned.
- 5) Diskuses[®] will not be assigned for a given visit number if they have already been assigned beyond that visit number. For example, if a participant had Diskuses[®] assigned at Visit 5, no Diskuses[®] will be assigned for Visits 1-4. If additional Diskuses[®] are requested at Visit 5, the coordinator will be taken through the backup Diskus[®] assignment process as outlined below.

Backup Diskus[®] Assignments

If a participant loses his/her medication supplies between visits, then he/she will require the assignment of new (backup) blinded Diskus(es)[®]. To generate new Diskus[®] numbers, the study coordinator should access the BARD Randomization Module on the secure AsthmaNet website and enter the applicable visit number (i.e., the same visit number for which the previous (lost) Diskus[®] number(s) was/were generated) from a dropdown menu, the participant's BARD ID number, and the performance site at which he/she is being seen for the visit. The randomization module will recognize that the participant has already had one or two Diskuses[®] assigned for this visit number and will provide a warning message giving the coordinator a chance to cancel out of the module if a mistake has been made. If the coordinator chooses to generate a new Diskus[®] number, the module will ask if one or two Diskuses[®] are needed.

The assigned Diskus[®] number(s) should be logged on the Participant-Specific Drug Accountability Log for Post-Randomization Diskus[®] (P5_DRG_SCH) for the applicable visit number. Information on the participant's assigned Diskus[®] backup number(s) at each visit will also be included on the BARD Participant Status Report. A BARD Scheduled Diskus[®] single form (P5_MED) should be completed and data entered any time one or more backup Diskuses[®] are dispensed to a study participant. Affix labels from the pouches of all dispensed Diskuses[®] to the form. See the Study Medications discussion in this section and section 4 for further details.

Backup Randomization Procedures

In the rare event that the BARD Randomization Module is unavailable during any visit when it is required (i.e., visits 1-12 or backup medication dispensations for any of these visits), clinical personnel must contact the DCC for assistance. During week days (Monday through Friday) between 8 AM and 5 PM ET, calls should be made to the AsthmaNet main line at 717-531-3663. The BARD scientific coordinator, project coordinator, or one of the data management staff will be able to assist with backup randomization procedures. After regular work hours, calls should be made to the AsthmaNet main line and the option for after-hours emergency contact for BARD should be chosen. The BARD scientific coordinator will answer and facilitate backup randomization procedures.

It is extremely important that Diskuses[®] are assigned through the BARD Randomization Module. Randomly choosing an available Diskus[®] at Visits 2-12 and assigning it to a participant in lieu of the randomization module is inappropriate, as it may not contain the participant's assigned treatment regimen for the current treatment period. If an incorrect Diskus[®] is dispensed to a participant, a protocol violation will be assigned.

2.39 Recruitment

This information is applicable for all three BARD age tracks.

BARD visits will commence on February 10, 2014. Nine clinical center partnerships composed of approximately 30 participating performance sites will recruit for BARD.

A recruitment period of 15 months has been established for BARD with the final randomization visit occurring by the end of May 2015 in order to complete the trial by the end of the funding period in June 2016. It has been mandated by NHLBI that we complete the trial before the original grant runs out.

The gender and minority status of individuals screened and enrolled at Visit 0A and individuals randomized in BARD will be summarized by clinical center partnership and, within each partnership, by performance site on the BARD accrual report. This report will be available on the secure AsthmaNet website in the Reports: Accrual: BARD folder shortly after recruitment begins. Minority status will be summarized, as usual, as some of the BARD participants may self-identify as Caucasian. Partnerships should strive to screen at least 50% female participants.

For the BARD trial to be successful, the Network needs to randomize 236 adolescents/adults (participants in the BARD Age 12-17 and Ages 18+ Tracks) and 258 children (participants in the BARD Age 5-11 Track) for a total of 494 randomized participants. Target sample sizes for each partnership are based on the number of participants who are successfully screened, entered into the run-in, and subsequently randomized in the BARD trial. Each of the nine clinical center partnerships is expected to randomize approximately 55 participants across the age groups. With a recruitment period of 15 months, that is equivalent to 3.67 randomized participants per partnership per month.

Recognizing that some partnerships are underrepresented by African American/Blacks and others have greater access to this population, no restrictions will be set on the maximum number of participants that can be randomized by a given partnership.

Approximate BARD Timelines

February 10, 2014: First participant screened (Visit 0A) (study launch date)

February 28, 2014: First participant randomized (Visit 1)

April 1, 2015: Final screening visit (Visit 0A)

May 31, 2015: Final randomization visit (Visit 1)

June 30, 2016: Final participant visit (Visit 13)

2.40 Re-Enrollment

Re-enrollment procedures are applicable for all three BARD age tracks.

Participants who do not successfully complete the BARD screening or run-in phases for reasons that may be overcome with time or additional training (e.g., lack of compliance, use of excluded medications or insufficient washout, etc.) may be suitable candidates to re-enroll in BARD for a second attempt. Individuals who remain in the study through Visit 0D and never achieve eligibility for randomization generally should not be re-enrolled. Randomized participants who drop out early also may not re-enroll in the trial.

Visit 0A Screen Failures

Participants who do not qualify for the BARD study at Visit 0A for reasons that may be overcome with time (e.g., respiratory tract infection in past 4 weeks, failure to wash out from leukotriene modifiers for 1 week, etc.) may be invited to repeat Visit 0A at a later date. Data collected during the unsuccessful Visit 0A should not be entered into the AsthmaNet database and forms should not be forwarded to the DCC regardless of whether the participant will re-enroll in the study or not. The Visit 0A packet should be stored at the performance site in a section of folders denoted as 'BARD Visit 0A Screen Failures.'

Participants who present at the performance site for a second attempt at screening should repeat all of the Visit 0A procedures as listed on BARD Visit Procedure Checklist 0A (P5_VISIT0A). A new visit packet should be completed.

When re-enrollment occurs, the following procedures apply:

- The participant must be given a new BARD participant ID number from the Participant Assignment Log (P5_LOG). See the Participant Assignment Log and Enrollment discussion in this section and section 4 for further details. This new ID will need to be linked to the participant through the protocol enrollment process before data can be entered into the BARD database. For information on the protocol enrollment process, refer to section 7 of the AsthmaNet General Manual of Operations.
- The participant and/or his/her guardian must read and sign new copies of the current IRB-approved BARD and BioLINCC informed consent/assent documents. The documents signed at the initial enrollment should reside in the folder created for the participant's original ID number. The new signed consent documents

should reside in the participant's current study folder. Informed consent documents should not be updated with a new signature and date, as this practice violates institutional procedures at some of the performance sites.

- The Adult or Pediatric Participant Contact Information (CONTACT_ADULT or CONTACT_PED) form should be reviewed and updated by the participant or his/her guardian, as applicable. A photocopy should be made and stored with the participant's original Visit 0A packet. The original form with updates should be stored in his/her new study folder.
- A new Visit 0A packet with the participant's new ID number should be completed and submitted to the DCC if the participant is now eligible. Do not attempt to update previously-completed forms with the participant's new information *unless some of the medical history forms indicated eligibility and require very few changes/updates* (see the list in the section below). A new study folder should be created to house the participant's forms under his/her new study ID number.

After a Successful Visit 0A and Prior to Randomization

Once a participant is deemed eligible at Visit 0A, he/she is formally enrolled in the BARD study. The data collection forms from Visit 0A should be entered into the study database and forwarded to the DCC.

If a participant withdraws consent or is deemed ineligible during the run-in, then he/she must be formally terminated from the study. A BARD Termination of Study Participation form (P5_TERM) should be completed and entered into the database. All of the forms completed at the termination visit should be entered into the AsthmaNet database and sent to the DCC. If a baseline urine sample was collected during the run-in, it should be discarded.

Such participants should not be invited to re-enroll unless their reason for withdrawing or being withdrawn was such that there is a very high probability that re-entry will result in randomization and full participation in BARD. For example, if extenuating circumstances caused a participant to miss visits or not be able to carry out daily procedures for a period of time, then he/she may be a good candidate to re-enroll, after life settles down and adequate time can be devoted to study procedures. Participants who are terminated from the study at Visit 0D because they never are able to meet randomization eligibility criteria (i.e., lack of acceptable asthma control and high levels of spirotel[®] and dosing compliance at the same time), should not be re-enrolled.

Participants who are good candidates for re-enrollment must re-enter the BARD study starting anew at Visit 0A.

The following guidelines apply when the participant is re-enrolled:

- The participant must be given a new participant ID number from the Participant Assignment Log (P5_LOG). See the Participant Assignment Log and Enrollment discussion in this section and section 4 for further details. This new ID will need to be linked to the participant through the protocol enrollment process before data can be entered into the BARD database. For information on the protocol enrollment process, refer to section 7 of the AsthmaNet General Manual of Operations.
- The participant and/or his/her guardian must read and sign new copies of the current IRB-approved BARD and BioLINCC informed consent/assent documents. The documents signed at the initial enrollment should reside in the folder created for the participant's original ID number. The new signed consent documents should reside in the participant's current study folder. Informed consent documents should not be updated with a new signature and date, as this practice violates institutional procedures at some of the performance sites.
- The Adult or Pediatric Participant Contact Information form (CONTACT_ADULT or CONTACT_PED) should be reviewed and updated by the participant. A photocopy should be made and stored with the participant's original Visit 0A packet. The original form with updates should be stored in his/her new study folder.
- The Adult or Pediatric Asthma and Allergy History form (ASTHMA_HX_ADULT or ASTHMA_HX_PED), Prior Conditions for Adult Participants form (PRIOR_COND_ADULT), Prior Conditions for All Participants form (PRIOR_COND_ALL), Prior Asthma/Allergy Treatment form (PRIOR_TRT), and Cold History form (COLD_HX) may be updated and reused. These forms must be reviewed with the participant or his/her guardian in detail and updated appropriately. The participant's new ID number and visit date must be written on the forms. A photocopy should be made and stored with the Visit 0A packet from the participant's original enrollment. The form with the handwritten updates should be stored in his/her new study folder.

Open-label Flovent[®] study medication administered as part of the BARD trial should not be considered when completing or updating the PRIOR_TRT form.

The participants' usual asthma treatment off-study should be entered on the form.

- Albuterol reversal tests and methacholine challenges performed during the participant's original enrollment (at Visit 0A and 0B, respectively) that satisfy study asthma verification criteria may be used as source documentation at Visit 0A to satisfy this criterion. Note that the tests must have been done within 1 year of the re-enrollment date to qualify. Further note that the participant must complete new reversal and methacholine challenge tests at Visits 0A and 0B, respectively, during his/her re-enrollment. See the Eligibility Criteria discussion in this section for further details.
- All study procedures must be carried out anew, with the exceptions noted above, beginning with Visit 0A. This includes the long physical exam that is required at Visit 0A. Complete and submit new data collection forms for the participant using his/her new participant ID number and current dates. A new study folder should be created to house the participant's forms under his/her new study ID number.

After Randomization in BARD

Participants who withdraw consent after they have been randomized in the BARD study at Visit 1 are NOT eligible to re-enroll. Each participant can contribute only one set of data for the analysis.

2.41 Reference Peak Flow (PEF)

Reference peak flow procedures are applicable for all three BARD age tracks.

General Information

Reference peak flow (PEF) values are determined at Visit 0A and are reviewed and updated, as needed, at all run-in visits through Visit 1 for all participants. For individuals over the age of 21, the reference PEF does not change after randomization. For individuals who are less than 21 years of age at randomization, reference PEF is reviewed and possibly updated at post-randomization visits, on the basis of updated predicted PEF values, until the time they turn 21. As the participant ages and grows, his/her predicted PEF values will increase. If his/her PEF reference value is lower than 50% of the predicted PEF for his/her current age and height, then the reference value will be updated to 50% of the current predicted PEF. No updates to the reference value will be made after the participant turns 21.

Reference PEF values are important to the goals of the BARD study, as they are used for two purposes:

1. To establish a participant's green, yellow, and red zones as part of his/her Asthma Action Plan
2. To define times of 'lack of acceptable asthma control' during the run-in to support a participant's study eligibility (while on 1xICS) or ineligibility (while on 2-2.5xICS)

In general, the BARD PEF reference value is interpreted as the participant's 'personal best PEF.' At each run-in visit (0A, 0A1, 0B, 0C, 0D, 1), the participant will perform three technically acceptable (pre-bronchodilator) peak flow maneuvers on his/her spiroteI[®] using an 'unscheduled' session in the device. Data will be downloaded through the BreezeSuite software and a BARD SpiroteI[®] Reference Peak Flow Report (P5_PEF_REF) will be generated. At each visit the report chooses the participant's highest pre-bronchodilator PEF from the following measurements:

1. Current PEF reference value (value programmed in the spiroteI[®] as the peak flow reference at the previous visit)
2. Pre-bronchodilator PEFs completed at scheduled AM and PM sessions and saved in the e-diary between the last visit and the current visit
3. Best PEF observed at the current visit (during the unscheduled session)

Peak flow reference values calculated at each visit are subject to the following minimum and maximum values:

1. Minimum Value: The reference PEF value can never be lower than 50% of the participant's current predicted PEF value using published equations based on age, height, gender and race. If the participant's PEF values result in a 'personal best PEF' that is less than this value, then the PEF reference value is set to 50% of the predicted PEF. This minimum is a safeguard in that it doesn't allow the participant's reference values that trigger his/her Asthma Action Plan to fall too low.
2. Maximum Value: The PEF reference value cannot increase by more than 20% from one visit to the next. If the participant's PEF values result in a jump in his/her personal best value of more than 20% compared to his current reference value, then the new PEF reference value is set to 120% of the current reference value. The Reference Peak Flow Report will include a message alerting the coordinator when a 20% jump occurs in the reference value. In these cases, the coordinator should review the data on the Spirotek[®] BARD Participant Visit Report (P5_SPIROTEL_RPT) to look for erroneous data that might have contributed to the large increase.

It should be noted that the participant's reference PEF value can never decrease over time; it can increase or stay the same from visit to visit.

The Spirotek[®] BARD Reference Peak Flow Report (P5_PEF_REF) doubles as a data collection form. At each visit where the participant's reference peak flow is evaluated and possibly updated, the report should be generated, reviewed, and printed for submission with the visit packet.

If it appears that erroneous data may have contributed to an artificially high reference PEF value, the coordinator should discuss the situation with the participant (or his/her parent/guardian) to determine what (other than significantly improved lung function) may have caused the high values. Data on the Spirotek[®] BARD Participant Visit Report (P5_SPIROTEL_RPT) should be reviewed with the participant (and his/her guardian, if applicable). If spurious values occurred because the participant shared his/her Spirotek[®] with a friend or family member, or for another readily identifiable reason, then the coordinator should eliminate the spurious values from consideration when calculating the reference value. Unfortunately, this will need to be done manually by evaluating all of the valid pre-bronchodilator AM and PM PEF values on the report to find the highest, and then comparing that value to the current PEF reference value and the participant's best (unscheduled) PEF at the visit. If a coordinator chooses to override the calculation provided on the report, then the reference PEF value printed in

Q1000 should be crossed out and a data correction made. A comment should be included on the form explaining why the override was made. The altered reference PEF value can then be programmed into the participant's device. Specific visit procedures related to evaluation of reference PEF values follow.

Visit 0A

Program spirotel[®] with participant's information. Select BARD from protocol drop-down. Use 900 for the reference peak flow value.

Have participant perform three technically acceptable maneuvers on his/her assigned spirotel[®] device (unscheduled peak flows)

Download spirotel[®] and convert the data using DBTools

Select the participant in Breeze, enter the DOB, and select gender and race

Open the visit (either 0A1 or 0B)

Enter height and weight on Medgraphics machine and calculate predicted PEF

Print Spirotel[®] Reference Peak Flow Report (P5_PEF_REF)

Complete header information on P5_PEF_REF

Update the peak flow reference value in spirotel[®]

At Visit 0A the participant is just starting the BARD run-in period and is being given his/her spirotel[®] peak flow meter and e-diary device for the first time. Therefore, no peak flow data has been recorded by the participant to this point in the study. The participant will need to provide peak flows during Visit 0A for calculation of a reference PEF for use during the beginning of the run-in (until Visit 0A1 or 0B). To facilitate this process, the coordinator should complete the following steps:

- Program the spirotel[®] with the participant's information. Use the arbitrary value of 900 for the reference peak flow value at this point in the visit. The value must be set to 900 for the report code to work properly. Set a return visit number of 0A1 or 0B, depending on which step-down group the participant is in (step-neutral, 1 step step-down, or 2 step step-down). See the discussion of Inhaled Corticosteroid (ICS) Step-Down Groups and Assessment in this section for further details.
- Have the participant perform three technically acceptable peak flow maneuvers using his spirotel[®]. At this point in the visit the participant has already been introduced to the device and has passed the spirotel[®] performance assessment. This step must be completed prior to administering albuterol in preparation for the post-albuterol spirometry session. Follow the order of procedures on the Visit 0A Procedure Checklist (P5_VISIT0A).
- Download the spirotel[®] and convert the data using DBTools.

- Select the participant in Breeze and enter the participant's date of birth, gender and race on the participant screen. These should be the same values that are entered into the spirometry software; they will be used to calculate predicted PEF for use in determining the participant's reference PEF value. Values should be taken directly from the participant's Registry Report following normal procedures for spirometry.
- Open the visit (either 0A1 or 0B). Enter the participant's height and weight on the visit screen. These values should be taken from the physical exam form (LEXAM_PED or BODYMEAS_ADULT) completed at the visit. Click on 'Calculate' to compute the participant's current predicted peak flow (PEF) value.
- Print the Spirotek[®] Reference Peak Flow Report (P5_PEF_REF). The participant's reference PEF value is shown in Q1000. This is the value that should be programmed into his/her spirotek[®]. If Q1000 shows a reference value of 900, then something went wrong. If the report does not show the highest PEF from the unscheduled session or 50% of the participant's predicted PEF (whichever is higher), then something went wrong. In either of these scenarios, the coordinator should check the participant's information in the Visit Tab in Breeze and update/correct it, as necessary. The report should then be rerun to obtain the correct reference value.
- Complete the header information on P5_PEF_REF (visit number, visit date, coordinator ID).
- Update the PEF reference value in the spirotek[®]. This value will define the participant's green-yellow-red zones and will determine when he/she should activate his/her Asthma Action Plan. It is used to trigger alerts that will appear when the participant's PEF is in the yellow or red zone.

The reference PEF value from Q1000 on P5_PEF_REF is recorded on several participant handouts as follows:

- Participant Identification Card (P5_ID_P for Age 5-11 Track and P5_ID_A for Age 12-17 and Age 18+ Tracks)
 - Record PEF reference value in space provided on the front
 - Record 80% of the PEF reference value in space provided on back
 - Record 50% of the PEF reference value in space provided on back

-
- BARD Asthma Action Plan (P = pediatric version and A=adolescent/adult version)
 - Record PEF reference value in space provided at the top of the card
 - Record 50% of the PEF reference value in the red zone space
 - Record 50% and 80% of the PEF reference value in the spaces for the yellow zone
 - Record 80% of the PEF reference value in the green zone space
 - BARD Asthma Monitoring Log (P5_ASTHMA_LOG)
 - Record 80% of the PEF reference value in the space provided in the text at the top of the form

Visits 0A1, 0B, 0C, 0D, 1

Have participant perform three technically acceptable maneuvers on his/her assigned spirotel[®] device (unscheduled peak flows)

Download spirotel[®] and convert the data using DBTools

Open the visit in Breeze

Verify/update height and weight on MedGraphics machine for participants <21 years of age

Calculate predicted PEF

Print Spirotel[®] Reference Peak Flow Report (P5_PEF_REF)

Complete header information on P5_PEF_REF

Update reference PEF and return visit number in spirotel[®]

At Visits 0A1, 0B, 0C, 0D, and 1, the following steps should be followed for all participants:

- Have the participant perform three technically acceptable peak flow maneuvers using his spirotel[®]. This step should be completed early in the visit, prior to completion of spirometry or methacholine challenge at the applicable visits.
- Download the spirotel[®] and convert the data using DBTools.
- If the participant is <21 years of age, verify his/her height and weight on the visit screen. Refer to the physical exam form (SEXAM_PED) completed at the visit for participants in the Age 5-11 and Age 12-17 tracks and to the Pulmonary Procedure Checklist (P5_PULMONARYCHK) (Visits 0B and 1) or clinic notes (Visits 0A1, 0C, 0D) for updated heights for participants in the Age 18+ track who are less than 21 years old.

Height and weight should match the values collected at Visit 0A on the Adult Body Measurements form (BODYMEAS_ADULT) for individuals who are 21 years of age or older when they enroll.

- Click on the 'Calculate' button to compute the participant's current predicted PEF value.
- Print the Spirotek[®] Reference Peak Flow Report (P5_PEF_REF). The participant's updated reference PEF value is shown in Q1000. This is the value that should be programmed into his/her spirotek[®].
- Complete the header information on P5_PEF_REF (visit number (Visit 0A1 and 0B only), visit date, coordinator ID).
- Update the PEF reference value and return visit number in the spirotek[®]. This value will define the participant's green-yellow-red zones and will determine when he/she should activate his/her Asthma Action Plan. It is used to trigger alerts that will appear when the participant's PEF is in the yellow or red zone.

The reference PEF value from Q1000 on P5_PEF_REF should be updated on several participant handouts as follows:

- Participant Identification Card (P5_ID_P for Age 5-11 Track and P5_ID_A for Age 12-17 and Age 18+ Tracks)
 - Record reference PEF in space provided on the front
 - Record 80% of the PEF reference value in space provided on the back
 - Record 50% of the PEF reference value in space provided on the back
- BARD Asthma Action Plan (P = pediatric version and A=adolescent/adult version)
 - Record PEF reference value in space provided at the top of the card
 - Record 50% of the PEF reference value in the red zone space
 - Record 50% and 80% of the PEF reference value in the spaces for the yellow zone
 - Record 80% of the PEF reference value in the green zone space
- BARD Asthma Monitoring Log (P5_ASTHMA_LOG)
 - Record 80% of the PEF reference value in the space provided in the text at the top of the form

Note: If a participant is seen for Visit 0A1 or Visit 0B and the visit is not completed due to non-compliance, and the participant will return to complete the visit at a later date, then the reference PEF value should not be updated at the time of the interim visit. In general, reference PEF values should be updated only when these visits (and other run-in visits, including 0C, 0D and 1) are fully completed. The Reference Peak Flow Report (P5_PEF_REF) is submitted to the DCC only with visit packets.

Visits 2-12 (applicable only for participants less than 21 years of age at the time of the visit – participants who are age 21 or older will not have P5_PEF_REF generated at these visits)

Download spirotel[®] and convert the data using DBTools

Perform height and weight measurements (SEXAM_PED) – Age 5-11 and Age 12-17 Tracks only

Perform height measurement (P5_PULMONARYCHK) – Age 18+ Track, only for individuals <21 years of age at the time of the visit

Open the visit in Breeze

Verify/update height and weight on MedGraphics machine and calculate predicted PEF

Print Spirotel[®] Reference Peak Flow Report (P5_PEF_REF)

Complete header information on P5_PEF_REF

Update reference PEF and return visit number in spirotel[®]

At Visits 2-12, the following steps should be completed only for participants who are less than 21 years of age at the time of the visit:

- Download the spirotel[®] and convert the data using DBTools.
- If the participant is <21 years of age, open the visit and verify/update his/her height and weight on the visit screen. Refer to the physical exam form (SEXAM_PED) completed at the visit for participants in the Age 5-11 and Age 12-17 tracks and to the Pulmonary Procedure Checklist (P5_PULMONARYCHK) for updated heights for participants in the Age 18+ track who are less than 21 years old. Click on the 'Calculate' button to compute the participant's current predicted PEF.
- Print the Spirotel[®] Reference Peak Flow Report (P5_PEF_REF). The participant's updated reference PEF value is shown in Q1000. This is the value that should be programmed into his/her spirotel[®].

Note that the value may remain the same from visit to visit. Changes are only being made on the basis of the participant's updated predicted PEF at this point in the study.

- Complete the header information on P5_PEF_REF (visit date, coordinator ID).
- Update the PEF reference value (if needed) and return visit number in the spirotel®.

At Visits 2-12 P5_PEF_REF is entered as a packet form for participants in the Age 5-11 and Age 12-17 Tracks. It is entered as a single form for those ages 18-20 in the Age 18+ Track. These forms should be entered at each applicable visit, even if the reference PEF value does not change from one visit to the next.

If it changes, the reference PEF value from Q1000 on P5_PEF_REF should be updated on several participant handouts as follows:

- Participant Identification Card (P5_ID_P for Age 5-11 Track and P5_ID_A for Age 12-17 and Age 18+ Tracks)
 - Record reference PEF in space provided on the front
 - Record 80% of the PEF reference value in space provided on the back
 - Record 50% of the PEF reference value in space provided on the back
- BARD Asthma Action Plan (P = pediatric version and A=adolescent/adult version)
 - Record PEF reference value in space provided at the top of the card
 - Record 50% of the PEF reference value in the red zone space
 - Record 50% and 80% of the PEF reference value in the spaces for the yellow zone
 - Record 80% of the PEF reference value in the green zone space

A new Asthma Monitoring Log (P5_ASTHMA_LOG) is needed at each visit. Complete the following:

- Record 80% of the PEF reference value in the space provided in the text at the top of the form

2.42 Registration

Registration is applicable for all BARD age tracks.

Visit 0A or Earlier

Register participant in AsthmaNet Registry

Before a participant can be enrolled in the BARD trial, he/she must be present in the AsthmaNet Registry with 'complete' status. ACRN and CARE Network participants who completed Registry forms in those networks already will have 'complete' status in the AsthmaNet Registry. Any participants from the earlier networks who have 'incomplete' status, or individuals who are new to the NHLBI asthma networks, will need to undergo the full AsthmaNet registration process.

All individuals who are enrolled in the BARD trial will need to have AsthmaNet label sheets and reports printed and stored with the AsthmaNet Registry documentation.

Complete Registry procedures are documented in section 9 of the AsthmaNet General Manual of Operations.

Visit 0A

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 AsthmaNet master ID number and serves as a reference during the protocol enrollment process.

Include REG_CHK behind the Visit Procedure Checklist (P5_VISIT0A) in the participant's Visit 0A packet.

2.43 Satisfaction Questionnaire

This questionnaire is applicable for all BARD age tracks.

Participant's termination visit

Give participant 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 SATQX is posted on the secure AsthmaNet website in the visit packet corresponding to the final study visit for a given protocol. For BARD, it is present in the Visit 13 packet. In addition, the questionnaire is also posted appended to the single BARD Termination of Study Participation form (P5_TERM) for use with participants who terminate from the study before Visit 13.

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.

Only BARD participants who successfully complete Screen Visit A (Visit 0A) and enter the run-in should be given a questionnaire at the time of their study termination.

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

Distribute a copy of the questionnaire to any participant who successfully completes Visit 0A, then terminates, whether he/she completes the study or terminates early (for his/her own reasons, due to ineligibility, or for other reasons).

Download the questionnaire from the secure AsthmaNet website along with the BARD Termination of Study Participation (P5_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 P5_TERM forms will have only protocol number completed. Coordinators should complete the site number before distributing the questionnaire to a participant.

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

Complete the participant's final study status in the gray box at the top of page 1 of the form. Individuals who terminate during the pre-randomization phases of the study should be coded as 'Run-in termination.'

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.

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 being 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.

Personnel at performance sites who have access to the secure AsthmaNet website can generate Satisfaction Questionnaire Reports for sites to which they have been granted access in the database. The reports summarize the site's response rate, by study and overall, as well as the frequencies of responses to each of the questions on the questionnaire, by study and overall.

The DCC will provide periodic reports of the data from the questionnaires for all sites for the QCC. Response rates will be compared across the performance sites and clinical center partnerships to ensure that all sites are participating fully in the survey process.

2.44 Serum ImmunoCAP, Total IgE and Cotinine Tests

All of these blood tests are applicable for all three BARD age tracks.

Visit 1

Obtain blood sample for ImmunoCAP/IgE and cotinine tests (one 8 ml tiger top (SST))
Log on P5_SERUM_SAMP_LOG
Complete P5_LAB

At Visit 1, a blood draw for the serum ImmunoCAP, total IgE, and cotinine tests should be attempted for all participants who achieve randomization. Individuals who are not eligible for randomization should not have blood drawn. The order of blood draws outlined in the Blood Samples and Tests discussion in this section must be observed.

Supplies

The following supplies are required to collect, process, and store serum samples for these tests:

Item	Vendor	Catalog #	# Per Collection
8.5 ml tiger-top serum separator tube (SST) (BD #367988)	Fisher Sci. (1-800-766-7000)	02-683-96	1
SST label (Avery #5160)	Staples	209882	1
2.0 ml cryovial (USA Scientific Saf-T-Seal screw cap tubes #50-819-765; no substitutes)	Fisher Sci. (1-800-766-7000)	1420-9700	3-6
Disposable pipette 6", 7.5 mL capacity	Fisher Sci. (1-800-766-7000)	13-711-9D	1
Fiberboard storage box for cryovials (Fisherbrand Cryo/Freezer boxes, 5x5x2" with 81 cells; no substitutes)	Fisher Sci. (1-800-766-7000)	03-395-464	1 box per 81 cryovials stored
White Laser Cryo-Tags, 1.5" x 0.75" http://divbio.com/lasercryo-tags150x0751200pk.aspx	Diversified Biotech (1-800-796-9199)	LCRY-1200	3-6, as described in table below

Barcode Labels Needed for Serum Processing (generated through BST module)

BST Sample Type	Barcode Number	Sample Purpose	# Labels Needed Per Collection
BARD_IMMUNOCAP	5IMCAP0001-5IMCAP9999	ImmunoCAP/ Total IgE	1
BARD_COTININE	5COT0001-5COT9999	Cotinine Test	1
BARD_SERUM	5SER00001-5SER99999	Excess serum for storage	2-4

Blood Collection, Processing, and Storage Procedures

1. Fill one 8.5 ml tiger top (red/grey stopper) SST with the participant's blood. The vacutainer must be labeled with participant ID and initials. A template for labels for the SSTs (Avery #5160) can be found on the AsthmaNet secure website in the Protocols: BARD: Labels folder, or a Sharpie marker can be used to write the information directly on the tube.
2. Complete an entry for the blood draw on the BARD Serum Sample Log (P5_SERUM_SAMP_LOG). Complete the participant's BARD ID number and collection date/time.
3. Invert the SST 5 times. Allow the blood sample to clot at room temperature for 20 to 60 minutes.
4. While the blood is clotting, prepare the 2.0 ml cryovials (specified in the above table; no substitutions) for the participant's serum samples. Each participant should have enough serum to provide one ImmunoCAP/IgE sample, one cotinine sample, and up to four 1.0 ml aliquots of excess serum to be stored for future analyses. Label the cryovials with barcode labels as follows:

ImmunoCAP/IgE: Label one tube with a BARD ImmunoCAP barcode label generated through the Biological Sample Tracking (BST) module of the AsthmaNet database management system. The barcode label includes a preprinted 10-digit barcode number, starting with 5IMCAP0001, which is unique for every BARD participant-sample. The sample type associated with the serum tubes in the BST module is "BARD_IMMUNOCAP."

Sample ImmunoCAP barcode:



Cotinine: Label one tube with a BARD Cotinine barcode label generated through the BST module of the AsthmaNet database management system. The barcode label includes a preprinted 8-digit barcode number, starting with 5COT0001, which is unique for every BARD participant-sample. The sample type associated with these tubes in the BST module is “BARD_COTININE.”

Sample Cotinine barcode:



Serum for Storage: Label 2-4 tubes with BARD Serum barcode labels generated through the BST module of the AsthmaNet database management system. The barcode label includes a preprinted 9-digit barcode number, starting with 5SER00001, which is unique for every BARD participant-sample. The sample type associated with these tubes in the BST module is “BARD_SERUM.”

Sample Storage Serum barcode:



5. At the end of the clotting period, complete the time spinning is initiated on P5_SERUM_SAMP_LOG. Centrifuge the clotted blood at 1100 to 1300g for 10 minutes to separate the serum from cells.
6. Using a pipette, taking care not to touch the gel barrier, carefully remove the cell-free serum and aliquot it into 2.0 ml cryovials as follows:
 - ImmunoCAP/IgE
Aliquot 1.25 ml into the labeled BARD ImmunoCAP tube.
 - Cotinine
Aliquot 0.25 ml into the labeled BARD Cotinine tube.

- Serum for Storage

Aliquot 1.0 ml of remaining serum volume into tubes labeled for BARD storage serum. Tubes should not contain less than 1.0 ml serum. If less than 1.0 ml of serum remains, allocate it equally among the cryovials that already contain 1.0 ml. Take care not to put more than 2.0 ml into any of the cryovials, as they may rupture once frozen.

7. Screw each cryovial shut. Be sure the cap is secure.
8. Access the BST module and scan the barcodes to insert a record for each sample. Input the participant ID information to link the barcode to the correct BARD participant. It is imperative that all samples are scanned on the day of collection so that they are associated with the correct participant ID and are available for inclusion in the next shipment. For details on accessing and interacting with the BST Module in the AsthmaNet Database Application, see the AsthmaNet Computing and Networking Environment details in section 7 of the AsthmaNet General Manual of Operations.
9. Record sample barcode numbers and serum volume for each aliquot on P5_SERUM_SAMP_LOG.
10. Complete Question #2 on the BARD Laboratory Results form (P5_LAB). See section 4 of this manual for further details regarding completion and entry of this form.
11. Store the samples for ImmunoCAP/IgE and cotinine analysis in one chipboard storage box. Organize the box such that all cryovials of one sample type are together on one side and vials of the other sample type are together on the opposite side. This organization will make creation of shipments easier when accessing the BST module on the day of a shipment. These samples will be shipped to ADx labs in Denver every 6 months. See the shipping instructions and schedule below.
12. Store the excess serum samples for storage in a separate chipboard box. These samples will be shipped to ADx labs at the end of the trial. They will serve as backup serum in the event that the ImmunoCAP/IgE and cotinine samples are lost or damaged en route to Denver.
13. Store the serum samples at -70 or -80 degrees Celsius until the shipment day. Record the date/time the samples are placed in the freezer and the current freezer temperature on P5_SERUM_SAMP_LOG.

Shipping Schedule

All accumulated ImmunoCAP/IgE and Cotinine samples, along with all accumulated urine samples (see the Urine Cortisol:Creatinine Laboratory Test discussion in this section of the BARD MOP for details), will be shipped priority overnight to ADx Labs at National Jewish Health in Denver on the second Tuesday of each January and July. The first shipment will occur on July 8, 2014. Scheduled shipment dates follow:

2014: July 8

2015: January 13 and July 14

2016: January 12 and July 12

2017: January 10 and July 11

The DCC will send a reminder to the coordinators approximately one week ahead of each scheduled shipment. If a performance site has a conflict with a particular shipment date, arrangements should be made with ADx lab staff to ship the samples on an alternate date. Samples should not be held at the site until the next 6-month shipment. Samples should not be shipped on alternate dates without first clearing the dates with lab staff to ensure that they are available to receive and process the shipment.

Serum for storage will be kept at the performance sites until the end of the trial. At that time a designated shipment date will be determined. These serum samples will be used as a backup in the event that a shipment to Denver is lost or damaged and the original ImmunoCAP/IgE and Cotinine samples are unusable.

Creating a Shipment

To create a shipment, scan the barcodes for all samples available to ship into the AsthmaNet BST system. Include a shipment comment detailing the contents of the shipment (i.e., human serum). Each shipment of each sample type from each site will receive a unique shipment ID number. A shipment inventory will be generated for each sample type 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 inventory for each sample type for inclusion in the shipment.

An export file containing shipment information in .csv format will be e-mailed automatically to ADx Labs (to Michael Aron at aronm@njhealth.org, Billy Moua at

mouab@njhealth.org, and Michael Hubbard at HubbardM@njhealth.org) following the performance site's confirmation of the shipment of each sample type.

Packaging Samples for Shipment to ADx Labs at National Jewish in Denver

Before packaging available samples for shipment, they must be scanned into the BST system and an inventory of the shipment generated and printed as described above. After the samples have been scanned and the shipment has been confirmed by the performance site, the samples should be packaged for shipment. The following materials are required:

Item	Vendor	Catalog #	# Per Shipment
ThermoSafe Styrofoam mailer in corrugated carton	Fisher Sci. (1-800-766-7000)	03-525-36	1
FisherBrand Biohazard Polyethylene Transport Bag 8x8" (or larger)	Fisher Scientific (1-800-766-7000)	01-800-07 (8x8")	1
FisherBrand Biohazard Wipes, standard absorbency (4x4")	Fisher Sci. (1-800-766-7000)	06-670-35	2
Packaging tape	Staples	380107	
Exempt Human Specimen labels Therapak 2.5"x2"	Fisher Sci. (1-800-766-7000)	22-130-070	1
Therapak Dry Ice Label - UN1845 (5.5x5.5")	Fisher Sci. (1-800-766-7000)	221-30-065	1
Shipment inventory from BST			1 for each sample type

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

Shipment assembly instructions:

1. Cryovials will be shipped in the fiberboard boxes used for storage at the sites. Urine and serum samples can be combined into one box if less than 81 vials are being shipped. Store all vials of a given sample type in the same box location so that sample types are separated and organized.
2. Place one sheet of absorbent material on top of the samples inside the chipboard box. Close the box.
3. Place the closed box into the plastic transport bag.
4. Place a second sheet of the absorbent material in the plastic transport bag.
5. Seal the transport bag tightly.
6. Fill the bottom of the Styrofoam shipper with approximately 1 inch of cubed/chipped dry ice.
7. Place the plastic transport bag containing the samples on top of the ice layer.
8. Cover the transport bag with more crushed dry ice so that the box of tubes cannot be seen. Continue to fill the Styrofoam box with as much dry ice as possible. Sufficient dry ice should be included to ensure that samples will remain frozen until they reach the lab. When in doubt, add more! Do not ship more than one fiberboard storage box in a Styrofoam shipper. If more than 81 vials need to be shipped, use multiple Styrofoam shippers. They can be combined into one large cardboard box for shipment.
9. Place a copy of the shipment inventories for each sample type (in a plastic Ziploc bag) on top of the dry ice and close the Styrofoam mailer tightly.
10. Seal the Styrofoam mailer with tape. Do not completely seal the box so that it is airtight. Carbon dioxide from the dry ice must be allowed to escape.
11. Place the Styrofoam mailer inside a cardboard mailing sleeve (the specified shipper in the table above comes with a cardboard mailer).
12. Attach one “Exempt Human Specimen” sticker and one “DRY ICE – UN 1845” label to the cardboard carton. Mark the appropriate weight of dry ice in kg on the label.



13. Include the name, address, and phone number of the person responsible for the shipment on the box.

14. Address the shipment to:

ADx at National Jewish Health
Attn: Client Services
1400 Jackson Street
Room M013
Denver, CO 80206
ATTN: Michael Hubbard
Tel: (303) 270-2264
E-mail: hubbardm@njhealth.org

15. Specify FedEx priority overnight shipment (AM receipt not required). No other form of shipping is acceptable.

Shipping Charges

Costs related to shipping BARD serum and urine samples to ADx Laboratory in Denver have been included in the clinical site's BARD budget. The local site's FedEx account should be used for these shipments

ADx Laboratory Contacts

Michael Hubbard, Pre-Analytical Supervisor
National Jewish Health
Advanced Diagnostic Laboratories (ADx)
E-Mail: hubbardm@njhealth.org
Tel: (303) 270-2264

Michael Aron, MBA, PMP (Primary contact)
Project Manager Lead
Advanced Diagnostic Laboratories (ADx)
National Jewish Health
1400 Jackson St.
Denver, CO 80206
E-Mail: aronm@njhealth.org
Tel: (303) 270-2578

Lab Test Results

ImmunoCAP, serum total IgE, and serum cotinine results will be run in batches following each 6-month shipment. ADx Laboratories has CLIA certification and is accredited through the College of American Pathologists (CAP). Approximately 3-4 months after each shipment, reports showing results for ImmunoCAP and total IgE (for each study participant for whom serum samples were present in the shipment) will be posted to the secure website. Reports will be located in folder Protocols: BARD: ImmunoCAP/IgE Reports under a site-specific sub-folder. The DCC will notify the coordinators when the next batch of reports becomes available. Coordinators should consult their local investigator to determine the best way to disseminate the information based on a given participant's study status. It will be up to the local investigator to provide an interpretation of the results and to answer any questions the participant has.

Investigators will be notified directly via e-mail of the participant ID numbers for any participants who have a total IgE value over 1000 IU/mL. The e-mail message will be cc'd to the lead coordinators at the site. Investigators will be asked to review the history for these participants and to determine if additional follow-up is warranted (due to a potential diagnosis of allergic bronchopulmonary aspergillosis (ABPA)). Decisions for each case should be documented in the participant's study folder along with his/her ImmunoCAP/IgE report.

Contingency Plan for Difficult Blood Draws

At Visit 1 the required blood draw should be attempted for all randomized participants. If adequate blood for these tests cannot be obtained (due to a hard stick or other issues related to the blood draw process), and the participant is amenable, attempts can be made at subsequent visits. If the blood draw is successful at a later visit, data corrections should be submitted for Question #2 on the Visit 1 BARD Laboratory Results form (P5_LAB).

2.45 Significant Asthma Exacerbation

Significant asthma exacerbation procedures are applicable for all three BARD age tracks.

Visits 0A, 0A1, 0B, 0C, 0D, 1-13

Complete Significant Asthma Exacerbation form (P5_SIGEX), if applicable

Definition

In this study an asthma exacerbation will be defined according to the recommendation of the NIH Outcomes Workshop (Fuhlbrigge 2012 JACI 129:S34-48) as a worsening of asthma requiring the use of a systemic corticosteroid to prevent a serious outcome. In accordance with the Expert Panel recommendations, data will be captured on the following exacerbation-related outcomes:

1. All worsening asthma events in which systemic corticosteroids were initiated to prevent a serious outcome, including use of systemic corticosteroids in association with any form of healthcare provider encounter
2. All asthma-specific emergency department or urgent care visits that involved treatment with systemic corticosteroids
3. All asthma-specific hospitalizations that involved treatment with systemic corticosteroids (also reported as a serious adverse event)
4. All asthma-specific intensive care unit admissions or intubations (also reported as a serious adverse event)
5. All deaths (all cause and asthma-related; also reported as a serious adverse event)

For the purposes of this study, and to standardize our approach among AsthmaNet studies, two courses of systemic corticosteroids must be separated by at least one week to count as two exacerbations and to be documented as such.

An asthma exacerbation will usually be recognized by the development of an increase in symptoms of cough, chest tightness, shortness of breath, phlegm/mucus, and/or wheezing or by a decrease in the participant's peak flow or by an increase in the need for rescue bronchodilator use. Events will be defined solely by the use of systemic corticosteroids to treat the participant's asthma symptoms. No criteria based only on

peak flow levels or number of rescue bronchodilator puffs are defined for this study for assignment of exacerbation status.

Accurate recording and reporting of asthma exacerbations is important to the success of the BARD trial. The primary study outcome is a hierarchical asthma measure that uses the frequency of asthma exacerbations as the first tier to compare the study treatments to determine which, if any, is superior. If a given treatment produces one or more exacerbations less than a comparison treatment, then it is classified as the superior treatment.

Accurate reporting of exacerbations is also important from the standpoint of participant safety. If an individual experiences two exacerbations on the same blinded regimen during the post-randomization portion of the trial, then he/she should be categorized as a treatment failure and transitioned to the next blinded regimen following a 2-3 week washout from his/her final dose of prednisone or other systemic corticosteroid. See the Treatment (Arm) Failure discussion in this section for further details.

Note: One and two dose treatments with dexamethasone (e.g., Decadron) are commonly prescribed for asthma exacerbations for children ages 5-11 in an urgent care or emergency department setting. These treatments are referenced as effective for this age group in the Asthma Outcomes Workshop papers, and the authors left the door open for evidence to emerge for effectiveness of these treatments in the adolescent/adults populations. Although most participants who experience exacerbations during the trial will be treated with the standard 5-day prednisone course outlined in the BARD protocol and dispensed to participants to keep at home for emergencies, some individuals will receive alternate treatments in an emergency environment. Dexamethasone-treated events for participants in all age tracks should be recognized as asthma exacerbations for purposes of the study outcomes.

Documentation

When a participant experiences an asthma exacerbation during the BARD study, he/she should notify the performance site as soon as possible, preferably within 24 hours. Timely reporting ensures that the exacerbation is documented accurately and that the participant receives appropriate treatment. Once the significant asthma exacerbation has been confirmed, the following forms should be completed:

- Clinical Adverse Events (AECLIN)

All significant asthma exacerbations should be documented on AECLIN using ICD-9 code 493.92.

The start date recorded for an exacerbation should correspond to the date systemic corticosteroids were prescribed/started for exacerbation conditions.

- Concomitant Medications for Asthma/Allergy and Adverse Events (CMED)

Any non-study medications used to treat the exacerbation event should be recorded on the CMED form. Examples include oral or parenteral corticosteroids (e.g., rescue prednisone). Nebulized beta-agonist administered in a doctor's office or at the performance site also should be recorded as a concomitant medication.

Medications used for treatment of exacerbations and listed on the CMED form should be linked to the exacerbation adverse event recorded on the AECLIN form.

- BARD Significant Asthma Exacerbation form (P5_SIGEX)

P5_SIGEX must be completed any time the participant meets the criteria for an asthma exacerbation. This form is always treated as a single form.

If a participant meets asthma exacerbation criteria between regular study visits, use the number of the last regular visit completed as the visit number on the form.

- Serious Adverse Event Reporting Form (SERIOUS)

If a participant is hospitalized due to a significant asthma exacerbation event, or the event is considered to be life-threatening or meets other criteria in the definition of a serious adverse event (SAE), a SERIOUS form should be completed. SERIOUS forms should be submitted to the DCC within 72 hours of the notification of a SAE. See the Adverse Events discussion in this section for further details. In this case, if the event occurred post-randomization, the participant also meets treatment failure status.

Rescue Algorithm

The approach to rescue medications will be based on the consensus report presented in the National Heart, Lung and Blood Institute Guidelines and structured according to the protocols successfully implemented in previous ACRN, CARE and CAMP trials. Each participant will be given specific guidelines for decision-making and institution of rescue management (action plan). Two medications, albuterol and/or oral prednisone,

will be employed when increasing symptoms and/or a fall in peak flow require treatment. Participants will be given an adequate supply of Ventolin[®] (albuterol) for use throughout the trial. At Visit 0A they also will be dispensed a 5-day course of prednisone (as described below) to keep at home for rescue use on the advice of a study physician. For a severe acute asthma exacerbation, participants will be provided medication according to the best medical judgment of the treating physician. The treatment approaches outlined below have been safely and effectively used in previous CARE (CLIC, PACT, and BADGER) and ACRN (LARGE and TALC) trials.

Once an asthma exacerbation has occurred, the participant should contact the study coordinator and/or be evaluated at the performance site or the nearest medical emergency facility as quickly as possible.

Home care:

The onset of an asthma exacerbation will be recognized by symptoms such as coughing, dyspnea, chest tightness, phlegm/mucus, and/or wheezing, or by a decrease in the participant's PEF. Caretakers and participants will be educated to recognize the signs and symptoms of an asthma exacerbation and the significance of falls in their peak flow readings so that prompt rescue treatment may be instituted and morbidity decreased.

Participants who experience symptoms of cough, dyspnea, chest tightness, wheeze, phlegm/mucus and/or PEF less than 80% of their post-randomization reference value will initiate use of albuterol (2-4 puffs) by MDI every 20 minutes for up to 1 hour, and then every 4 hours if necessary. If the participant cannot achieve a PEF of at least 80% of his/her reference value, or if symptoms persist after three treatments, the performance site should be contacted. If the participant's peak flow reaches 80% of his/her reference value, but the participant requires albuterol every 4 hours for 24 hours in order to maintain a peak flow of at least 80% of the reference value, or if symptoms persist, the performance site should be contacted. At the time of performance site contact, a clinic visit may be necessary. The initiation of oral prednisone therapy will be based on specific guidelines and on physician discretion.

If symptoms are severe, the participant has retractions, evidence of cyanosis based on saturations on room air of < 90% based on pulse oximetry, has evidence of increased work of breathing, shortness of breath and/or "air hunger", and/or the PEF is less than 50% of reference value after 8 puffs of albuterol, the participant **must seek immediate medical care** and should contact the performance site.

Physician's office or emergency room:

In the primary physician's office or emergency room, the participant with an acute asthma exacerbation will be treated according to usual medical care that may include nebulized albuterol or high dose MDI albuterol (6-8 puffs every 20 minutes x three or more often, if needed). The dose of albuterol for the doctor-supervised situation is 0.10 – 0.15 mg/kg up to 5 mg per treatment. Albuterol can be delivered by nebulizer driven with oxygen, and treatments will be given every 20 minutes for up to three treatments. If after three treatments, the participant is not stable as described below, the physician may use additional albuterol treatments or other medications as is in his/her best clinical judgment. The participant will be assessed for general level of activity, color, pulse rate, use of accessory muscles and airflow obstruction determined by auscultation, and FEV₁ and/or PEF before and after each bronchodilator treatment. Measurement of oxygenation with a pulse oximeter may also be indicated for complete participant assessment during the acute exacerbation. The following assessments will also be made:

- If the participant has a favorable response to initial albuterol nebulizer treatment (FEV₁ at least 80% of predicted and PEF at least 80% of reference value), the participant will be observed for 1 hour prior to being discharged home with instructions to continue albuterol every 4 hours, as needed, and to report any decline in PEF and/or symptom fluctuation promptly.
- If the participant does not improve (FEV₁ less than 80% of predicted or PEF less than 80% of reference value) after the initial albuterol nebulizer treatment, nebulized albuterol therapy will be continued for at least two more trials (for a total of three times in 1 hour). If the participant's clinical symptoms are stabilized and FEV₁ or PEF is between 50-80% of predicted or reference value, the participant will be discharged home to continue use of albuterol (2 puffs every 4 hours) and to start a five-day course of oral prednisone.
- If the participant's FEV₁ is less than 50% of predicted or PEF is less than 50% of reference value after three treatments with nebulized albuterol in 1 hour, the physician may use his/her best medical judgment to treat the participant. Such clinical judgment may include the need for hospitalization and inpatient monitoring.

Prednisone Courses

Oral prednisone will be administered for the treatment of impending episodes of severe asthma when bronchodilator therapy is inadequate. The decision concerning the

initiation or continuation of a course of oral prednisone will be at the physician's discretion. Prednisone should be prescribed if:

- The participant uses more than 12 puffs of albuterol in 24 hours (excluding preventive use before exercise or allergen exposure) and has an e-diary symptom code of 3 (i.e., symptom graded severe) or PEF less than 70% of reference value before each albuterol use, or
- The participant has symptom code of 3 (severe) for 48 hours or longer, or
- PEF drops to less than 50% of reference value despite albuterol treatment

For both adults and children, the recommended prednisone dose for acute exacerbations is 2 mg/kg/day (maximum 60 mg) as a single morning dose for three days followed by 1 mg/kg/day (maximum 30 mg) as a single morning dose for two days. All administered doses will be rounded down to the nearest 5 mg in children/adolescents (i.e., participants aged 17 or younger). The dose of prednisone for children in the Age 5-11 Track should be calculated with their updated weights at the beginning of the four treatment periods (Visits 1, 4, 7, and 10). Replacement supplies should be dispensed, if necessary.

In general, prednisone should be prescribed in tablet form for use as a rescue medication during the BARD study. Parents may crush prednisone tablets and administer them in applesauce or pudding if their child cannot swallow them. In cases where the child absolutely cannot or will not take the prednisone tablets, liquid may be prescribed as an alternative. Record the correct formulation on the CMED form reflecting the dose in mg (weight, not volume). Liquid prednisone should only be prescribed if absolutely necessary. No formal exception from the DCC is required to substitute the liquid formulation.

If a participant initiates prednisone treatment on his/her own without input from study staff, the prednisone use should be recorded on the CMED form as usual, even if only a partial course was taken. The study physician should be consulted to determine if the course was warranted and if a significant asthma exacerbation should be recorded. The participant's supply of rescue prednisone should be replenished, as needed. The participant should be reminded that prednisone should only be initiated on the advice of study medical professionals. He/she should contact the performance site for advice and to be seen if symptoms and/or peak flow indicate that he/she may be experiencing an exacerbation.

Timing of Asthma Exacerbations and Trial Management

Run-In Exacerbations:

If a participant who requires 2 steps to step down to 1xICS in the run-in experiences an exacerbation while on the 2-2.5xICS step, he/she is ineligible for further study participation, as he/she cannot tolerate a decrease in ICS dose. In that case a Termination of Study Participation form (P5_TERM) should be submitted along with a P5_SIGEX form.

Participants who experience an exacerbation while on 1xICS in the run-in may be eligible for randomization if they meet all other criteria, including compliance requirements for study drug dosing and e-diary/PEF completion, and their e-diary data reflects 'lack of control' as required for randomization. If the participant meets all criteria with the exception of 'lack of control', the DCC must be contacted with details so that the BARD investigators can review the case and approve moving forward with randomization, if appropriate. Participants must wash out from their final dose of prednisone for 2-3 weeks prior to completing the randomization visit (Visit 1). During the washout period they will remain on 1xICS. If a second exacerbation occurs prior to randomization, the run-in will be extended further to allow for a 2-3 week washout period from the final dose of the second prednisone course. If a third exacerbation occurs, then the participant is ineligible for further study participation for safety reasons. In that case a P5_TERM form should be submitted. P5_SIGEX forms should be completed for each of the exacerbation events.

Participants who experience an exacerbation while on 1xICS in the run-in and do not meet compliance requirements for randomization are ineligible for further study participation. These individuals will be terminated from the study and may re-enroll, at the discretion of study staff, after meeting all applicable washouts. P5_TERM and P5_SIGEX forms should be submitted.

Note: If a participant experiences an exacerbation on 1xICS prior to completing Screen Visit B (Visit 0B), and he/she meets all eligibility requirements for randomization, then he/she may stay in the study but will be unable to complete the methacholine challenge at Visit 0B. The remainder of the visit procedures should be completed at Visit 0B and arrangements should be made for the participant to return for the randomization visit (Visit 1) after meeting the 2-3 week washout period from the prednisone treatment. If the participant did not meet at least one of the asthma verification criteria (either source documentation of reversibility, change in FEV₁, or PC₂₀, OR reversibility confirmed at Screen Visit A (Visit 0A)), then he/she should be terminated from the study. A Termination of Study Participation form (P5_TERM) should be submitted. These

participants may re-enroll in the study after meeting the 4-week prednisone washout prior to Visit 0A.

Post-Randomization Exacerbations:

Participants who experience an exacerbation during the first 2 weeks of a double-blind treatment period (prior to the treatment period's baseline visit) will have their baseline visit delayed for at least 1 week (but no more than 2 weeks) from their final dose of prednisone. Participants will remain on their double-blind study medication during this washout period. If a second exacerbation occurs during the washout period or a second prednisone taper is required to treat the exacerbation, the participant meets treatment failure conditions and will go off double-blind medication and on open-label 5xICS while washing out from the final dose of prednisone, in preparation for starting the next treatment period. If possible, the participant should start on open-label 5xICS while taking the final course of prednisone. Prednisone treatment should not be delayed if this is not possible. See the discussion of Treatment (Arm) Failures in this section for further details.

Participants who experience their first exacerbation of a treatment period in the final two weeks of the 14-week period will delay the start of the following treatment period by 2-3 weeks following their final dose of prednisone. Participants will receive open-label 5xICS during the washout period (and during the prednisone course, if possible). These individuals are treated in the same fashion as those who achieve treatment failure status. See the discussion of Treatment (Arm) Failures in this section for further details.

Following clinical assessment and appropriate medical management, regular study visits will continue in accordance with the participant's visit schedule, unless a defined washout period post-prednisone is required to prepare for the next regular visit, as outlined above, or unless the participant meets treatment failure status and will be transitioning to the following treatment period right away. See the discussion of Treatment (Arm) Failure in this section for further details.

2.46 Spirometry

All spirometry procedures are applicable for all three BARD age tracks.

Visits 0A, 0A1, 0B, 1-13

Complete Pulmonary Procedure Checklist (P5_PULMONARYCHK)
Perform Spirometry Testing (SPIRO)

Visits 0A, 1 (sputum induction participants only), 4, 7, 10, 13

Administer 4 puffs of albuterol, wait 10-15 minutes, and perform post-bronchodilator testing (PALB4_SPIRO)

Spirometry procedures are carried out at all BARD visits, with the exception of Screen Visits 0C and 0D. Pulmonary function data are very important, as they confirm the participant's eligibility for the study and provide data for assessment of the composite primary outcome that determines which treatment(s) is (are) superior for each participant.

General Instructions

The BARD trial utilizes the MedGraphics spirometry system. The Spirometry Manual of Operations is located in Appendix 1 of the AsthmaNet General Manual of Operations (MOP).

When performing baseline spirometry at Visits 0A, 0A1, and 1-13 and post-albuterol spirometry at Visits 0A, 1 (sputum induction participants only), 4, 7, 10 and 13, the MedGraphics PreChgPost protocol should be used; do not use the Maximum Reversal Testing protocol for any BARD visits. At Visit 0B the MedGraphics AsthmaNet Methacholine protocol should be used. Invoking the appropriate protocol will ensure that the correct MedGraphics reports will be available for submission with the data packets and will allow for overreading of the tests.

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

Note that AsthmaNet now has two levels of spirometry certification: pediatric (ages 5-11) and adolescent/adult. Any individual who performs spirometry on a participant who is 5-11 years of age must possess pediatric spirometry certification. Pediatric certification is transferrable to adolescent and adult testing. Adolescent/adult certification is not transferrable to pediatric testing. Requirements for both levels of certification are outlined in the Spirometry MOP.

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

In general, before a participant can proceed with spirometry testing, he/she must meet all of the medication and substance holds specified on the BARD Pulmonary Procedure Checklist (P5_PULMONARYCHK) with 'gray box' exclusions. If a participant has taken any of the listed substances within the specified washout period prior to a visit, he/she generally may not proceed with spirometry testing at the visit. In this case the visit should be rescheduled within the visit window. If the participant has almost met a required washout period, contact the BARD scientific coordinator at the DCC. An exception may be allowed.

If an exception is granted through the DCC, Q1150 on P5_PULMONARYCHK should be marked 'Yes' even though one or more of the 'gray boxes' corresponding to drug or substance washouts is completed. This conflict will result in a data error which the coordinator should mark unresolvable; the exception should be explained in a comment.

Demographics

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

Height

Participants who are less than 21 years old (i.e., participants who have not yet had their 21st birthday) will have their height measured and recorded at each visit until they turn 21. Height is recorded on different data forms depending on the participant's BARD age track:

Age 18+ Track: Heights for individuals who are enrolled in the BARD Age 18+ track who are under age 21 will be recorded in Q1160 on the P5_PULMONARYCHK form at all spirometry visits, with the exception of Visits 0A and 13 when height is recorded for all adult participants on the Adult Body Measurements form (BODYMEAS_ADULT).

Participants who are at least 21 years old at enrollment will have their height measured and updated in the spirometry system only twice during the study (at Visit 0A and Visit 13). Once a participant is over the age of 21, he/she should not be re-measured until Visit 13. Height values should be updated in the spirometry system each time they are measured.

Age 5-11 and Age 12-17 Tracks: Heights for children and adolescents enrolled in the Age 5-11 and Age 12-17 tracks will be measured at each visit and recorded on the applicable Physical Exam form (LEXAM_PED or SEXAM_PED) at the visit. These forms are data entered. Height values should be verified and updated in the spirometry system each time spirometry is performed on participants in these age tracks.

Race/Ethnicity

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

Note that eligible individuals for the BARD study must have at least one biological grandparent of African descent or self-identify as African-American/Black. It is possible that eligible participants may not self-identify as African American/Black. In fact, they may choose another primary racial identification in Q1150 on the REGISTRY form (e.g., White/Caucasian) and their spirometry race/ethnicity on the Registry report may be something other than African American/Black (e.g., White/Caucasian). The BARD study will follow normal spirometry procedures in terms of entry of race/ethnicity and other demographics information into the MedGraphics software. We are hoping to recruit a wide range of individuals as concerns their African ancestry in order to have enough statistical power to perform analyses with respect to degree of African ancestry. Including individuals who identify as Caucasian, Asian, or Hispanic will increase our power to carry out these analyses and will provide a richer database.

Gender

Individuals who are transgendered or transitioning to the opposite gender should have their biological sex entered into the AsthmaNet Registry (under 'gender'). Biological sex should be entered into the MedGraphics software for purposes of calculating predicted lung function values.

Age

It should be noted that predicted lung function equations differ depending on the age of the participant. The Spirometry MOP lists the equations used for participants age 5 versus ages 6-12 versus ages 12 and older. Depending on a participant's age at enrollment, some individuals may 'jump' equations as they age during the study. For example, an African American participant who is 5.5 years old at Visit 0A will turn 6 during the study and will switch from Eigen-African American equations to Dockery-African American equations. As a result, coordinators may notice a significant change in predicted lung function values when the age category changes.

Visits 0A, 0A1, 0B, 1-13

Complete the Pulmonary Procedure Checklist (P5_PULMONARYCHK)
Perform Spirometry Testing (SPIRO)

At Visit 0A baseline spirometry is used to determine study eligibility. Results are recorded on the Spirometry Testing form (SPIRO) and are referenced on BARD Eligibility Checklist 3 (P5_ELIG3).

At Visit 0A1 baseline spirometry is used to determine the participant's percent predicted FEV₁ which is needed to complete Question 7 on the Asthma Control Questionnaire (ACQ7) and to score the instrument. The ACQ score is used to determine if the participant's run-in inhaled corticosteroid (ICS) dose can be reduced to 1xICS for the remainder of the run-in.

At Visit 0B baseline spirometry is used to qualify the participant for methacholine challenge. It is also used to assess study eligibility as concerns asthma verification.

At Visit 1 baseline spirometry data will be used to characterize the study population.

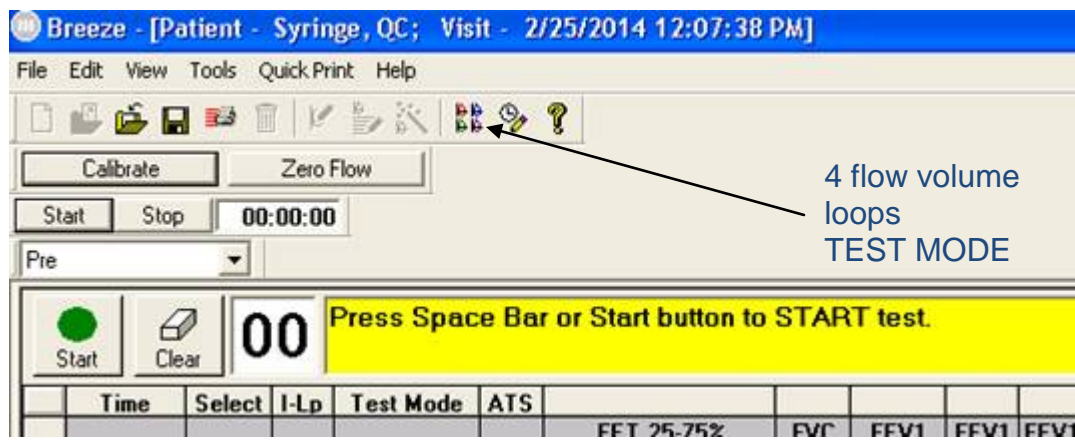
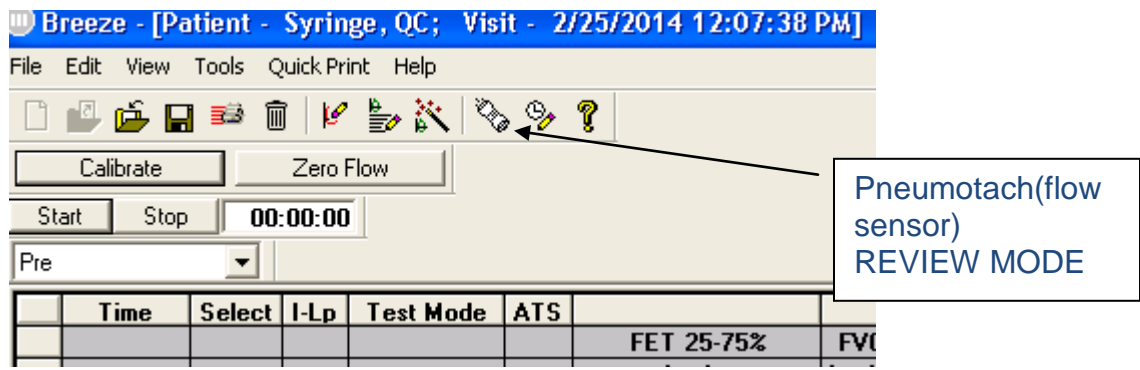
At Visits 2-13, FEV₁ from baseline spirometry will be used to evaluate the third tier in the composite primary outcome to determine superiority among treatments for a given individual and as a longitudinal secondary outcome measure.

Visit 0A, 1, 4, 7, 10, 13

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

At Visit 0A, post-albuterol spirometry is used to determine study eligibility. Results are recorded on the Post-Albuterol (4 puffs) Spirometry Testing form (PALB4_SPIRO) and are referenced on BARD Eligibility Checklist 3 (P5_ELIG3). At this visit the participant’s reversibility to 4 puffs of albuterol will also be used to qualify him/her on the asthma verification criteria that are assessed on P5_ELIG3. All participants should complete the pre/post spirometry sessions at Visit 0A, regardless of whether or not they provided source documentation from a previous pre/post spirometry test to support their eligibility.

At Visit 0A, spiroteI[®] tasks occur between baseline spirometry and post-albuterol spirometry sessions. When going back into Breeze to initiate the post-albuterol session, the software may be in “review mode” instead of “test mode”. To begin the post-albuterol session, click on the pneumotach (flow sensor) icon at the top of the screen. It will change to four flow volume loops which indicate that the software is now in “test mode”. At that point, testing can begin. Screen shots of the two icons follow.



At Visit 1, participants in the Age 12-17 and Age 18+ tracks will be assessed for eligibility to perform sputum induction at the visit. To qualify the participant, he/she should perform baseline spirometry, then be given 4 puffs of albuterol from his/her RESCUE albuterol MDI (Ventolin[®]) and be allowed to rest for **10-15 minutes**. After the 10-15-minute wait, spirometry should be repeated and the results recorded on the PALB4_SPIRO form. Results of the post-bronchodilator spirometry session will be used to qualify the participant for sputum induction. Note that participants who are not being qualified for sputum induction will only complete baseline spirometry at the visit.

At Visits 4, 7, 10, 13, post-albuterol spirometry will be collected to compute and analyze reversibility at the end of the four treatment periods.

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

2.47 Spirotel®

Spirotel® procedures are applicable for all three BARD age tracks.

The spirotel® is a peak flow meter and electronic diary (e-diary) combined into one device. The BARD trial will use the spirotel® II, which is an upgraded version of the spirotel® device used in the VIDA and INFANT studies. Participants will be given a device and trained in its use at the beginning of the run-in period, during Visit 0A. Participants will be expected to complete scheduled AM and PM sessions daily for the duration of the study. A scheduled session includes answering a set of questions in the e-diary and performing three peak flow maneuvers. Data collected in the device between visits will be downloaded to the MedGraphics database during each visit to the performance site. After the most recent data have been downloaded, clinical personnel will generate and print reports to review with the participant.

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

The BARD spirotel® Process reference card (P5_SPIROTEL_PROC) has been created to guide coordinators through the spirotel®-related procedures at each BARD study visit. The order of procedures laid out on the relevant visit procedure checklist should be followed, using P5_SPIROTEL_PROC as a quick reference.

Participant Instruction

Visit 0A

Instruct participant in use of spirotel® (use BARD/SIENA demo device) (HTSPIROTEL, P5_SPIROTEL_REF)

The DCC will provide each performance site one or two demonstration (demo) devices loaded with the BARD and SIENA demo programs. These devices are only to be used for instructional purposes; they should not be dispensed to participants for use during the trial. Demo devices do not store data.

BARD/SIENA Demo devices have been programmed with the BARD e-diary questions (AM and PM) and one alert:

- “Take 1 Puff/Inhalation from the Study Diskus” – follows each scheduled AM and PM e-diary/PEF session

At Visit 0A when the spiroteI[®] is first introduced to the participant, performance site personnel should review the information on the “How to Use Your SpiroteI[®] Electronic Diary and Peak Flow Meter” handout (HTSPIROTEL). Version 2.0 of this handout must be referenced so that directions correspond to the SpiroteI[®] II device. The participant should be educated on the steps for completing scheduled morning and evening assessments and on the expectation that these sessions are to be completed twice a day, every day, during the study. The participant should also be educated on how to use the device to perform unscheduled (extra) peak flows throughout the day, if needed to monitor lung function and to aid in determining if the participant needs to seek additional care for his/her asthma.

After the participant has reviewed the HTSPIROTEL handout, performance site personnel should introduce him/her to the BARD/SIENA demo device. When the device is turned on, two options appear: BARD or SIENA. Select “BARD”. Two additional options will appear: English or Spanish. Most participants should choose the English option. After making this choice, three new options will appear: AM, PM and PEF. Select “AM” to take the participant through a scheduled morning session with e-diary questions and peak flow maneuvers. The participant should be instructed to perform three peak flow maneuvers during each scheduled session. The number of maneuvers performed will be stored in the device’s memory. Select “PM” to take the participant through a scheduled evening session with e-diary questions and peak flow maneuvers. Select “PEF” to take the participant through an unscheduled peak flow maneuver-only session. Reinforce to the participant that all data entered into the device will be stored for download and review at his/her next visit to the performance site.

In addition to the HTSPIROTEL handout that covers the spiroteI[®] procedures in general, a BARD-specific handout (BARD SpiroteI[®] Reference Card (P5_SPIROTEL_REF)) has been created to fit into the spiroteI[®]’s case for quick reference by the participant at home during a session. This reference includes each question abbreviation (i.e., the limited representation the participant sees on the device), along with the longer text question that it represents. The reference also supplies clarification for certain questions, such as the difference between preventive albuterol puffs and rescue puffs, as well as explanations for the symptom scores. Clinical personnel should show the participant this reference and review it upon dispensing his/her device. It should also be emphasized that bronchodilator puffs taken as part of visit procedures should not be counted when reporting rescue use values.

Spirotel[®] Performance Check

Visit 0A

Complete Spirotel[®] Performance Checklist (SPIROTEL_PERF, P5_ELIG3) (use BARD demo device)

After the participant has had a chance to experiment with the BARD/SIENA demo device, he/she should undergo a formal spirotel[®] performance assessment using the steps on the Spirotel[®] Performance Checklist (SPIROTEL_PERF). Version 2.0 of this form should be used to correspond to the spirotel[®] II used in the BARD trial. The participant must pass the performance check with a score of 13 to remain eligible for the study. Results of the performance check are recorded in Q1040 on BARD Eligibility Checklist 3 (P5_ELIG3).

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

Preparing the BARD Spirotel[®] for Participant Use

Visit 0A

Program spirotel[®] with participant's information; select BARD from protocol drop-down
Use 900 for the reference peak flow value

Determine which spirotel[®] device will be assigned to the participant. Configure the device for the participant. The setup screen pictured below will appear. Choose BARD from the protocol drop-down list. The device serial number, software version number, and first digit of the participant ID (5) will auto-populate. Check the device date/time to be sure they are set to local date/time. Choose the language option that is desired (English or Spanish) from the drop-down menu¹⁷.

¹⁷ Note that the BARD Spirotel[®] Reference Card (P5_SPIROTEL_REF) has not been translated in Spanish and there are no plans to have the translation performed at this time. The Protocol Writing Committee (PWC) has agreed that the population to be recruited for BARD should not require Spanish-translated materials (forms, questionnaires, handouts, etc.), in general.

Several participant-specific pieces of information must be entered by clinical personnel, including:

Participant ID: This is the participant's assigned BARD ID number. The ID is broken into three sections: protocol number (5 pre-completed), performance site number, and ID number. Clinical personnel must complete the site number and ID number portions.

Participant initials: This is the set of initials by which the participant will be referenced during the study. These initials must match those used when entering the participant into the AsthmaNet Registry. If a participant's initials have changed since the time he/she was registered, current initials should be entered into the spiroteI[®] and a Registry Data Correction form (REG_CORRECT) should be submitted to the DCC. See the AsthmaNet Registry Manual of Operations in section 9 of the General MOP for details.

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

Visit Number: The return visit number should be selected. At Visit 0A the return visit number should be specified as 0B (if the participant is in the step-neutral or 1-step step-down groups and will start the run-in on 1xICS) or 0A1 (if the participant is in the 2-step step-down group and will start the run-in on 2-2.5xICS). See the discussion of Inhaled Corticosteroid (ICS) Step-Down Groups and Assessment in this section for details. The visit number will be updated by clinical personnel at each regular visit.

PEF Ref Value [L/min]: This is the participant's peak flow (PEF) reference value. At the beginning of visit 0A, the participant does not have any collected data on which to base the calculation of a reference PEF. To set up the device for the participant to perform blows to establish the PEF reference at Visit 0A, the reference value initially should be set at 900. After the participant performs three technically acceptable blows during the visit, the data will be downloaded and the real PEF reference value will be obtained from Q1000 on the BARD Spirotel[®] Reference Peak Flow Report (P5_PEF_REF).

See the Reference Peak Flow (PEF) discussion in this section for details on the derivation of the reference value and required updates while the participant progresses through the study. Note that the reference peak flow itself is being entered/updated, not the 80% and 50% cutoffs for yellow and red zones, respectively.

Turbine Serial Number: This is the number etched in the turbine that has been installed in the device.

Rescue Ref Value: Note that this field is grayed out for the BARD trial because no rescue use reference value is defined for the study.

A sample completed setup screen with information for participant 5-111-001 CAT at Visit 0A follows. Note that this person is in the 1-step step-down group so that her return visit number is set at 0B.

Visit 0A

Have participant perform three technically acceptable maneuvers on his/her assigned spiroteI[®] device (unscheduled peak flows)

Download spiroteI[®] and convert the data using DBTools

Select participant in Breeze, enter DOB, and select race and gender

Open the visit (either 0A1 or 0B)

Enter height/weight on MedGraphics machine and calculate predicted PEF

Print SpiroteI[®] Reference Peak Flow Report (P5_PEF_REF)

Complete header information on P5_PEF_REF

Update the peak flow reference value in spiroteI[®]

At Visit 0A the first download of spiroteI[®] data will occur after the participant does his/her three technically acceptable peak flow maneuvers to establish a reference peak flow (PEF) value. Data should be downloaded following normal procedures. Following download and data conversion in DBTools, open BreezeSuite. Locate the participant's data. Enter the participant's date of birth, gender, and race. The race category (Caucasian, Black, Asian, Hispanic) must match the participant's spirometry race/ethnicity designation printed on the participant's Registry Report. These parameters will be used to calculate the participant's predicted PEF value, which is needed to compute the participant's reference PEF value (see the Reference Peak Flow (PEF) discussion in this section for details). Once the date of birth, gender and race are entered for a given participant, they will not need to be re-entered at subsequent visits. A sample Breeze screen for participant 5-181-004 PAY follows:

Breeze - [Participant - 5181004 / PAY]

File Edit View Tools Quick Print Help

Calibrate Zero Flow

Start Stop 00:00:00

Bard Participant

Protocol: 5 ID: 5181004 Initials: PAY

DOB: 04/01/1972 Gender: Female Race: Caucasian

Visits

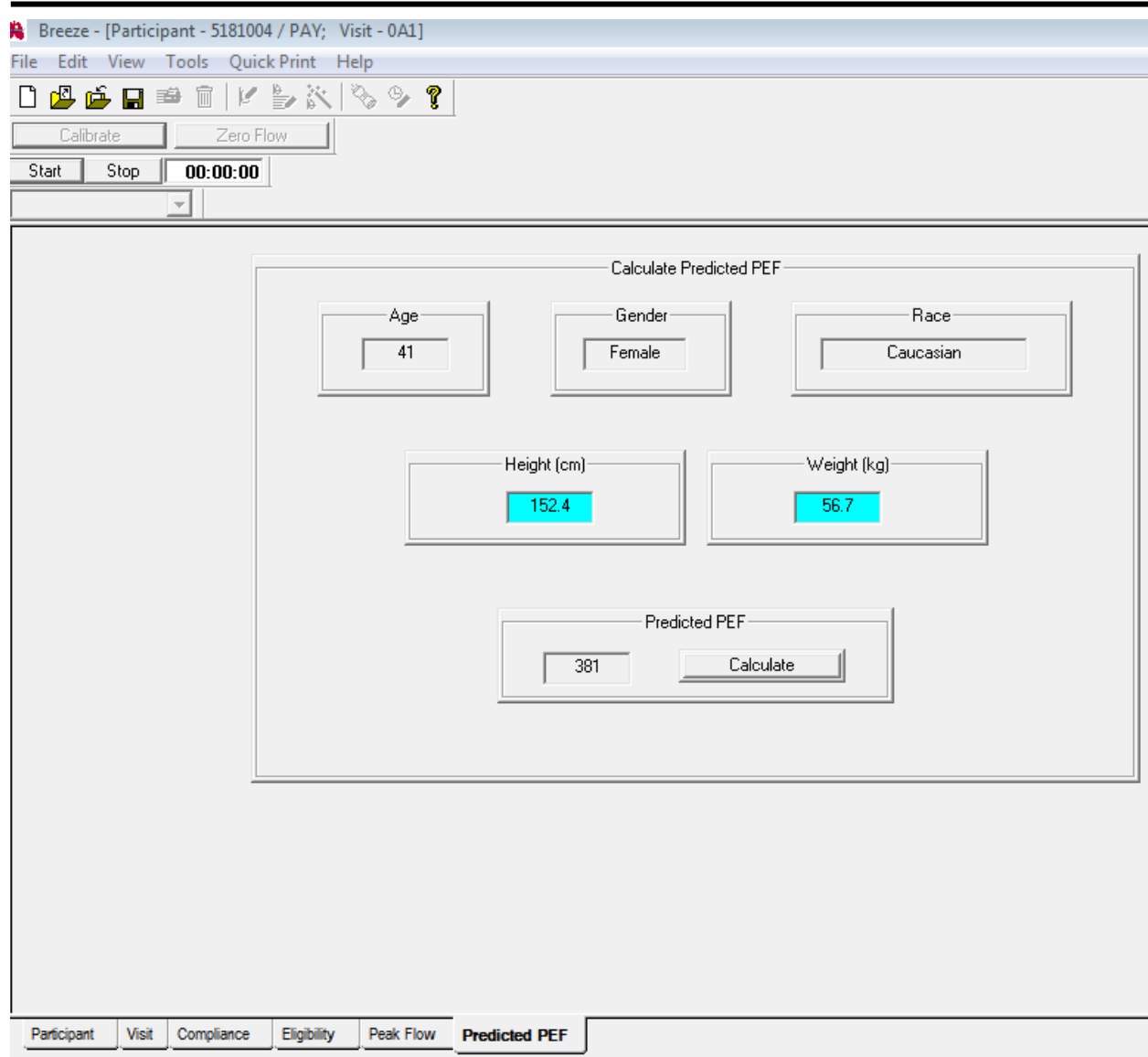
Visit ID	Date/Time
0A1	8/10/2013
0B	9/1/2013
1	10/9/2013
2	10/14/2013
10	10/16/2013

Open Visit

When opening new visit 0A1 or 0B, Breeze will automatically default to the Predicted PEF tab. The participant's height and weight will need to be entered for purposes of calculating the participant's predicted PEF value. Height and weight should be obtained from the participant's physical exam form completed at Visit 0A (either Pediatric Long Physical Exam (LEXAM_PED) for participants ages 5-17 or Adult Body Measurements (BODYMEAS_ADULT) for participants age 18+). Once the height and weight are entered, click on the Calculate button to compute the participant's current predicted PEF value. This value is needed to determine the participant's reference PEF value.

Note: Height and weight will need to be measured and updated and predicted PEF recalculated at each visit for participants who are under age 21. The forms on which the height and weight are recorded vary from visit to visit. These steps have been built into the visit procedure checklists for individuals under age 21 with the appropriate form references.

Following is a sample BreezeSuite Visit 0A1 screen for participant 1-181-004 PAY:



After the participant’s demographic and height/weight information has been entered and his/her reference PEF has been calculated, the Spirotek® Reference Peak Flow Report (P5_PEF_REF) should be generated. This report calculates the participant’s reference PEF following the rules laid out in the protocol and presents the correct value in Q1000. See the BARD Spirotek Reports section below for further details on this report. See the Reference Peak Flow (PEF) discussion in this section for the definition of the PEF reference value. See section 4 of the BARD MOP for details on the setup of the MedGraphics tabs and steps for generating the reports.

The correct reference PEF value, once available from the report, should be updated in the participant's device. If the participant leaves the visit with 900 L/min still programmed as his/her reference, the yellow and red zones will inevitably activate with every scheduled session, and his/her action plan will not be implemented successfully. Coordinators should double-check all spirotel[®] settings prior to distribution to the participant at the end of each visit.

PEF Ref Value [L/min]: This is the participant's new reference peak flow value obtained from the Spirotel[®] Reference Peak Flow Report (P5_PEF_REF). The value recorded in Q1000 on the report generated at each visit should be entered into the device. Note that the reference peak flow is being entered; not the 50% or 80% cutoff value for determining the red and yellow zones.

Note: If a participant completes a partial Visit 0A, including download of the three spirotel[®] blows for reference peak flow determination, but he/she must return at a later date to complete the visit (due to drug hold issues or other complications), special procedures apply, as follow:

- Data from the partial visit should not be uploaded to the Central Database.
- The participant ID number associated with the three blows should be changed to the next available high number (e.g., 500, 499, 498, etc.) that does not correspond to a real BARD participant. Changing the ID number will ensure that reports generate correctly at the rescheduled Visit 0A and subsequent visits.
- At the rescheduled visit, after confirming appropriate medication holds for spirometry, follow the Visit 0A checklist anew. This includes having the participant perform three blows on the spirotel[®] for reference peak flow determination. The blows must be done on the same day that Visit 0A is completed and the participant formally enters the run-in. Download the data, generate reports, and upload the data to the Central Database following normal procedures.

If data have already been uploaded to the Central Database for a partial Visit 0A that will need to be rescheduled, contact the BARD data managers so they can arrange to have the data deleted.

Visits 0A1-1

Have participant perform three technically acceptable maneuvers on his/her assigned spirotel[®] device (unscheduled peak flows)

Download spirotel[®] and convert the data using DBTools

Open the visit

Verify/update height/weight on MedGraphics machine and calculate predicted PEF
Print Spirotel[®] Reference Peak Flow Report (P5_PEF_REF)
Complete header information on P5_PEF_REF
Update reference PEF in spirotel[®]

Every participant will have an opportunity during visits 0A1, 0B, 0C, 0D, and 1 to have his/her reference PEF value updated. All participants will perform three technically acceptable (unscheduled) peak flow (PEF) maneuvers on their assigned devices at each of these visits. Only participants who are under 21 years of age need to be re-measured at each of these visits and to have their updated height/weight entered in the visit window. Predicted PEF should be recalculated as described above for everyone. The Spirotel[®] Reference Peak Flow Report (P5_PEF_REF) calculates the updated reference PEF value at each visit.

After the updated reference PEF value has been determined, it must be programmed into the participant's device for use in determining yellow and red zones for giving him/her alerts. The following field should be updated:

PEF Ref Value [L/min]: This is the participant's new reference peak flow value obtained from the Spirotel[®] Reference Peak Flow Report (P5_PEF_REF). The value recorded in Q1000 on the report generated at each visit should be entered into the device. Note that the reference peak flow is being entered; not the 50% or 80% cutoff value for determining the red and yellow zones.

Visits 2-12

Download spirotel[®] and convert the data using DBTools
Open the visit
Verify/update height/weight on MedGraphics machine and calculate predicted PEF
Print Spirotel[®] Reference Peak Flow Report (P5_PEF_REF)
Complete header information on P5_PEF_REF
Update the reference PEF in spirotel[®] (if applicable)

Only participants who are under 21 years of age need to be re-measured at each of these visits and to have their updated height and weight entered in the visit window and their predicted PEF recalculated. The Spirotel[®] Reference Peak Flow Report (P5_PEF_REF) should be generated at each of these visits for everyone who is less than 21 years of age. It is possible that their PEF reference values will change on the basis of an increasing predicted PEF value. If the participant's reference PEF has changed, the following field should be updated in his/her spirotel[®]:

PEF Ref Value [L/min]: This is the participant's new reference peak flow value obtained from the Spirotel[®] Reference Peak Flow Report (P5_PEF_REF). The value recorded in

Q1000 on the report generated at each visit should be entered. Note that the reference peak flow is being entered; not the 50% or 80% cutoff value for determining the red and yellow zones.

Visits 0A1-12

Update return visit number in spirotel®

When a participant returns to the performance site and completes a visit, the Visit Number in his/her device must be manually changed to the next return visit number. Choose the appropriate return visit number from the dropdown menu. For example, if a participant is at the site and completes Visit 0B and will be scheduled for Visit 0C, the visit number setting in his/her device must be incremented to 0C before he/she leaves the visit. This setting ensures that all stored data will be associated with the correct visit number.

Note that if a participant needs to have the interval between Visit 0A and 0B extended due to non-compliance, the PEF reference value should remain the same (do not update it) and the Visit Number in his/her device should remain 0B. Likewise, if the participant is being rescheduled for Visit 0A1 due to noncompliance, his/her return visit number should remain 0A1 until the next visit and the PEF reference value should not be updated. Before a participant leaves a visit, ensure that the device is set up appropriately for the next visit he/she will complete.

If a participant is deemed a treatment failure or treatment period drop-out during treatment period 1, 2, or 3, and he/she will skip remaining visits in the treatment period and will return for the next cross-over visit (i.e., 4, 7, 10), the return visit number should be set to the cross-over visit number. If the event is identified between visits, all data downloaded at the time treatment failure or drop-out determination is made should also be associated with the cross-over visit number. Coordinators should make the visit number change in BreezeSuite in that case.

Spirotel® Quality Control Procedures

Visits 0A1-13

Perform spirotel® QC (SPIROTELQC)

Perform a quality control test on the unit following the directions in the spirotel® Manual of Operations (appendix 6 of the AsthmaNet General Manual of Operations). Once the combination unit consisting of the device and turbine passes the quality control process, print out the Spirotel® Quality Control report (SPIROTELQC) for inclusion in the visit packet and data entry. Forms for failed device/turbine combinations should be printed

and stored in the participant's study folder at the performance site; do not forward them to the DCC.

Spirotel[®] quality control procedures may be performed in advance of the Visit 0A date to prepare the device for the visit.

Logging Dispensation and Return of Spirotel[®] Equipment

Visit 0A

Log/dispense spirotel[®] (SPIROTEL_DEVICE, SPIROTEL_TURBINE)

Visit 13 or whenever a participant leaves the study or returns faulty equipment

Collect/Log spirotel[®] (SPIROTEL_DEVICE, SPIROTEL_TURBINE)

Each time a spirotel[®] device or turbine is assigned to a participant, the Spirotel[®] Device Log (SPIROTEL_DEVICE) or Spirotel[®] Turbine Log (SPIROTEL_TURBINE) must be completed. At the time of dispensation, complete the device or turbine serial number, the participant's BARD ID number, the date the device or turbine is being dispensed, and the initials of the person dispensing the materials to the participant.

Each time a spirotel[®] device or turbine is returned by a participant at the end of his/her study participation or because of equipment failure, SPIROTEL_DEVICE and SPIROTEL_TURBINE must be updated to reflect receipt of these items. At the time of collection, complete the date the device and turbine are being returned, the initials of the person collecting the materials, and information regarding whether the device and/or turbine failed quality control testing. If the device and/or turbine failed QC testing, or they are otherwise malfunctioning, note the date the device and/or turbine was shipped back to the DCC. The DCC will test the defective units and will work with Respitech to secure replacements, as needed.

If a device and/or turbine fails quality control testing at a regular visit, update the applicable log accordingly for return of the defective materials. Create a new record on the appropriate log indicating the dispensation of new materials to the participant. If a device and turbine are lost during the study, enter this information into the logs in the comment column and notify the DCC. All turbines and devices must be accounted for at all times.

BARD Asthma Monitoring Log (P5_ASTHMA_LOG)

The Asthma Monitoring Log (P5_ASTHMA_LOG) is an administrative form that was created to give participants a centralized location to record their scheduled peak flows and rescue use (in puffs) each day. The spirotel[®] device does not allow participants to scroll back to view data entered for previous days; the P5_ASTHMA_LOG is the only

reference the participant will have to assess how his/her lung function and rescue Ventolin[®] use may have changed over recent days, possibly signaling the onset of an exacerbation. The log also includes space to record unscheduled peak flows, any non-study medications that are taken between visits, and any medical problems the participant experiences. This information is useful in recording concomitant medications and adverse events at the participant's next study visit. The participant should be instructed to complete this form and to return it at his/her next visit.

P5_ASTHMA_LOG form has been set up as a fillable pdf file with an auto-populating date field. When preparing a log for a participant, the coordinator should complete the current date (date of the visit) in the first date field at the top of the form. All dates will be completed automatically throughout the rest of the form. The participant should begin completing the log with his/her PM scheduled session on the day of the visit.

Visits 0A-12

Complete and distribute Asthma Monitoring Log (P5_ASTHMA_LOG)

At each of visits 0A through 12 a new P5_ASTHMA_LOG form should be completed with participant information in the key fields area and dates, starting with the date of the current visit. The participant's '80% Reference PEF' value from the Participant ID Card (P5_ID) should be recorded in the blank field in the text at the top of the form. The form should be given to the participant to complete until the next regularly scheduled visit.

Visits 0A1-13

Collect Asthma Monitoring Log (P5_ASTHMA_LOG)

Near the beginning of each visit, the participant's completed P5_ASTHMA_LOG form should be collected and reviewed with him/her for any recorded comments, concomitant medications, or adverse events experienced since the last visit. Completed forms should be stored in the participant's BARD study folder at the performance site; these forms should not be forwarded to the DCC.

Downloading the spirotel®**Visits 0A-13**

Download spirotel®

At each visit to the performance site, the data stored in the participant's spirotel®'s memory will be downloaded to the local machine, converted, and uploaded to the MedGraphics Breeze database. Once the data have been downloaded successfully, they will no longer be available on the participant's device. Data must be downloaded from a device before it can undergo the quality control process at a visit.

Note that data must be downloaded prior to generating reports at a visit. Do not upload data to MedGraphics prior to generating the reports. Premature upload can result in missing variables, such as height, weight, and predicted peak flow, in the master database.

If the participant forgets to bring his/her spirotel® to a visit, arrange for him/her to bring it to the clinic as soon as possible for download and change in return visit number. The longer a participant keeps the spirotel® at home, the more likely the device will run low on memory or battery, possibly resulting in data loss. Data will also continue to accumulate in the device under an incorrect visit number, resulting in the need for substantial data corrections following download. Participants must be reminded to bring their devices with them to every study visit.

General e-Diary and Peak Flow Compliance Assessments**Visits 0A1-13**

Print and review Spirotel® Participant Compliance Report (P5_COMPLY)
Complete header information on Spirotel® Participant Compliance Report (P5_COMPLY)

The e-diary questions serve as a daily log that should be completed by the participant twice a day, every day, during his/her study participation. Peak flows should also be

performed twice a day, on schedule, throughout the study. Compliance with these procedures is especially important because peak flow is part of the BARD asthma action plan and increases in symptoms (recorded in the e-diary) often signal impending exacerbations which contribute to the study's primary outcome.

Participants cannot perform the scheduled peak flow maneuvers without first having completed all of the AM or PM e-diary questions. Participants who do not meet high standards of compliance with measurement of peak flow and completion of e-diary questions will not be eligible to continue with screening for BARD or to become randomized at Visit 1. If a participant's compliance begins to decline during the trial, he/she should be counseled regarding the importance of carrying out his/her home procedures, including e-diary procedures. Compliance percentages less than 75% are considered unacceptable.

At each visit 0A1-13, the participant's spiroteI[®] device will be downloaded to the local PC, converted, and uploaded to the MedGraphics Breeze database. The SpiroteI[®] Participant Compliance Report for the current visit should be generated through the BreezeSuite software. This report includes all data collected between the previous visit number and the current visit number. If multiple downloads were performed between visits and the return visit number was correctly specified, all data from the combined downloads will be used in the compliance assessment. This report is not download-specific.

The SpiroteI[®] Participant Compliance Report serves as a data collection form (P5_COMPLY) that includes the following information:

- Q1000: Number of full days since the last visit: This value does not include the current visit date or the date of the previous visit. Only days since the last visit when the participant should have completed both AM and PM scheduled sessions are included/counted.
- Q1010: Number of days where AM and PM scheduled sessions are complete: A complete session is defined as a scheduled session where all e-diary questions have been answered and at least one peak flow maneuver has been completed. Note that participants are generally expected to do three peak flow maneuvers at each session, but they will be considered compliant for this report if they perform at least one. For a given day to be considered 'compliant', all AM and PM e-diary questions must be answered and at least one AM peak flow maneuver and at least one PM peak flow maneuver must be present in the dataset. This compliance definition is more stringent than the requirements for eligibility during

the run-in and for randomization. See the Eligibility Criteria discussions in this section for more information.

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

Cleaning Requirements

To ensure that the participant's device will function properly over the duration of his/her study participation, the turbine must be removed from the device and cleaned thoroughly at Visits 1, 4, 7, and 10. This timing during the study was chosen because these visits mark the beginning of a new treatment period and they cannot be missed. Minimal cleaning requirements have been specified; more frequent cleaning may be performed at the discretion of clinical personnel.

For complete instructions on cleaning spirotel[®] turbines, refer to the Spirotel[®] Manual of Operations in appendix 6 of the AsthmaNet General Manual of Operations.

Visits 1, 4, 7, 10

Remove and clean/disinfect spirotel[®] turbine
Replace turbine in spirotel[®]

Near the beginning of Visits 1, 4, 7 and 10, remove the turbine from the participant's spirotel[®] device and initiate the cleaning process. Other study procedures should be performed while the turbine is in the cleaning solution.

Near the end of the visit, reassemble the device and then perform quality control procedures on the unit. Follow normal quality control procedures in the event that the unit does not pass the quality control process.

Charging Requirements

Visits 0A1, 0B, 0C, 0D, 1-12

Charge spirotel[®]

Coordinators should ensure that the spirotel[®] is completely charged prior to dispensing it to the participant at Visit 0A.

At subsequent visits, to ensure that the participant's device will have enough battery power to make it until the next visit, the spirotel[®] should be charged. Near the beginning of the visit, attach the participant's device to a "USB Type A Male to USB

Micro Type B Male” cable and plug it in. Allow the battery to charge fully while the visit is taking place.

Cables will not be provided for participants to charge their spirotel[®] devices at home; however, some may have the correct type of cable for other electronics. If a participant has the correct cable at home, he/she may charge the spirotel[®], if desired, between visits.

For complete instructions on charging spirotel[®] devices, refer to the Spirotel[®] Manual of Operations in appendix 6 of the AsthmaNet General Manual of Operations.

BARD Spirotel[®] Reports

Visits 0A1-13

Print and review Spirotel[®] Participant Visit Report

Print and review Spirotel[®] Participant Compliance Report (P5_COMPLY)

Visit 0A1-1

Print and review Spirotel[®] Eligibility Assessment Report (P5_ELIG_RPT)

Visit 0A-1 (all participants)

Print Spirotel[®] Reference Peak Flow Report (P5_PEF_REF)

Visit 2-12 (participants under the age of 21 years only)

Print Spirotel[®] Reference Peak Flow Report (P5_PEF_REF)

Four spirotel[®] reports will be generated and consulted during the BARD trial. Reports are accessed through the MedGraphics BreezeSuite software after a participant's spirotel[®] data are downloaded and converted at a given visit by doing the following:

1. Open the BreezeSuite software. The 'Open Patient' screen will display.
2. Select the BARD checkbox and select Refresh.
3. Double-click on the applicable participant ID, or select the applicable participant ID and click on the 'Open' button. A list of visits for this participant will appear.
4. Double-click on the desired visit, or select the desired visit and click on the 'Open Visit' button.
5. At Visits 0A1 through 1 for all participants and Visits 2-12 for participants who are less than 21 years of age: The first time a visit is opened, the user will be

defaulted to the 'Predicted PEF' tab. Enter the participant's height and weight and click on the 'Calculate' button. The software will compute the participant's current predicted peak flow value.

6. Select 'Quick Print' and 'Spirotel BARD Reports' from the toolbar.
7. Five options are available for printing: All Reports, the Participant Visit Report, the Participant Compliance Report, the Eligibility Assessment Report (available only at Visits 0A1-1), and the Reference Peak Flow Report (available at Visits 0A-12).

Note: Do not upload data to MedGraphics prior to generating the reports. Premature upload can result in missing variables, such as height, weight, and predicted peak flow, in the master database.

Descriptions of the BARD reports follow.

- Spirotel[®] Participant Visit Report (P5_SPIROTEL_RPT): This report serves as a 'data dump' of all the information the participant entered into his/her e-diary/peak flow device between visits.

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

The body of the report shows all the data entered into the device sorted by trial date and the time each trial started. Variables include: trial date, trial type (AM session, PM session, extra PEF), time trial started (military time), BARD diary questions Q1-Q20, number of peak flow maneuvers completed during a session, FVC, FEV1, PEF, FEF25-75, and FET. BARD diary questions correspond to the order in which the participant answers them in the device. Refer to the BARD Spirotel[®] Coordinator Reference Card (P5_SPIROTEL_CREF) when reviewing the report with a participant. Questions and their possible responses are listed below:

Q1: Number of times the participant woke up last night due to asthma (0-9)

Q2: Number of puffs the participant will take from his/her study Diskus this morning (0-9)

Q3: Has the participant taken any puffs from his/her RESCUE albuterol inhaler during the past 4 hours? (1=yes, 0=no)

Q4: Shortness of breath score overnight (0,1,2,3)

-
- Q5: Chest tightness score overnight (0,1,2,3)
Q6: Wheezing score overnight (0,1,2,3)
Q7: Cough score overnight (0,1,2,3)
Q8: Phlegm/mucus score overnight (0,1,2,3)
Q9: Number of puffs the participant will take from his/her study Diskus tonight (0-9)
Q10: Has the participant taken any puffs from his/her RESCUE albuterol inhaler during the past 4 hours? (1=yes, 0=no)
Q11: Shortness of breath score since waking this morning (0,1,2,3)
Q12: Chest tightness score since waking this morning (0,1,2,3)
Q13: Wheezing score since waking this morning (0,1,2,3)
Q14: Cough score since waking this morning (0,1,2,3)
Q15: Phlegm/mucus score since waking this morning (0,1,2,3)
Q16: Number of albuterol puffs the participant took during past 24 hours to prevent symptoms (before exercise, before smoke exposure, or before exposure to pets) (0-40)
Q17: Number of RESCUE albuterol puffs the participant took for asthma symptoms or low peak flow during past 24 hours (0-40)
Q18: Was the participant absent from daycare, school or work during the past 24 hours due to asthma symptoms? (1=yes, 0=no, 9=N/A)
Q19: Was the participant seen by a healthcare provider (doctor's office, ER, urgent care, study site) for an unscheduled visit in the past 24 hours due to asthma symptoms? (1=yes, 0=no)
Q20: Did the participant take prednisone in the past 24 hours for treatment of his/her asthma? (1=yes, 0=no)
Q21: Current reference peak flow value (will not print on report as Q21 – this is for use in the BARD database)

The Spirotel[®] Participant Visit Report should be reviewed with the participant at each visit, starting with Visit 0A1 or Visit 0B, to ensure that he/she is following study procedures.

Coordinators should review the participant's answers to Q16 and Q17 (rescue albuterol use information) to ensure that the participant is using albuterol for primary treatment of asthma symptoms appropriately, and to confirm that he/she understands the difference between the two questions (i.e., preventive versus symptom-related use) and how to calculate each.

Coordinators should review Q2 and Q9 (study Diskus[®] use) at each visit to ensure that the participant is following instructions for inhaled corticosteroid (ICS) dosing as dictated by the protocol. Study dosing schedule remains the same (1 puff BID) throughout the study, even though ICS doses will change.

If a participant is seen for an exacerbation between regular visits, the Spirotel[®] Participant Visit Report should be generated and reviewed at that time. The visit number on the report will be the number of the next regular visit which was pre-programmed into the device. The report should be filed in the participant's study folder; it will not be forwarded to the DCC. At the next regular visit, following downloading of the participant's data, a new report should be generated. This report will show the data from both downloads and should be submitted to the DCC with the regular visit packet.

If a participant is deemed a treatment (arm) failure between regular visits, the Spirotel[®] Participant Visit Report should be generated and reviewed at that time. If the participant will be skipping visits in the treatment period and coming in for the next cross-over visit (4, 7, or 10), data in the download performed at the treatment failure visit should have visit number changed to the number of the next cross-over visit. After the visit number is changed in Breeze, the report should be rerun. The report should be stored in the participant's folder; do not forward it to the DCC. When the participant arrives for the cross-over visit, the report should be regenerated to contain data from multiple downloads. The updated report should be forwarded to the DCC with the cross-over visit packet.

This report is cumulative in that it shows all data associated with a given visit number, even if multiple downloads take place.

- Spirotel[®] Participant Compliance Report (P5_COMPLY): This report summarizes a participant's compliance with completing his/her e-diary questions and peak flows in the interval between visits. If multiple downloads are done between visits, all data corresponding to a given visit number will be included in one summary report.

Coordinators should complete the visit date and coordinator ID in the header of this report. The report doubles as a data collection form.

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

If a participant is seen for an exacerbation between regular visits, the Spirotel[®] Participant Compliance Report (P5_COMPLY) should be generated and reviewed at that time. The visit number on the report will be the number of the next regular visit which was pre-programmed into the device. The report should be filed in the participant's study folder; it will not be forwarded to the DCC. At the next regular visit, following downloading of the participant's data, a new report

should be generated. This report will show the data from both downloads and should be submitted to the DCC with the regular visit packet.

If a participant is deemed a treatment (arm) failure or a treatment period drop-out between regular visits, the Spirotel[®] Compliance Report should be generated and reviewed at that time. If the participant will be skipping visits in the treatment period and coming in for the next cross-over visit (4, 7, or 10), data in the download performed at the treatment failure visit should have visit number changed to the number of the next cross-over visit. After the visit number is changed in Breeze, the report should be rerun. The visit ID in the spirotel[®] device should also be updated to the cross-over visit ID.

Information on the double-blind Diskus[®] counter(s) returned at the interim visit should be recorded on P5_COMPLY at the time of the interim visit. The report should be stored in the participant's folder; do not forward it to the DCC. When the participant arrives for the cross-over visit, the report should be regenerated to contain data from multiple downloads. Information from the double-blind Diskus[®] counter(s) will be combined with information from the open-label Flovent[®] counter(s) returned at the cross-over visit. The updated report should be forwarded to the DCC with the cross-over visit packet.

This report is cumulative in that it shows all data associated with a given visit number, even if multiple downloads take place.

- Spirotel[®] Eligibility Assessment Report (P5_ELIG_RPT): This report is used at Visits 0A1, 0B, 0C, 0D, and 1 to determine if the participant's e-diary/peak flow compliance and symptoms meet the BARD eligibility criteria.

The top of the report shows the participant's BARD ID number, initials, and run-in visit number.

Asthma Control Assessment

The next section of the report shows the participant's asthma control information cumulatively across all run-in visits. This section is used to determine if the participant meets the 'lack of acceptable asthma control' criteria as defined for eligibility for randomization. See the Eligibility Criteria (Randomization) discussion in this section for further details.

Asthma Control Assessment variables include:

Visit: This is the visit number associated with a given data download.

Download Date: This is the download date associated with a given set of data. There may be multiple downloads associated with a given visit number. Note that two download dates appear on days when a download occurred. The first date corresponds to the date on which the original download occurred (when AM e-diary and PEF information should have been stored for that day in the Spirotek[®]). The second date corresponds to the date of the next download (when PM e-diary and PEF information should have been stored for that day).

Calendar Date: This column includes all calendar dates starting with the visit 0A date (represented as return visit 0A1 or 0B on the report) and ending with the current download date. All calendar days are represented, even if the participant did not complete either of his AM or PM sessions that day.

Symptom/PEF/Rescue Flag: This column shows an 'X' for any day during which the participant met at least one of the following criteria:

- AM or PM symptom score of 1 (mild), 2 (moderate), or 3 (severe) for shortness of breath, chest tightness, wheezing, or phlegm/mucus
- AM or PM symptom score of 2 (moderate) or 3 (severe) for coughing
- scheduled AM or PM PEF that was less than 80% of his/her current reference PEF value (i.e., in the yellow or red zone)
- used at least one puff of albuterol for symptom relief

Awakening Flag: This column shows an 'X' for any day during which the participant recorded waking up at least one time due to asthma symptoms (Q1 during the morning assessment is >0)

Lack of Asthma Control Criteria Met: This column shows an 'X' for any day on which the participant has met either of the following criteria for randomization eligibility:

- Experienced three or more days with symptoms (as defined above) and/or low PEF (defined above) and/or rescue albuterol use in a given one week (7 day) period. Rolling weeks across the run-in will be used to determine if the participant has ever met this criterion. Symptom/PEF/Rescue Flag will be used to assess if the participant meets this criterion for any given 7 day period leading up to a given calendar date on the report. If the participant has flags for at least 3 out of 7 days, including the current calendar date, then the Lack of Asthma Control Criteria Met column will have an 'X' in it

- Experienced two or more nights with awakenings due to asthma symptoms in a two week (14 day) period. Rolling weeks across the run-in will be used to determine if the participant has ever met this criterion. Awakening Flag will be used to assess if the participant meets this criterion for any given 14 day period leading up to a given calendar date on the report. If the participant has flags for at least 2 out of 14 days, including the current calendar date, then the Lack of Asthma Control Criteria Met column will have an 'X' in it.

If no 'X's are present in the 'Lack of Asthma Control Criteria Met' column of the report, the participant has not met either of the above criteria for randomization.

Information in the Asthma Control Assessment portion of the Eligibility Assessment Report is used to answer Q1010 on the BARD ICS Step-down Assessment form (P5_STEPDOWN_ASSESS) and Q1035 on the BARD Randomization Eligibility Checklist (P5_RAND_ELIG). When answering Q1035 at Visit 0B, consider only the data collected since the last visit in cases where the participant was rescheduled due to initial noncompliance.

Spirotel[®] Compliance

The next section of the report summarizes the participant's e-diary and PEF compliance for purposes of qualifying for randomization. This calculation is different from that provided on the generic Spirotel[®] Participant Compliance Report described above. This report generally computes the number of full days elapsed between visits and the number of AM and PM scheduled sessions the participant has completed (a session is considered complete if all e-diary questions were answered and at least 1 PEF was done). The compliance percentage is calculated as:

$(\# \text{ Complete AM Sessions} + \# \text{ Complete PM Sessions}) / (2 \times \# \text{ Full Days}) * 100\%$
This value is interpreted as the percentage of sessions the participant completed. The BARD protocol requires a minimum session completion percentage of 75% for the participant to be eligible for randomization.

Information in the Spirotel[®] Compliance portion of the Eligibility Assessment Report is used to answer Q1040 on the BARD ICS Step-down Assessment form (P5_STEPDOWN_ASSESS) and Q1040 on the BARD Randomization Eligibility Checklist (P5_RAND_ELIG).

Note: When the Eligibility Assessment Report is run for Visit 0A1 or Visit 0B, it will include only data collected since the last download for the same visit number when calculating the Spirotel[®] compliance percentage. This allows participants who are initially non-compliant to extend the visit interval by 2 weeks to show that they can learn the procedures and meet the standards required for the study. Reports that are generated for an initial (non-compliant) visit should be printed and submitted with the single form on which the eligibility data are recorded (either P5_STEPDOWN_ASSESS at Visit 0A1 or P5_RAND_ELIG at Visit 0B). At the point when another set of data are downloaded for the same visit number, coordinators will be unable to regenerate the report from the initial visit.

Note: When the Eligibility Assessment Report is run for Visit 1, it is possible that there will be no full days for evaluation between the previous visit and the randomization visit. In that case the Spirotel[®] compliance percentage cannot be calculated. The report will show 0 full days and blanks for number of AM and PM sessions complete and the compliance percent. Q1040 on P5_RAND_ELIG should be answered 'N/A' in that case.

Note: When the Eligibility Assessment Report is run for Visits 0C, 0D, and 1, it will include all data downloaded for the same visit number when calculating the Spirotel[®] compliance percentage.

- Spirotel[®] Reference Peak Flow Report (P5_PEF_REF): This report is used at Visits 0A, 0A1, 0B, 0C, 0D, and 1 to determine the participant's reference peak flow (PEF) value to be programmed into his/her spirotel[®]. The reference PEF is used to define the participant's green-yellow-red zones for use with his/her asthma action plan. This report doubles as a data collection form which is included in the visit packets for these visits for every participant. The report calculates the PEF reference value following the definition laid out in the protocol. For more information on the calculations see the discussion of Reference Peak Flow (PEF) in this section. For more information on specific visit procedures related to the generation of this report, see the Preparing the BARD Spirotel[®] for Participant Use section above.

Individuals who are age 21 and older will not have their PEF reference values recalculated and adjusted beyond randomization at Visit 1. Individuals who are under age 21 (i.e., all participants in the Age 5-11 and Age 12-17 Tracks, as well as individuals age 18-20 in the Age 18+ Track) will continue to be measured at each study visit and have their predicted PEF updated, accordingly. These individuals may experience updates to their reference PEF values on the basis of an increasing predicted PEF value. Therefore, the Reference Peak Flow Report

(P5_PEF_REF) will continue to be run at each visit 2-12 and included in the visit packets for participants in the Age 5-11 and Age 12-17 Tracks. The report will continue to be run at each visit for participants who are between 18 and 20 years of age and will be included as single form for the affected individuals in the Age 18+ Track.

The top of the Reference PEF Report shows the participant's BARD ID number, initials, visit number, visit date, and coordinator ID. The coordinator should complete visit number for visits 0A, 0A1, and 0B only; it will pre-print for all other visits. The coordinator should complete the visit date and coordinator ID for all visits.

The report includes a section that shows all the demographic and height information the program used to compute the participant's predicted PEF value as part of its calculations. Values that are printed in this section include:

- Participant's date of birth
- Participant's age (in years)
- Participant's gender
- Participant's spirometry race/ethnicity
- Participant's current height (cm)
- Participant's current predicted PEF (L/Min)

Coordinators should verify at each visit that these parameters have been entered correctly. If mistakes are made in entering this information, the participant's reference PEF value may be incorrect.

Q1000 contains the computed reference PEF value (in liters/minute). This value should be programmed in the participant's spirotel[®] at the current visit.

BARD Spirotel[®] Alerts

Several alert messages have been programmed into the BARD spirotel[®] device in an effort to improve participant compliance with taking study medications, recognizing exacerbation events, and alerting the coordinator if he/she may have met eligibility criteria during the run-in. Alerts appear following a completed scheduled AM or PM session (after the last PEF maneuver) when certain criteria are met. If multiple alerts apply, a 5 second pause will occur between alerts. Alert definitions follow.

- "Take 1 Puff/inhalation from the Study Diskus" Alert

This alert appears after every scheduled AM and PM session is complete, including three peak flow maneuvers. This alert applies throughout the study.

- “Peak flow is in the yellow or red zone. Follow your action plan.” Alert

This alert appears after a completed scheduled AM or PM session when the participant’s highest PEF (best of three blows) is <80% of the current peak flow reference value. This alert applies throughout the study.

- “Data entered into your e-diary indicate that you might be ready for randomization. Please call the clinic.” Alert

This alert appears during the run-in (return Visit 0C, 0D, or 1) when e-diary data support that the participant may have met the ‘lack of acceptable asthma control’ criteria required for randomization. See the discussion of Eligibility Criteria (Randomization) in this section and the description of the BARD SpiroteI[®] Eligibility Assessment Report (P5_ELIG_RPT) above for criteria that must be met. Once triggered, this alert will continue to be presented after each scheduled AM and PM session until the spiroteI[®] is downloaded and the data saved in the device’s memory are deleted. Note that this alert cannot assess data collected across the applicable visits because data are deleted each time the device is downloaded. It is possible that no alert will be triggered between visits, but the participant will qualify for randomization when the Eligibility Assessment Report (P5_ELIG_RPT) is generated at the next visit.

SpiroteI[®] Traffic Light Settings

The spiroteI[®] device has red, yellow, and green zones on its display. Zones have been defined as follows for the BARD study:

Green:	Highest PEF > 80% of reference PEF
Yellow:	$50 \leq$ Highest PEF \leq 80% of reference PEF
Red:	Highest PEF < 50% of reference PEF

Following the third peak flow maneuver during a scheduled morning or evening session, the participant’s ‘Highest PEF (L/M)’ will appear on the spiroteI[®]’s screen. This value will be accompanied by an indicator in the green, yellow, or red zone that corresponds to the above defined zones. The indicator will appear in the center of the appropriate zone; it does not vary its location based on how low or high the actual peak flow is relative to the participant’s current reference value.

If the participant's highest peak flow during a scheduled session is in the red zone, he/she should be cognizant of possible exacerbation conditions and the need for treatment. A spirote!® alert will appear telling the participant to activate his/her action plan.

Note that the traffic light indicator does not appear during a scheduled session until the participant has completed his/her third maneuver and the 'Highest PEF (L/M)' has appeared.

Also note that the traffic light indicator is not applicable to individual unscheduled peak flows the participant performs, unless he/she performs more than one measurement within a 20 minute period. In that case, a 'Highest PEF (L/M)' will show after the second or third maneuver with the traffic light indicator.

Handling participant travel

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

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

The participant should be asked to note the measurements that were affected by travel on his/her BARD Asthma Monitoring Log (P5_ASTHMA_LOG) as another source of information when reviewing spirote!® reports at a visit.

2.48 Sputum Induction

Sputum induction procedures are applicable only for the BARD Age 12-17 and Age 18+ tracks.

Visit 1

Administer 4 puffs of albuterol; wait 10-15 minutes and perform post-bronchodilator testing

Complete Post-Albuterol (4 puffs) Spirometry Testing form (PALB4_SPIRO)

Complete Sputum Induction Checklist (SPUTUMCHK)

Perform Sputum Induction (SPUTUM)

Complete Additional Treatment Post Sputum Induction (SPUTUM_ADD_TRT), if needed

Enter sputum sample data into Biological Sample Tracking module

Sputum induction provides important characterization information for the BARD study. The Sputum Induction Manual of Operations is located in appendix 7 of the AsthmaNet General Manual of Operations. Individuals performing sputum induction must be AsthmaNet-certified in this procedure.

Pre-sputum induction spirometry

Participants must undergo reversal with 4 puffs of albuterol to be assessed for procedure eligibility. Participants should take albuterol puffs from their Ventolin[®] rescue MDI. Results of the reversal testing are recorded on the Post-Albuterol (4 puffs) Spirometry Testing form (PALB4_SPIRO). The Spirometry Report generated through the MedGraphics system (Pre/Post report) provides the % predicted value needed to complete the Sputum Induction Checklist (SPUTUMCHK) and assess the participant for eligibility for the sputum induction procedure.

The FEV₁ value (in liters) after reversal prior to sputum induction is recorded in Q1030 and the corresponding % predicted value in Q1040 on the SPUTUMCHK form. The % predicted value must be at least 50% for the participant to continue with sputum induction at the visit.

Exacerbations and prednisone treatment prior to Visit 1

Participants who meet criteria for a significant asthma exacerbation during the run-in will wash out from their final dose of prednisone for at least 2 weeks prior to completing Visit 1. These participants may proceed with sputum induction as long as all criteria on

SPUTUMCHK are met and as long as the study physician has cleared the participant for the procedure.

Sputum processing criteria

In order for the resulting sputum sample to be processed, its volume must be deemed adequate for processing by the technician processing the sputum sample and the duration of the procedure (not including spirometry maneuvers) must be at least 4 minutes. No minimum volume is required for processing. If the duration of the procedure was less than 4 minutes, the sample must not be processed. No exceptions are allowed. These criteria are recorded on the Sputum Induction form (SPUTUM).

The processing of induced sputum to make sputum slides, pellets, and supernatant is explained in the Sputum Induction Manual of Operations. Samples **MUST** be processed immediately in order to ensure that the slides are of acceptable quality.

Sputum shipments to San Francisco

For the BARD trial, sputum slides, supernatant and pellets will be shipped to San Francisco every 6 months for overnight receipt. Shipments will take place on the second Tuesday of the months of January and July, on the same day that regular shipments are made to ADx Labs in Denver (study serum and urine). Scheduled shipment dates follow:

2014: July 8

2015: January 13 and July 14

2016: January 12 and July 12

2017: January 10 and July 11

If a performance site has a conflict with a particular shipment date, arrangements should be made with San Francisco lab staff to ship the samples on an alternate date. Do not ship on an alternate date without first clearing it with lab personnel. There may not be anyone available to accept the shipment.

Shipping costs for sputum samples have been included in the clinical partnership budget for BARD; therefore, each site should use its own FedEx account for these shipments.

All accumulated slides from BARD participants should be forwarded to San Francisco with each scheduled shipment; do not hold slides until a minimum of 40 have been collected (as suggested by the Sputum MOP).

Sputum quality issues

If the sputum reader in San Francisco determines that a sputum sample has $\geq 80\%$ squamous cells present, any supernatant and pellets associated with the sample should be excluded in the Biological Sample Tracking (BST) module and discarded appropriately; these samples should not be shipped to the Sputum Core Lab in San Francisco. Likewise, any supernatant samples saved for the Small Molecule Sub-Study should also be excluded in BST and not shipped to the Reisdorph Laboratory in Denver. Coordinators will be sent an e-mail message automatically upon entry of the Sputum Induction Read form (SPUTREAD) into the BARD database. If supernatant and/or pellets had already been shipped to the labs at the point when the notification arrives, coordinators should contact the relevant lab so that samples can be excluded by lab staff.

Inter-Site Sputum Procedures

Several participating BARD performance sites have indicated that they plan to use an alternate site within their clinical center partnership to perform tasks related to the sputum induction procedure. These sites do not have sputum induction equipment or certified personnel to conduct the procedure and do not wish to receive such equipment and training, or they do not have someone on staff certified in the processing aspect of the procedure. This section provides guidelines for completion of Visit 1 when two sites are involved due to the sputum induction procedure. "Home site" refers to the site where the participant normally completes his/her study visits. "Sputum induction site" refers to the site performing the sputum induction procedure and/or processing the sputum sample.

For sites referring their participants to an alternate site for sputum induction, the following alterations in procedures should be followed:

Pre-Sputum Induction

- **Sputum Induction Site:** If the site coordinator does not already have access to the home site's data in the BARD database, the lead coordinator from the sputum induction site should modify an AsthmaNet User Account Checklist requesting access. This step must be completed before the sputum induction site can insert sputum samples into BST or enter the Sputum Induction Lab form (SPUTLAB).
- **Home Site:** Steps #46-69 on Visit Procedure Checklist 1 (P5_VISIT1_A) may be completed after step #39 (completion of Pulmonary Procedure Checklist). This

alteration allows the coordinator to randomize the participant, have him/her complete the Household Socioeconomic Information (HOUSEHOLD_SEI) form, perform drug-related tasks, take blood samples, and schedule the next visit prior to completing spirometry to qualify the participant for sputum induction.

This adjustment to the visit procedures allows the participant to conclude the visit and leave from the sputum induction site after the sputum procedures have been completed, rather than returning to the home site. If the home site prefers to complete the visit following sputum induction, and it is not a burden on the participant to do so, the normal visit procedure order on P5_VISIT1_A may be followed.

- Home Site: Just before transporting the participant to the sputum induction site, steps #40-43 should be completed. These steps include baseline spirometry, administration of albuterol, post-albuterol spirometry, and completion of the Sputum Induction Checklist (SPUTUMCHK).

The SPUTUMCHK form will include a tech/coordinator ID corresponding to staff at the participant's home site.

Note: Baseline and post-albuterol spirometry must be completed on the same MedGraphics computer.

Note: The coordinator should ensure that baseline spirometry takes place at a time that will be consistent with timing of baseline spirometry at subsequent visits. A +/-3 hour spirometry window relative to timing of baseline spirometry at Visit 1 has been established. See the discussion of Visit Schedule and Visit Windows in this section for details.

Note: Sputum induction must be completed within 2 hours (maximum window) of dosing with albuterol prior to the post-albuterol spirometry session. Home site personnel should ensure that minimal time elapses between qualifying the participant for sputum induction and the induction procedure itself.

- Home Site: Accompany the participant to the sputum induction site. If the home site chooses to alter the order of the visit procedures as described above, the participant should have his/her study materials, including randomized Diskus[®], Spirotel[®], and updated handouts in hand as he/she leaves the home site. There will be no need to return to the home site following sputum induction if these procedures are followed.

The home site coordinator should take the following information to the sputum induction site:

- Copy of the Sputum Induction Checklist (SPUTUMCHK): For qualifying FEV₁ in Q1030 and Q1040
- Participant's demographics (ID number, initials, date of birth, spirometry race/ethnicity, gender, height, weight) for use in MedGraphics system

Sputum Induction Procedure

The following procedures will be completed by the sputum induction site.

- Set up the participant in the MedGraphics computer. His/her demographics, including the most recent height measurement, should be provided by the home site's coordinator. The home site's coordinator should verify that the information has been entered into the system correctly.
- Have participant complete three technically acceptable peak flows using a demo SpiroTel[®] device, as usual. Complete the top of the Sputum Induction Worksheet (SPUTUM_INDUCTION_WKS) using the best PEF and post-albuterol FEV₁ information supplied by home site.
- Complete step #44 on P5_VISIT1_A (sputum induction procedure). Complete SPUTUM_INDUCTION_WKS during induction, as usual.

Complete Sputum Induction form (SPUTUM). This form will have a tech/coordinator ID corresponding to someone from the sputum induction site.

- Complete step #45 (additional treatment post-sputum induction, only if needed). Complete Additional Treatment Post Sputum Induction form (SPUTUM_ADD_TRT). This form will have a tech/coordinator ID corresponding to someone from the sputum induction site.
- Add a note to the post-sputum spirometry session indicating that maneuvers were done post-sputum induction. Print the sputum induction spirometry report (SI_RPT).
- Upload the participant's spirometry session immediately following completion of the induction procedure. The overreader will check the post-sputum induction spirometry for technical acceptability, but the maneuvers will not be scored.

-
- Make copies of the SPUTUM and SPUTUM_ADD_TRT forms and the SI_RPT. Give the originals to the coordinator from the home site. Home site personnel will be responsible for entering these data and submitting forms to the DCC with the visit packet.
 - Maintain a folder that includes the following sputum documentation:
 - Participant's demographic data
 - SPUTUMCHK copy
 - SPUTUM copy
 - SPUTUM_ADD_TRT copy
 - SPUTUM_INDUCTION_WKS original
 - SI_RPT copy

Sputum Processing/Labeling

The following procedures will be completed by the sputum induction site. These procedures also apply if the home site performs the induction procedure and the sputum induction site is only performing sputum processing tasks.

- Generate sputum labels using normal procedures. Barcode numbers will be associated with the sputum induction site, not the participant's home site.
- Process the sputum sample. Complete the Sputum Processing Worksheet (SPUTUM_PROCESS_WKS).
- Complete the Sputum Induction Lab Values form (SPUTLAB). This form will have a technician ID corresponding to the sputum induction site.
- Enter the samples into Biological Sample Tracking. The sputum induction site must have been granted access to the home site's data to complete this step.
- Enter the SPUTLAB form into the BARD database. The sputum induction site must have been granted access to the home site's data to complete this step.
- Make a copy of SPUTLAB and forward the original to the DCC.
- Store the sputum samples. The sputum induction site will be responsible for shipping samples to San Francisco on the designated dates. The home site's samples will be included in the same shipment (and on the same BST shipment log) as samples collected for participants originating at the sputum induction site.

This is possible because barcodes generated for the sputum induction site will be used for all sputum samples regardless of the site from which a participant originates.

- File SPUTLAB and SPUTUM_PROCESS_WKS in the folder referenced above. As per usual procedures, a copy of the processing worksheet should be forwarded to UCSF with the sputum slides.

Sputum-related Queries

- The home site will be responsible for answering any queries related to the SPUTUMCHK form.
- The sputum induction site will be responsible for answering any queries related to the SPUTUM, SPUTUM_ADD_TRT, and SPUTLAB forms. The sputum induction site must have been granted access to the home site's data to answer these queries.

Note: It is the home site's responsibility to contact the sputum induction site to alert the appropriate personnel when sputum-related queries are generated that they need to address. Sputum induction site personnel should not be expected to monitor the query load at the home site to determine when their input is necessary.

Sputum Quality Control Reports

- Sputum quality data for samples processed by an alternate site will be included in the reports generated for the alternate site.

2.49 Study Handout Folder

The study handout folder is applicable for all three BARD age tracks, with differences in handouts for participants in the various Age Tracks as outlined below.

Starting with their entry into the run-in period at Visit 0A, BARD study participants will be given several handouts related to study procedures. Each handout contributes to increased adherence in areas such as dosing with study medications, using the spirotel[®] device, and monitoring for asthma exacerbations. Participants should be given an AsthmaNet folder to use for carrying and storing the handouts. The participant should store the study folder in a convenient location, as it will serve as a reference throughout his/her BARD participation. The folder should be brought to each study visit so that clinical personnel can review and/or update handouts, as necessary.

BARD Study Handout Folder Contents

- BARD Daily Activities (P5_DAILYACT) – distributed at all visits from 0A-12

The “Daily Activities” handout contains a simple summary of the activities the participant should carry out each day during the BARD study. Other handouts provide details on the execution of these activities. The Daily Activities handout also details how to handle multiple Diskuses[®] between visits to ensure that no expired inhalers are used during the study. Although the daily activities of the participant do not change over the course of the study, a new copy of this handout should be distributed (and reviewed, if necessary) at each study visit when Diskuses[®] are being dispensed.

If two Diskuses[®] are being dispensed during the post-randomization treatment periods, study personnel should complete the spaces on the back of the handout for the participant to reference when he/she opens the pouch of the second Diskus[®] at home. The participant will need to write this information on the new Diskus's[®] label:

Visit #: Visit at which the Diskuses[®] were dispensed

Visit Date: Date of the visit at which the Diskuses[®] were dispensed

Do Not Use After: This is the date on which the Diskus[®] will expire if it is opened on the “Use From” date listed on the label on the Diskus[®] pouch. This date should be 30 days after the “Use From” date and should correspond to the “Use To” date.

Initials: Participant's initials

ID: Participant's BARD ID number

The above information will be necessary to reconcile collected Diskuses[®] on various drug logs when they are returned to the performance site and the site's pharmacy.

Most of the time only one Diskus[®] will be dispensed during run-in visits. In the rare situation where two are required, the Diskus[®] labels will be loose in the Ziploc bag that contains the Diskuses[®] in their pouches. The coordinator will remove the first Diskus[®] from its pouch and affix labels to it with all information completed. He/she should complete the labels for the second Diskus[®] and give them to the participant. The "Use ___ to ___" fields should be completed on the label of the pouch of the second Diskus[®]. On the "Use from" date, the participant will remove the Diskus[®] from its pouch and affix the pre-completed labels to the front and back. The coordinator should note clearly the date when the second Diskus[®] needs to begin use on the participant's P5_DAILYACT handout and on his/her Asthma Monitoring Log (P5_ASTHMA_LOG).

- BARD Asthma Action Plan (P5_ACTION_PLAN_A, P5_ACTION_PLAN_P)
- Participant Identification Card (P5_ID_A, P5_ID_P)

Two Asthma Action Plans have been developed for the BARD study: a pediatric version with text addressing 'the child' (P5_ACTION_PLAN_P) and an adolescent/adult version with text addressing 'you' (P5_ACTION_PLAN_A). Both action plans have space to record emergency contact information, as well as reference peak flow values with 50% and 80% cutoff values for defining red and yellow zones. Both plans include the algorithm for treating symptoms and determining when additional care should be sought. Coordinators should use their discretion (or ask the participant) in deciding which version to give to adolescent participants. Children and adolescents may wish to have multiple copies of their Action Plan so that a copy can be given to the school nurse and/or daycare teacher and a copy can be kept at home.

Two Participant Identification (ID) Cards have been developed for the BARD study: a pediatric version listing study treatments for the Age 5-11 Track and an adolescent/adult version listing study treatments for the Age 12-17 and Age 18+ Tracks. The appropriate ID card should be given to each participant based on his/her assigned age track. Both versions include space to record the participant's reference peak flow value and the 50% and 80% cutoff values for determining when and how to initiate treatment.

The ID card and Asthma Action Plan facilitate the identification and treatment of asthma exacerbations according to the protocol, both by the participant and by healthcare providers. They are introduced at Visit 0A. Both handouts contain peak flow reference values for initiating albuterol treatment and defining exacerbations, and instructions for emergency treatment. The ID card should be carried in the participant's wallet (or backpack) so that it is available at all times. A copy of the Asthma Action Plan should be given to teachers, school nurses, and other professionals who interact with the child

regularly. Peak flow reference values will need to be updated on both handouts as the participant progresses through the study. See the Participant Identification Card, Reference Peak Flow (PEF), and Significant Asthma Exacerbation discussions in this section for further details.

- How to Use Your Metered Dose Inhaler (HTMDI)

This is a standard handout that provides information on MDI closed-mouth inhalation technique and instructions for cleaning the inhaler. It is introduced at Visit 0A along with the albuterol rescue (Ventolin[®]) inhaler.

- How to Use Your Diskus[®] (HTDISKUS)

This is a standard handout that provides information on dry powder inhalation technique and use of the Diskus[®] device. It is introduced at Visit 0A along with the participant's Flovent[®] Diskus[®].

- How to Use Your Spirotel[®] Electronic Diary and Peak Flow Meter (HTSPIROTEL)
- BARD Spirotel[®] Reference Card (P5_SPIROTEL_REF)

HTSPIROTEL is a standard handout that provides instructions for home use of the spirotel[®] e-diary and peak flow meter. It has been updated for the upgraded spirotel[®] II device with the touchscreen that will be used in the BARD trial. Only version 2.0 of this handout should be given to participants.

P5_SPIROTEL_REF is a BARD-specific reference card that gives the participant additional information on the BARD e-diary questions and alerts. This reference is printed as a tri-fold card that fits in the spirotel[®]'s carrying case.

The spirotel[®] handouts are introduced at Visit 0A while training the participant on spirotel[®] e-diary and peak flow procedures. For more information see the Spirotel[®] discussion in this section.

- BARD Visit Preparation Checklist (P5_VISPRP)

This handout is a tool for improving the participant's adherence with respect to keeping scheduled visits and preparing for the visits appropriately. The handout should be photocopied/printed two-sided. The P5_VISPRP handout includes a checklist on one side that itemizes the medications and other study materials the participant should bring to each visit. The participant should check off each item as he/she prepares for each visit to ensure that nothing is overlooked. If clinical personnel notice that the participant

is not using the checklist, and he/she is not always prepared for visits, use of the checklist should be reinforced. This handout is introduced at Visit 0A and should be referenced throughout the participant's study participation.

- BARD Visit Scheduler Report

A copy of the current Visit Scheduler Report should be included in the participant's handout folder for personal reference. Old versions should be discarded to avoid confusion. See the Visit Schedule discussion in this section for further details.

- BARD Overnight Urine Collection Procedures (P5_URINE_COLLECT)

This handout describes the urine collection materials and the process that should be followed to collect a 12-hour overnight urine sample for cortisol:creatinine analysis. The handout also has space for the participant to record the collection start date and time, as well as the collection stop date and time. This information will be needed to complete the BARD Laboratory Results form (P5_LAB) when the collection is returned to the performance site.

This handout is introduced at Visit 0B for those who remain eligible for the study. The baseline urine sample can be returned to the performance site any time on or before Visit 1. New handouts are given to participants at Visits 3, 6, 9, and 12 ahead of the end of treatment urine collections. See the Urine Cortisol:Creatinine Laboratory Test discussion in this section for further details.

- BARD Asthma Attack Kit Instructions

This handout is applicable only for participants in the Age 12-17 and Age 18+ Tracks. It describes how and when the forms in the Asthma Attack Kit they are given at Visit 0A should be completed. See the discussion of Asthma Attack/Exacerbation Kit in this section for further details.

2.50 Study Medications

Study medications differ by BARD age track. Specific differences are explained below.

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

Rescue medications

During the BARD trial, all participants will receive the following study rescue medications:

- Albuterol rescue drug (Ventolin[®]), an inhaled beta-agonist to be used as-needed throughout the BARD trial to treat asthma symptoms following the participant's Asthma Action Plan (P5_ACTION_PLAN_P, P5_ACTION_PLAN_A).

Ventolin[®] rescue drug will be labeled with a red label supplied by the DCC that includes the BARD study name and space for the visit number, current date, expiration date, participant initials and participant ID number. Ventolin[®] will be dispensed from bulk supplies provided by the DCC. Pediatric participants may be dispensed multiple rescue inhalers if school nurses or daycare workers need to keep a supply on-site.

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

Rescue prednisone will be obtained through the individual performance site pharmacies and dispensed to each participant upon successful completion of Visit 0A. Packaging should be childproof. See the Significant Asthma Exacerbation discussion in this section for protocol taper details.

Run-in medications

To qualify for randomization, participants must be evaluated on open-label low dose inhaled corticosteroids (ICS) (referred to as the 1xICS dose). The ICS used in the BARD trial is Flovent[®] Diskus[®] (fluticasone dry powder inhaler) supplied by GlaxoSmithKline. The 1xICS dose depends on the participant's age track as follows:

- Age 5-11 Track: 50 mcg Flovent[®] Diskus[®], 1 puff BID

-
- Age 12-17 Track: 100 mcg Flovent[®] Diskus[®], 1 puff BID
 - Age 18+ Track: 100 mcg Flovent[®] Diskus[®], 1 puff BID

Some participants will start the run-in on 1xICS and others will require an initial period on an intermediate dose of ICS (referred to as 2xICS for participants in the Age 5-11 Track and 2.5xICS for participants in the Age 12-17 and Age 18+ Tracks). Individuals who enter the study on asthma therapy considered to be asthma guideline step 2 or 3 will start on 1xICS at Visit 0A. Individuals who enter the study on asthma therapy considered to be guideline step 4 or 5 will start on 2xICS if in the Age 5-11 Track (100 mcg Flovent[®], 1 puff BID) or 2.5xICS if in the Age 12-17 or Age 18+ Track (250 mcg Flovent[®], 1 puff BID). Flovent[®] dosing will always be 1 puff BID.

See the discussion of Inhaled Corticosteroid (ICS) Step-Down Groups and Assessment in this section for details on determining a participant's step-down group and initial run-in ICS dose.

The BARD Flovent[®] Dose Determination Reference Card (P5_FLOVENT_DOSE) summarizes the run-in doses for each of the age tracks.

Open-label Flovent[®] Diskus[®] supplies will be shared among all three BARD age tracks.

Double-blind treatment period medications

Treatment period medications are double-blind. Participants, performance site staff, and DCC personnel involved in day to day decision-making for the study and statisticians on the project will not know what treatment regimen the participant is receiving during any of the four treatment periods. All Diskuses[®] will arrive in a silver/gray pouch and will be gray-brown in color. They will appear identical, but the contents will vary. All dosing is 1 puff BID. Treatment regimens differ by BARD age track as follows:

Age 5-11 Track:

- 2xICS: Flovent[®] Diskus[®] 100 mcg
- 2xICS/LABA: Advair[®] Diskus[®] 100/50 mcg (fluticasone/salmeterol combination)
- 5xICS: Flovent[®] Diskus[®] 250 mcg
- 5xICS/LABA: Advair[®] Diskus[®] 250/50 mcg (fluticasone/salmeterol combination)

Age 12-17 and Age 18+ Tracks:

- 2.5xICS: Flovent[®] Diskus[®] 250 mcg
- 1xICS/LABA: Advair[®] Diskus[®] 100/50 mcg (fluticasone/salmeterol combination)

- 5xICS: Flovent[®] Diskus[®] 500 mcg
- 2.5xICS/LABA: Advair[®] Diskus[®] 250/50 mcg (fluticasone/salmeterol combination)

Separate supplies of blinded medications will be maintained for the pediatric (Age 5-11 Track) and adolescent/adult (Age 12-17 and Age 18+ Tracks), even though they have treatment regimens in common. Individual blinded Diskuses[®] will be identified by a code number that is associated with their randomized treatment assignment in the BARD database. Codes for the Diskuses[®] designated for participants in the Age 5-11 Track will have format P____ where P stands for 'Pediatric' and code numbers range from 10000 to 49999. Codes for the Diskuses[®] designated for participants in the Age 12-17 and Age 18+ Tracks will have format A____ where A stands for 'Adult' and code numbers range from 50000 to 89999.

Open-label Flovent[®] Diskus[®] treatment period medication

Participants who experience an exacerbation near the end of a treatment period or who qualify as having had a treatment (arm) failure during a treatment period will receive open-label 5xICS for 2-3 weeks following their last dose of oral or parenteral corticosteroids, prior to starting the next double-blind treatment period. Participants in the Age 5-11 Track will receive open-label Flovent[®] Diskus[®] 250 mcg, 1 puff BID. Participants in the Age 12-17 and Age 18+ Tracks will receive open-label Flovent[®] Diskus[®] 500 mcg, 1 puff BID. See the discussions of Significant Asthma Exacerbation and Treatment (Arm) Failure in this section for further details.

Participants who are designated as treatment period drop-outs will receive open-label 1xICS until they are available to complete the next cross-over visit to begin the next treatment period. Participants in the Age 5-11 Track will receive open-label Flovent[®] Diskus[®] 50 mcg, 1 puff BID. Participants in the Age 12-17 and Age 18+ Tracks will receive open-label Flovent[®] Diskus[®] 100 mcg, 1 puff BID. See the discussion of Drop-out Status (Treatment Period) in this section for further details.

Open-label medications will be dispensed from bulk supplies. Open-label Flovent[®] Diskus[®] supplies will be shared among all three BARD age tracks.

The BARD Flovent[®] Dose Determination Reference Card (P5_FLOVENT_DOSE) summarizes the open-label Flovent[®] doses used for each of the age tracks for various reasons during the study.

Dispensing two Diskuses[®] at one visit

If two Diskuses[®] are being dispensed during a visit during the post-randomization treatment periods, study personnel should remove the first Diskus[®] (should be the one with the lower randomization number) from its foil pouch and complete the Diskus[®] label for normal dispensation. This Diskus[®] will expire 30 days after the date the pouch is opened. On the expiration date, the participant will need to remove the second Diskus[®] from its pouch and complete the Diskus[®] label at home. Instructions for carrying out these steps are outlined on the back of the Daily Activities handout (P5_DAILYACT). At the time of the visit, the coordinator should complete the following fields on P5_DAILYACT:

Visit #: Visit at which the Diskuses[®] are being dispensed

Visit Date: Date of the visit at which the Diskuses[®] are being dispensed

Do Not Use After: This is the date on which the second Diskus[®] will expire if it is opened on the “Use From” date listed on the label on the Diskus[®] pouch. The expiration date should be 30 days after the “Use From” date and should correspond to the “Use To” date on the pouch.

Initials: Participant’s initials

ID: Participant’s BARD ID number

When the participant removes the second Diskus[®] from its pouch, he/she will transcribe information from the handout onto the Diskus[®] label. This information will be necessary to reconcile collected Diskuses[®] on various drug logs when they are returned to the performance site and the site’s pharmacy.

Most of the time only one Diskus[®] will be dispensed during run-in visits. In the rare situation where two are required due to use of extended visit windows, the Diskus[®] labels will be loose in the Ziploc bag that contains the Diskuses[®] in their pouches. The coordinator will remove the first Diskus[®] from its pouch and affix labels to it with all information completed. He/she should complete the labels for the second Diskus[®] and give them to the participant with the Diskuses[®] in the Ziploc bag. The “Use ___ to ___” fields should be completed on the label of the pouch of the second Diskus[®]. On the “Use from” date, the participant will remove the second Diskus[®] from its pouch and affix the pre-completed labels to the front and back. The coordinator should note clearly the date when the second Diskus[®] needs to begin use on the participant’s P5_DAILYACT handout and on his/her Asthma Monitoring Log (P5_ASTHMA_LOG).

2.51 Study Treatment Questionnaires

These questionnaires are applicable for all three BARD age tracks.

Visits 4, 7, 10, 13 (or last post-randomization contact during a treatment period)

Administer Participant Study Treatment Questionnaire (P5_PARTTXQX)

Complete Coordinator Study Treatment Questionnaire (P5_CTXQX)

General Instructions

The study treatment questionnaires are used to assess how well the masking of the scheduled Diskuses[®] was carried out. The Participant Study Treatment Questionnaire (P5_PARTTXQX) was developed to evaluate the blind from the participant's perspective. The Coordinator Study Treatment Questionnaire (P5_CTXQX) was developed to evaluate the blind from the study coordinator's perspective. Under normal circumstances, each of these questionnaires is completed at the final visit of each of the four double-blind treatment periods (Visits 4, 7, 10, 13). Questions on the forms address the treatment the participant or coordinator thought the participant received over the prior 14 weeks of blinded treatment.

If a participant withdraws from the study following randomization and prior to Visit 13, both questionnaires should be completed at the time of the participant's final contact with the performance site. If the final contact is by phone, the coordinator may administer the P5_PARTTXQX questionnaire over the phone. In this case, no source documentation will be recorded. Single forms will need to be completed if the participant withdraws in the middle of a treatment period.

If a participant becomes a treatment period drop-out or treatment failure, or has an exacerbation during the final two weeks of the treatment period, then he/she will be given open-label Flovent[®] until the next treatment period can begin. In those cases, both questionnaires should be completed at the time the participant's status changes and he/she stops taking the blinded Diskus[®] and starts taking the open-label Diskus[®]. These questionnaires will be single forms in the database. The packet forms at the next cross-over visit should be marked missing; the participant/coordinator should not complete them again.

Participant Study Treatment Questionnaire

Near the conclusion of Visits 4, 7, 10 and 13, the participant should complete a Participant Study Treatment Questionnaire (P5_PARTTXQX). This form was designed to determine how well the blind on the BARD scheduled Diskus[®] performed with respect

to the participant's perceptions of the study medication he/she received over the previous 14 weeks. Clinical personnel should explain the purpose of the questionnaire to the participant and confirm that the participant understands that the form references the medication taken with the scheduled, blinded Diskus[®] only, not the rescue inhaler which is an open-label medication. Coordinators should go through the treatment choices listed for Question #2 (Q1010) and ensure that the participant understands which options are applicable for him/her based on his/her BARD Age Track.

The questionnaire is completed by the participant or his/her parent or guardian. It is short and should take no longer than five minutes to finish. Study personnel should not help the participant/guardian to answer questions on the form, as such assistance could influence the responses and result in bias. Participants/guardians should be asked to answer all questions to the best of their ability; they should not leave any blank. When the form is complete, the participant/guardian should initial and date the source documentation box on page 2. Coordinators should check the completed questionnaire to ensure that it has been completed correctly.

Coordinator Study Treatment Questionnaire

Near the end of Visits 4, 7, 10 and 13, the study coordinator who was primarily responsible for the participant's BARD study visits over the previous 14 weeks should complete a Coordinator Study Treatment Questionnaire (P5_CTXQX). This form was designed to determine how well the blind on the BARD scheduled Diskus[®] performed with respect to the coordinator's perceptions of the study medications the participant received over the previous 14 weeks. The coordinator should complete this form before reviewing the participant's questionnaire (P5_PARTTXQX) and before entering the participant's form into the study database. The participant should not review the coordinator's form, and the coordinator should not discuss his/her perceptions of the study treatment with the participant.

When the P5_CTXQX form is complete, the coordinator should initial and date the source documentation box at the bottom of the page. If the study coordinator primarily in charge of the participant's visits over the past treatment period is unavailable during Visit 4, 7, 10 or 13, or for the participant's early withdrawal visit or treatment failure/drop-out visit, the P5_CTXQX form should be completed as soon as possible on his/her return to the performance site, preferably within 1 week of the visit. Only one coordinator should complete the form, and only one form should be submitted per participant per treatment period.

If a randomized participant is lost to follow-up or withdraws early and is unavailable to complete the P5_PARTTXQX form, the study coordinator still should complete a P5_CTXQX form, as long as the participant had at least one follow-up visit or phone

contact during the double-blind treatment period. In this case the P5_CTXQX form should be submitted as a single form.

See Section 4 in this manual for further details regarding the completion of the P5_CTXQX and P5_PARTTXQX forms.

2.52 Transfer Participants

These procedures are applicable for all three BARD age tracks.

Transfer participants are defined as individuals who are enrolled in a trial and successfully complete at least one study visit at one performance site, then transfer to another performance site for a set number of visits or for the remainder of their study participation. General database procedures related to transfer participants are outlined in section 7.6.2 of the AsthmaNet General Manual of Operations. BARD-specific considerations follow.

- Participant Assignment Log: Complete the participant ID number and other information on the Participant Assignment Log (P5_LOG) (Not Pre-Filled) version. Maintain this log with the site-specific BARD log. The participant should retain his/her original ID that was assigned at the originating site.
- BARD Age Track Assignment form (P5 AGE TRACK): The originating site should provide the new site a copy of this form.
- Registry Report: Generate a copy of the participant's Registry Report to obtain demographics needed for spirometry and MedGraphics reports.
- Spirotel[®]: The originating site should note in the Comments section of the Spirotel[®] device and turbine logs (SPIROTEL_DEVICE, SPIROTEL_TURBINE) that the participant's materials went with him/her to the new site. The device/turbine will continue to be used by the participant until he/she completes the study. The device/turbine will not be returned to the originating site (unless the participant returns to the originating site). The new site should record the device/turbine information on its Spirotel[®] device and turbine logs and consider the equipment part of their supply. The new site should notify the DCC of the new location of the supplies by e-mailing the details to the AsthmaNet_BARD_DM@phs.psu.edu alias.

The new site should download the participant's spirotel[®] data to the site's BreezeSuite database and upload spirotel[®] data to the central database at MedGraphics following normal procedures. Depending on where the participant is in the trial, the applicable Spirotel[®] reports may not run correctly (because the

participant's prior data is not located on the local machine). To avoid problems with report generation, the originating site should send the new site the participant's spirote[®] data from his/her last data completed. The new site should import the data so that it is available in BreezeSuite prior to completing the participant's first visit at the new site. Instructions for exporting and importing data are located in the Spirote[®] MOP in Appendix 6 of the AsthmaNet General MOP in sections 6.27.3 (exporting) and 6.27.4 (importing). If the participant returns to his/her home site, the same process will need to be carried out to ensure that the home site has the most recent spirote[®] data available on the local laptop.

- **Randomization:** In the BARD Randomization Module, enter the participant ID and select the location where the randomization is taking place (i.e., 'new' site). If the enrollment site is chosen by mistake, the Randomization Module will return Diskus[®] numbers that are physically located at the transfer participant's enrollment site, not the site of the current visit. If this occurs, the DCC should be contacted immediately.
- **Study ID Card and Action Plan:** A new study ID card and Action Plan should be distributed to the participant (with updated study personnel and primary physician information completed, as necessary).
- **Current Dosing Information and Exacerbation/Treatment Failure History:** The originating site should supply the new site details of the participant's current study treatment (either blinded medications or open-label Flovent[®]). The originating site should supply the new site a summary of all exacerbation (and treatment failure) events the participant has experienced in the study, along with their dates and any ongoing treatment (primarily prednisone, possibly with open-label Flovent[®] if the participant is recovering from a treatment (arm) failure). The new site may view the data collection forms from the enrollment site within the Participant Data module if appropriate database permissions have been requested/granted.
- **Physical Measurements:** For participants ≥ 21 years old, the new performance site may use the Participant Data module to view the Adult Body Measurements (BODYMEAS_ADULT) form completed at Visit 0A. The height and weight recorded on this form should be referenced when entering participant characteristics into the MedGraphics PC.

For participants under age 21, the originating site should supply the new site a copy of the most recent form that contains the participant's height measurement (SEXAM_PED or LEXAM_PED or P5_PULMONARYCHK). The originating site should also supply the most recent SpiroTel[®] Reference Peak Flow Report (P5_PEF_REF).

- Visit Schedule: The originating site should supply the new site a copy of the most recently generated Visit Scheduler Report.
- Prednisone Supply: If the participant has been randomized, the new site should verify that he/she has a supply of rescue prednisone on hand. If he/she does not, a new supply should be dispensed.
- Study Medication Documentation: At the participant's first visit at the new site, the transfer site will be responsible for collecting and logging medications the originating site dispensed. Documentation of the return should be captured in a note-to-file. The following information should be included: Summary of incident (i.e., participant normally seen by site #XYZ was approved by the DCC to be seen at site #ABC for Visit #), participant ID number, date of medication return, description of products returned (including Diskus numbers (if applicable), name of medication, and lot number (if applicable)).

Upon completion of the note-to-file, the transfer site must maintain a copy in their BARD participant-specific records and forward a copy to the originating site, the DCC, and the AsthmaNet IDS Pharmacy.

If the participant eventually returns to the originating site, then the originating site should follow these instructions for logging and documenting return of medications that the transfer site dispensed.

2.53 Treatment (Arm) Failure

Treatment failure procedures are applicable for all three BARD age tracks.

Visits 1-13

Complete Significant Asthma Exacerbation form (P5_SIGEX), if applicable

Definition

The treatment failure definition is applicable only for the post-randomization treatment periods; it does not apply during the study run-in period.

A participant will have experienced a treatment failure event if he/she meets at least one of the following criteria:

1. Participant hospitalized due to asthma

If a participant requires in-patient hospitalization for his/her asthma, then he/she will be considered to have experienced a treatment failure, as well as a significant asthma exacerbation. The event will also be reported as a serious adverse event.

2. Participant requires 10 or more days of treatment with prednisone for asthma exacerbation(s)

If a participant requires a prescription for 10 or more days of prednisone treatment for a single exacerbation event, then he/she will be considered to have experienced a treatment failure (even if he/she does not comply with taking the medication). This is equivalent to two or more prednisone tapers as defined in the BARD protocol.

If a participant experiences two distinct exacerbations during a given treatment period and receives two 5-day prednisone tapers as a result, then he/she also qualifies as having met this treatment failure criterion.

3. Participant experiences two distinct asthma exacerbations

For purposes of this study, and to standardize among AsthmaNet trials, two courses of systemic corticosteroids must be separated by at least one week (7 days) to count as two distinct asthma exacerbations and to be documented as

such. If a participant experiences repeated worsening of his/her asthma that requires treatment with prednisone or other systemic corticosteroid, and the treatments are at least one week apart, then two asthma exacerbations should be recorded (i.e., complete two Significant Asthma Exacerbation forms (P5_SIGEX)) and the participant should be classified as having met treatment failure criteria.

Note that in this study, when a participant experiences a significant asthma exacerbation, he/she won't necessarily meet the criteria for treatment failure. Each exacerbation needs to be evaluated for treatment failure status in order to determine if the current blinded regimen should be stopped and the participant should transition to the next blinded regimen. Further details are provided below.

Documentation

Treatment failure events are defined on the basis of the related significant asthma exacerbation(s). When completing the BARD Significant Asthma Exacerbation form (P5_SIGEX), it should be clear if the participant also meets failure conditions. Once the treatment failure has been confirmed, the following forms should be completed:

- Clinical Adverse Events (AECLIN)

All treatment failure events should be documented on AECLIN using ICD-9 code 000.00. Separate entries for the related significant asthma exacerbations should be recorded using code 493.92.

The start date recorded for the treatment failure event should correspond to the date treatment failure criteria were confirmed. The start dates for entries for an event that meets both treatment failure and exacerbation criteria may differ depending on the criteria that were met.

The stop date recorded for a treatment failure event should correspond to the end date of the exacerbation that qualified the participant as meeting treatment arm failure criteria. In general, the end date of an exacerbation is the last date the participant experienced asthma symptoms (which may not correspond exactly with the final day of systemic corticosteroid treatment). Treatment information is captured separately on the Concomitant Medications (CMED) form.

- Concomitant Medications for Asthma/Allergy and Adverse Events (CMED)

Any non-study medications used to treat the treatment failure event should be recorded on the CMED form. Examples include oral or parenteral corticosteroids (e.g., rescue prednisone). Nebulized beta-agonist treatments administered in a physician's office or other care facility should also be captured on the CMED form.

Usually the participant's scheduled blinded Diskus[®] is discontinued and the participant receives treatment with open-label Flovent[®] 5xICS following treatment failure designation (see details below). A BARD Change in Scheduled Diskus[®] form (P5_CHANGE_DISKUS) should be completed to document any time a scheduled Diskus[®] is discontinued or resumed. Open-label Flovent[®] (or any other open-label inhaled corticosteroids) given to the participant in lieu of his/her blinded scheduled Diskus[®] should be documented on the CMED form.

RESCUE Ventolin[®] inhaler puffs should not be recorded on CMED; these are documented by the participant in his/her daily e-diary responses.

Medications used for treatment of treatment failure events and exacerbations and listed on the CMED form should be linked to the applicable adverse event recorded on the AECLIN form. Prednisone and other systemic corticosteroids should be linked to the exacerbation event. Open-label Flovent[®] prescribed for a treatment failure should be linked to the treatment failure event.

- BARD Change in Scheduled Diskus[®] (P5_CHANGE_DISKUS)

When a participant experiences a treatment failure event, his/her scheduled Diskus[®] should be discontinued and he/she should be given open-label 5xICS Flovent[®] (see the Adjustment of Trial Medication discussion below).

Discontinuation of the scheduled blinded Diskus[®] should be recorded on the P5_CHANGE_DISKUS form, along with the date the change is effective. Q1000 should be answered 'Adverse Event' and the treatment failure event recorded on AECLIN should be provided in Q1010.

When the participant transitions to the next treatment period and begins treatment with a blinded scheduled Diskus[®] again, another P5_CHANGE_DISKUS form should be submitted. In this case Q1000 should be answered 'Started new treatment period.'

-
- BARD Significant Asthma Exacerbation form (P5_SIGEX)

The P5_SIGEX form captures the criteria the participant meets for treatment failure in conjunction with information on the related significant asthma exacerbation. Counter to previous AsthmaNet and ACRN studies, not every exacerbation will be categorized as a treatment failure, but every treatment failure will be categorized as an exacerbation.

The treatment failure date is recorded in Q1260. It should correspond to the date treatment failure criteria were confirmed for the current event. If multiple criteria for treatment failure were met, record the earliest date any of the applicable criteria were met. Guidelines by treatment failure criterion follow:

- If the participant was hospitalized, the treatment failure date should be the hospital admission date.
 - If the participant received ten or more days of prednisone for asthma exacerbations, the treatment failure date should be the date the second course was initiated. This applies whether the treatment was for two distinct exacerbations or extended treatment for a single exacerbation.
 - If the participant experienced two distinct exacerbations during a treatment period, the treatment failure date should be the date recorded for the second exacerbation. This date should correspond to the date systemic corticosteroids were prescribed/started for treatment of an asthma exacerbation.
- Serious Adverse Event Reporting Form (SERIOUS)

If a participant is hospitalized due to a treatment failure/significant asthma exacerbation event, or the event is considered to be life-threatening or meets other criteria in the definition of a serious adverse event, a SERIOUS form should be completed. SERIOUS forms should be submitted to the DCC within 72 hours of the notification of a SAE. See the Adverse Events discussion in this section for further details.

- Coordinator and Participant Study Treatment Questionnaires (P5_CTXQX, P5_PARTTXQX)

While not directly related to the documentation of the treatment arm failure event itself, the coordinator and participant versions of the Study Treatment

Questionnaires (P5_CTXQX, P5_PARTTXQX) should be completed at the time the participant is transitioned from his/her double-blind Diskus[®] to open-label Flovent[®]. See the discussion of Study Treatment Questionnaires in this section for further details.

Adjustment of Trial Medication

Once a participant has met treatment failure criteria during a treatment period, he/she should stop taking his/her blinded scheduled Diskus[®] and start taking open-label 5xICS 1 puff BID (250 mcg Flovent[®] for the Age 5-11 Track and 500 mcg Flovent[®] for the Age 12-17 and Age 18+ Tracks). Ideally the transition to open-label 5xICS will take place the same day the participant is prescribed and receives oral or parenteral corticosteroids to treat his/her exacerbation that qualifies him/her as a treatment failure. Participants should be seen at the performance site in order to be assessed for safety and to receive prednisone (if needed) and open-label Flovent[®] (and to turn in their blinded scheduled Diskuses[®]).

Rescue prednisone will be given to the participant at Visit 0A to keep at home to be used only on the advice of study staff. If a participant is advised over the phone to begin taking his/her rescue prednisone, and he/she cannot come to the performance site the same day to pick up open-label Flovent[®], then he/she should continue to take his/her blinded scheduled Diskus[®] while taking the prednisone course. Arrangements should be made to get open-label Flovent[®] to the participant as soon as possible, preferably through a visit to the performance site.

Participants will continue to take open-label 5xICS Flovent[®] until a minimum 14 day washout period from the final dose of prednisone (or other systemic corticosteroid) has been met. At that time, the participant may complete the cross-over visit and receive a scheduled blinded Diskus[®] corresponding to the next treatment regimen. A window of +7 days is allowed for scheduling the cross-over visit (corresponding to a 2-3 week total prednisone washout).

Alteration of Visit Schedule

When a participant has met treatment failure status during a given treatment period, no remaining visits in the treatment period should be completed. The participant will remain on 5xICS (as described above) for the required washout from systemic corticosteroids and will resume study visits with the cross-over visit that begins the next treatment period. For example, if a participant achieves treatment failure status between visits 5 and 6 during treatment period 2, then he/she will not complete Visit 6. This participant should be scheduled for Visit 7 (cross-over into treatment period 3) after the 14 day

washout from the final dose of prednisone has been met. Visit 6 should be marked missing in the BARD database.

If the participant meets treatment failure status during treatment period 4, he/she should be seen at the performance site. The participant should be treated with a course of prednisone and open-label 5xICS Flovent[®]. Following completion of the prednisone course, the participant should be seen for a final assessment to ensure that exacerbation and treatment failure conditions have resolved and that he/she has plans for follow-up care. The participant should be terminated from the trial when the study physician deems study exit appropriate.

Compliance Monitoring (P5_COMPLY)

When a participant meets treatment failure (or drop-out) criteria between visits, he/she should be seen at the clinic to be evaluated and to receive open-label Flovent[®] as described above. The Spirotel[®] reports, including the Spirotel[®] Compliance Report (P5_COMPLY), should be generated and reviewed at that time. If the participant will be skipping visits in the treatment period and coming in for the next cross-over visit (4, 7, or 10), data in the download performed at the treatment failure visit should have visit number changed to the number of the next cross-over visit. After the visit number is changed in Breeze, the report should be rerun. The visit ID in the spirotel[®] device should also be updated to the cross-over visit ID.

Information on the double-blind Diskus[®] counter(s) returned at the interim visit should be recorded on P5_COMPLY at the time of the interim visit. The report should be stored in the participant's folder; do not forward it to the DCC. When the participant arrives for the cross-over visit, the report should be regenerated to contain data from multiple downloads. Information from the double-blind Diskus[®] counter(s) recorded on the interim copy of the report will be combined with information from the open-label Flovent[®] counter(s) returned at the cross-over visit. The updated report (P5_COMPLY) should be forwarded to the DCC with the cross-over visit packet.

2.54 Urine Cortisol:Creatinine Laboratory Test

This test is applicable for all three BARD age tracks.

Visits 0C, 0D, 1, 4, 7, 10, 13

Collect/log overnight urine sample (P5_URINE_SAMP_LOG). Refrigerate and process same day.

Complete total volume and aliquot information on Laboratory Results form (P5_LAB)

Enter urine aliquot information into Biological Sample Tracking module

Log urine aliquot information (P5_URINE_SAMP_LOG)

Due to the escalating doses of inhaled corticosteroids (ICS) to be used in the BARD trial, along with limited data available on the dose-response relationship between escalating ICS dosing and hypothalamic-pituitary-adrenal (HPA) axis function in children and adults, and the use of high doses of ICS as defined by the NAEPP Guidelines, we will assess the potential for systemic effects on HPA axis function. Overnight urinary cortisol/creatinine (OUCC) will be used as the measure of systemic exposure in all participants, along with linear growth by stadiometry in children 5-17 years of age and young adults aged 18-20. OUCC provides minimal invasiveness, particularly in children, and sufficient sensitivity for detecting systemic activity in adults and children. It is also more convenient than 24 hour urine collection or overnight plasma cortisol sampling.

Samples for OUCC will be collected at baseline, prior to randomization, and at the end of each of the four treatment periods (visits 4, 7, 10, and 13). Collection supplies and instructions will be given to study participants at visits 0B, 3, 6, 9, and 12.

Baseline Overnight Urine Sample – Visit 0C, 0D or 1

The participant should be asked to return a baseline sample at his/her next scheduled run-in visit, whether that is Visit 1 or 0C. If the participant forgets to do the collection for return at 0C, then he/she should be asked to return the urine sample at his/her next scheduled visit, whether that is 0D or Visit 1. If a participant is randomized at Visit 1 and has not yet turned in a baseline overnight urine sample, then he/she should be asked to do the collection the evening of the day of Visit 1 and return it to the clinic the next morning. No baseline urine samples will be accepted more than one day following Visit 1. Participants who do not return a baseline sample still should be asked to collect and return an overnight collection at the end of each of the treatment periods.

If a participant has not yet turned in a baseline overnight urine sample and he/she experiences an exacerbation during the run-in, Visit 1 will be delayed for 2-3 weeks to

allow for washout of the prednisone treatment. In this case, the collection of the baseline urine sample should be delayed, as well, until the participant meets the washout criteria to complete Visit 1. The overnight urine sample should be collected the night prior to Visit 1 and turned in at the visit. No baseline urine samples should be collected while the participant is on prednisone treatment (for any reason) or in the 2-week washout period required post-prednisone.

Baseline samples will be processed following normal procedures detailed below. Stored samples for participants who eventually become randomized will be shipped to ADx Laboratories in Denver for urine cortisol:creatinine analysis and banking. If a baseline sample is collected for a participant who does not achieve randomization, his/her urine aliquots should be excluded from the Biological Sample Tracking database (using 'Other' as the reason with a comment). The aliquots should then be disposed of following each institution's policies and procedures.

End of Treatment Period Overnight Urine Samples – Visits 4, 7, 10, 13

If a participant forgets to complete the overnight urine collection process and does not turn in a sample at Visits 4, 7, 10, or 13, he/she may do the collection following the visit and return it to the performance site up to 2 days later. After 2 days have passed, no post-treatment urine samples will be accepted.

If a participant experiences treatment (arm) failure during a treatment period or has an exacerbation late in a treatment period, he/she is treated with prednisone and maintained on open-label 5xICS until a 2-week washout period from the final prednisone dose is realized. At that point the end of treatment period visit can be scheduled and completed. Because the participant is no longer taking his/her blinded scheduled Diskus[®] during the washout period, and because the prednisone treatment will likely have some residual effect on the urine cortisol results beyond 2 weeks, no overnight urine sample is required in this situation. The participant should be informed that he/she does not need to collect the sample. He/she may return the collection materials to the performance site or keep them at home for the next overnight collection, if applicable. Include a comment on the Laboratory Results form (P5_LAB) explaining why no urine sample was collected.

Participant Collection Supplies and Procedures – Visit 0B, 3, 6, 9, 12

Distribute urine collection materials and review instructions (P5_URINE_COLLECT)

At each designated visit, provide the participant supplies for collecting and storing his/her overnight urine sample. Provide a new copy of the BARD Urine Collection Procedures handout (P5_URINE_COLLECT) each time. A supply list with suggested vendors is included in the following table. Check with hospital services for available supplies.

Item	Vendor	Catalog #	# Per Collection
Urine storage container/jug, 3000 mL capacity (tall or squat) ¹⁸	Fisher Sci. (1-800-766-7000)	02-540-32 (tall) 22-026-360 (squat)	1
Urine storage jug label (Avery #6873)	Staples	391893	1
Urinals (for males) 1000 mL capacity	Fisher Sci. (1-800-766-7000)	NC 9975905	1 (male)
Toilet 'hat' (for females)	Vitality Medical (1-800-397-5899)	4014	1 (female)
Urine transport bag (optional – see below)	Kold-to-Go (1-888-216-1700)	Model LG (has writing on it) or LP (plain) (many options are available)	1
BARD Urine Collection Instructions (P5_URINE_COLLECT)			1 (prefill header information)

1. Complete the header information on the BARD Urine Collection Instructions handout (P5_URINE_COLLECT).
2. Complete the participant's ID number and return visit number on a BARD 12-Hour Urine Collection label. Affix the label to the participant's urine storage jug.
3. Review the urine collection instructions with the participant. Stress the importance of recording the start date/time and stop date/time of his/her collection. Help him/her determine when his/her collection should begin, based on his/her anticipated waking time on the morning of the next visit.

¹⁸ Use only storage containers without preservatives.

4. Make a notation on the participant's Asthma Monitoring Log (P5_ASTHMA_LOG) on the evening when the collection should start as a reminder.
5. Give the participant the following items to take with him/her:
 - a. Urine storage jug (labeled)
 - b. Urine collection container (urinal or "hat")
 - c. Urine collection handout (P5_URINE_COLLECT)
 - d. Urine transport bag or cooler

Note: If the participant is unwilling to store his/her urine sample in the refrigerator until it can be returned to the clinical site, then he/she will need an alternate way to keep it cool. It is up to each site to determine the storage method that will work best for their participants. Use of a small cooler with ice is acceptable and may be provided by the study. Alternatively, participants may be agreeable to storing their sample in the refrigerator if provided an opaque bag in which to place it to mask the contents. One suggested supplier of these bags can be found at the following link:

<http://www.storesupply.com/c-811-frosted-shopping-bags.aspx?page=1&size=16>.

Insulated bags that can be used for storage, as well as transport to the clinical site, can be found at the following link:

http://koldtogo.com/index.php?route=product/product&path=60&product_id=56.

Urine Processing and Storage Supplies

The following supplies are required to process and store BARD urine samples:

Item	Vendor	Catalog #	# Per Collection
2.0 ml cryovial (USA Scientific Saf-T-Seal screw cap tubes #50-819-765; no substitutes)	Fisher Sci. (1-800-766-7000)	1420-9700	10 for baseline sample; 2 for post-randomization samples
Disposable pipette 6", 7.5 mL capacity	Fisher Sci. (1-800-766-7000)	13-711-9D	1
Fiberboard storage box for cryovials(Fisherbrand Cryo/Freezer boxes, 5x5x2" with 81 cells; no substitutes)	Fisher Sci. (1-800-766-7000)	03-395-464	1 box per 81 cryovials stored
White Laser Cryo-Tags, 1.5" x 0.75" http://divbio.com/lasercryo-tags150x0751200pk.aspx	Diversified Biotech (1-800-796-9199)	LCRY-1200	2-10, as described in table below

Barcode Labels Needed for Urine Processing (generated through BST module)

BST Sample Type	Barcode Number	Sample Purpose	# Labels Needed Per Collection
BARD_CREATININE	5CREA00001- 5CREA99999	Random creatinine	1
BARD_CORTISOL	5CORT00001- 5CORT99999	Random cortisol	1
BARD_URINE	5URIN00001 5URIN99999	Excess urine for storage	8 for baseline sample only

Urine Processing and Storage Procedures

1. Samples should be refrigerated until the time of processing.
2. Start an entry for the urine sample on the BARD Overnight Urine Sample Log (P5_URINE_SAMP_LOG). Complete the participant's BARD ID number and collection start date/time and stop date/time (from the jug label or returned P5_URINE_COLLECT handout).
3. Estimate total collection volume from the storage container. Record this value on P5_URINE_SAMP_LOG.
4. Prepare the 2.0 ml cryovials (specified in the above table; no substitutions) for the participant's urine samples.

Label the cryovials with barcode labels as follows:

Creatinine: Label one tube with a BARD Creatinine barcode label generated through the Biological Sample Tracking (BST) module of the AsthmaNet database management system. The barcode label includes a preprinted 10-digit barcode number, starting with 5CREA00001, which is unique for every BARD participant-sample. The sample type associated with the urine creatinine tubes in the BST module is "BARD_CREATININE."

Sample Creatinine barcode:



Cortisol: Label one tube with a BARD Cortisol barcode label generated through the BST module of the AsthmaNet database management system. The barcode label includes a preprinted 10-digit barcode number, starting with 5CORT00001, which is unique for every BARD participant-sample. The sample type associated with these tubes in the BST module is “BARD_CORTISOL.”

Sample Cortisol barcode:



For the baseline sample only: Urine for Storage: Label 8 tubes with BARD Urine barcode labels generated through the BST module of the AsthmaNet database management system. The barcode label includes a preprinted 10-digit barcode number, starting with 5URIN00001, which is unique for every BARD participant-sample. The sample type associated with these tubes in the BST module is “BARD_URINE.”

Sample Storage Urine barcode:



5. Mix the sample well.
6. Using a pipette, carefully aliquot the following volumes into the prepared 2.0 ml cryovials as follows:
 - Creatinine
Aliquot 1.25 ml into the labeled BARD Creatinine tube.
 - Cortisol
Aliquot 1.25 ml into the labeled BARD Cortisol tube.
 - Urine for Storage (Baseline sample ONLY)
Aliquot 1.25 ml into 8 tubes labeled for BARD storage urine.

Do not overfill the cryovials. Samples will expand when frozen and could cause the vials to burst if they contain too much urine.

7. Screw each cryovial shut. Be sure the cap is secure.
8. Access the BST module and scan the barcodes to insert a record for each sample. Input the participant ID information to link the barcode to the correct BARD participant. It is imperative that all samples are scanned on the day of collection so that they are associated with the correct participant ID and will be available to include in a shipment at a later date. For details on accessing and interacting with the BST Module in the AsthmaNet Database Application, see the AsthmaNet Computing and Networking Environment details in section 7 of the AsthmaNet General Manual of Operations.
9. Record sample barcode number and aliquot volume for each tube on P5_URINE_SAMP_LOG.
10. Complete Question #3 on the BARD Laboratory Results form (P5_LAB). See section 4 of this manual for further details regarding completion and entry of this form.
11. Store the urine samples (including those barcode labeled for storage from the baseline sample) in a chipboard box such that all cryovials of one sample type are together. This organization will make creation of shipments easier when accessing the BST module on the day of a shipment. These samples will be shipped to ADx labs in Denver every 6 months along with the serum ImmunoCAP/IgE and cotinine samples. Urine and serum samples can be stored in the same chipboard box as long as all samples of a given type are organized together. The shipping instructions and schedule can be found in the Serum ImmunoCAP, Total IgE and Cotinine Tests discussion in this section of the BARD MOP.
12. Before discarding the excess urine in the storage jug, aliquot 1.25 ml into two cryovials that do not contain barcode labels. Write the last three digits of the participant's BARD ID and the visit number on the vial with a lab marker. Store these urine aliquots in a separate chipboard box marked 'BARD Backup Urine'. In the event that samples would be lost or destroyed during shipment to Denver, these extra samples will serve as backups. If the backups are needed, the appropriate AsthmaNet barcode labels will be adhered to them and they will be scanned into the BST module and tracked accordingly. Once the original barcoded samples have been received by the lab in Denver, these excess samples may be discarded.

13. Store the urine samples at -70 or -80 degrees Celsius until the shipment day. Record the date/time the samples are placed in the freezer and the current freezer temperature on P5_URINE_SAMP_LOG.

Urine-Specific Shipment Note

Samples should be shipped to Denver only for randomized participants. If a participant returns a baseline urine sample during the run-in, prior to randomization, and he/she does not qualify for randomization, his/her urine samples should be destroyed following local institutional policies and procedures. Access the BST module and mark the samples excluded using reason 'Other'. Provide a comment indicating that they were baseline samples for a nonrandomized participant.

Shift Workers

If a participant works the nightshift and normally sleeps during the daytime, he/she should collect his/her sample during normal sleeptime for him/her. For example, if a participant works the 11 PM to 7 AM shift and normally sleeps from 8 AM to 4 PM, he/she should collect the sample between 4 AM and 4 PM. Provide a comment on the P5_LAB form explaining the participant's unusual schedule.

2.55 Visit Schedule

These procedures are applicable for all three BARD Age Tracks.

Visits 0A, 0A1 (if applicable), 1, 2, 4, 5, 7, 8, 10, 11

Run BARD visit scheduler

Review planned visit schedule

A visit scheduler program has been included on the AsthmaNet secure website to allow clinical personnel to create a Visit Scheduler Report for a given participant's BARD study visits. The visit scheduler is run at Visits 0A, 0A1 (if applicable), 1, 2, 4, 5, 7, 8, 10, and 11.

The visit scheduler at Visit 0A creates the participant's schedule, based on the Visit 0A date, for Visits 0A1/0B, 0B phone contact, 0C, 0C phone contact, and 0D (study run-in period). Visit 1 is not included on this schedule because it can be completed only when the participant has met the randomization eligibility criteria, which is not on a defined schedule. Visit 0A1 and 0B dates are identical. If a participant is in the 2-step ICS step-down group (see the Inhaled Corticosteroid (ICS) Step-Down Groups and Assessment discussion in this section), he/she will require Visit 0A1 to assess whether he/she can have his/her ICS dose reduced to the 1xICS level. If the participant is eligible to proceed after that assessment is done, the Visit 0A1 scheduler will be run at that time.

The visit scheduler at Visit 0A1 is needed only for participants who require and successfully complete Visit 0A1 for assessment of ICS dose step-down to 1xICS. This scheduler creates the participant's schedule, based on the Visit 0A1 date, for Visits 0B, 0B phone contact, 0C, 0C phone contact, and 0D (study run-in on 1xICS dose). Visit 1 is not included on this schedule because it can be completed only when the participant has met the randomization eligibility criteria, which is not on a defined schedule.

Visit schedulers are run at the first two visits for each of the four treatment periods. The first visit in the period is the "cross-over" visit where the participant begins a different blinded study regimen. The second visit in the period is the 2-week "baseline" visit for the treatment period.

Each treatment period is 14 weeks long with a 2-week "washout" period at the beginning of the period. The washout period is intended to allow for the effects of the prior period's blinded treatment to diminish (i.e., to remove any carry-over effect). Only the data from the last 12 weeks will be used for analysis, which means that the 2-week visit serves as the "baseline" for the treatment period. Because there are no true washout periods built into the cross-over design to separate the blinded study

treatments, special requirements are in place for ensuring that any prednisone the participant takes leading up to the first two visits in the treatment period has met a minimum washout period. See the discussion of Prednisone Washout Requirements in this section for further details. Prednisone dosing near the end of a treatment period or during the first 2 weeks of a treatment period will necessitate delays in completion of the initial period visits. Therefore, their timing can be variable. To ensure that each period begins with 14 weeks of follow-up after any prednisone washout period has been met, a visit scheduler is run at the cross-over visit. To ensure that each period has 12 weeks of follow-up after the baseline visit is completed (following any necessary prednisone washout period from the first 2 weeks of the period), a visit scheduler is run at the 2-week baseline visit. Applicable visits for each period are summarized in the following table:

Treatment Period	Cross-Over Visit (study week)	Baseline Visit (study week)
1	1 (0)	2 (2)
2	4 (14)	5 (16)
3	7 (28)	8 (30)
4	10 (42)	11 (44)

Schedulers run at the cross-over visits provide dates for scheduled phone contacts and the remaining visits in the treatment period. For example, the Visit 1 scheduler report shows the dates for Visit 2, Visit 2 phone contact, Visit 3, Visit 3 phone contact, and Visit 4 (end of treatment period).

Schedulers run at the baseline visit in each treatment period provide dates for scheduled phone contacts and the remaining visits in the treatment period. For example, the Visit 2 scheduler report shows the dates for Visit 2 phone contact, Visit 3, Visit 3 phone contact, and Visit 4. If the baseline visit occurs on the 'ideal' date, then the dates reflected on the updated schedule will match the dates from the scheduler generated at the previous (cross-over) visit. In that case, no updated scheduler report needs to be run at the baseline visit.

The visit scheduler has been created in several pieces to adjust the dates for each participant such that each treatment period has appropriate follow-up and spacing between visits, per protocol. Resetting the schedule at the beginning of each period is necessary in situations of prednisone washout as discussed above. It is also necessary when visit windows are used for the first visit on a scheduler such that it did not occur on the 'ideal' date. The same holds true for baseline 2-week visits that are not completed on the 'ideal' date.

Visit Scheduler Reports should be run near the end of the applicable visits and reviewed with the participant. Reports are customized for each participant in that his/her actual visit dates are entered so that ideal dates and visit windows for all subsequent visits can be calculated and displayed on the report.

Instructions for accessing and generating the BARD Visit Scheduler Reports on the AsthmaNet secure website can be found in Section 3 of this manual.

Copies of the BARD Visit Scheduler Reports should be included in the participant's study handout folder for personal reference. An additional copy should be placed in the participant's study folder at the performance site.

2.56 Visit Windows

Visit windows are applicable for all three BARD age tracks.

The table below summarizes the regular and extended windows allowed by protocol around the ideal visit date for each of the BARD study visits. The run-in is up to 10-12 weeks long, depending on the inhaled corticosteroid (ICS) step on which the participant enters the study. If the participant starts the run-in on 1xICS, then the run-in can be up to 10 weeks long. If the participant enters the study requiring a 2-step step-down process to get to the 1xICS dose, then he/she will require Visit 0A1 and the run-in can be up to 12 weeks long (see the discussion of Inhaled Corticosteroid Step-Down Groups and Assessment in this section for further details). Additional run-in time may be required for instances of non-compliance or to meet washout requirements for prednisone received during the run-in. The visit windows presented below do not account for these exceptions.

The run-in consists of two screen visits (0A and 0B) that are mandatory for all participants. The participant must be on 1xICS for a minimum of 2 weeks (14 days) before completing Visit 0B. If the participant meets the eligibility requirements for randomization at the time of 0B, he/she can be scheduled to complete Visit 1 (randomization visit) the next day or as soon as possible (within 2 weeks maximum). Participants who remain eligible for the study, but who have not yet met the criteria for randomization, will be scheduled for 2-week phone contacts and Visits 0C and 0D. If the participant meets the eligibility requirements for randomization at any point during this time period, he/she will be scheduled to complete Visit 1 as soon as possible. If the participant qualifies at the time of Visit 0C or 0D, Visit 1 can be done the same day and will replace the screen visit. See section 4 of this manual of operations for further details on data management procedures for accommodating the transition of Visit 0C or 0D to Visit 1. Alternatively, Visit 0C or 0D can be completed (and data submitted) and Visit 1 can be scheduled for another day, as soon as possible (within 2 weeks maximum). If the participant has not yet met the eligibility requirements for randomization as of Visit 0D, he/she is ineligible to continue in the study and a Termination of Study Participation form (P5_TERM) should be completed. There is no set schedule for Visit 1.

Post-randomization visits occur approximately every 2-6 weeks with phone contacts at the mid-point of the longer intervals. Delays in some visits may occur due to prednisone washouts required prior to their completion. The visit windows presented below do not account for these exceptions. See the Prednisone Washout Requirements discussion in this section for further details.

The 2-week “baseline” visit of each treatment period must be scheduled after at least 2 weeks have passed from the “cross-over” visit preceding it. This is to ensure an adequate washout period from the prior blinded study regimen. For this reason there are no lower windows available for the baseline visits. See the Visit Schedule discussion in this section for further details on the baseline and cross-over visits.

Visits should be scheduled on the ideal date whenever possible. When this is not possible, the regular windows should be used. The extended windows should be used only to accommodate extenuating circumstances when a visit will otherwise be missed. When extreme scheduling conflicts arise and the extended windows do not provide enough flexibility, the BARD scientific coordinator at the DCC should be consulted before scheduling the visits to ensure that analysis- and drug-related repercussions of any mistimed visits have been considered. If a visit is being delayed to meet the prednisone washout requirements, e-mail the details, including participant ID number and visit number, to the BARD scientific coordinator at the DCC. Such exceptions to the visit schedule are granted automatically.

Regular and Extended Windows for BARD Study Visits and Phone Contacts

Visit Number	Study Week	Regular Window (days)		Extended Window (days)	
		Lower	Upper	Lower	Upper
0A/0A1 ¹⁹	-10	-	-	-	-
0B	-8	-	+3	-	+5
Phone Contact	-6	-3	+3	-5	+5
0C	-4	-3	+3	-5	+5
Phone Contact	-2	-3	+3	-5	+5
0D	-0	-3	+3	-5	+5
1 (randomization)	0	-	-	-	-
2	2	-	+3	-	+5
Phone Contact	5	-3	+3	-5	+5
3	8	-3	+3	-5	+5
Phone Contact	11	-3	+3	-5	+5
4	14	-3	+3	-5	+5
5	16	-	+3	-	+5
Phone Contact	19	-3	+3	-5	+5
6	22	-3	+3	-5	+5
Phone Contact	25	-3	+3	-5	+5

¹⁹ Participants who require Visit 0A1 2 weeks after Visit 0A and successfully achieve reduction of their ICS dose to 1xICS will have a new Visit Scheduler Report generated at the time of Visit 0A1. This scheduler will start with Visit 0B and will be on the same timeline as those who began the study on 1xICS at Visit 0A.

Visit Number	Study Week	Regular Window (days)		Extended Window (days)	
		Lower	Upper	Lower	Upper
7	28	-3	+3	-5	+5
8	30	-	+3	-	+5
Phone Contact	33	-3	+3	-5	+5
9	36	-3	+3	-5	+5
Phone Contact	39	-3	+3	-5	+5
10	42	-3	+3	-5	+5
11	44	-	+3	-	+5
Phone Contact	47	-3	+3	-5	+5
12	50	-3	+3	-5	+5
Phone Contact	53	-3	+3	-5	+5
13	56	-3	+3	-5	+5

Note that in addition to the visit windows, the time of day of the visits should also be considered. Because of the circadian variability associated with lung function, all subsequent post-randomization visits should be scheduled such that baseline spirometry at the visit occurs within +/-3 hours of baseline spirometry at Visit 1 (randomization visit). Timing of spirometry at screen visits (0A and 0B) is flexible, as the collected data are being used for characterization and eligibility assessment and will not be analyzed longitudinally. If a participant cannot be scheduled in the spirometry windows, contact the scientific coordinator at the DCC to seek an exception.

Ideal visit dates and regular and extended visit windows have been programmed into the BARD Visit Scheduler Reports for ease of scheduling participant visits. See the Visit Schedule discussion in this section and Section 3 for further details on these reports.

If a participant routinely fails to keep scheduled visits, he/she should be counseled by the performance site coordinator. If the problem persists, the local investigator should talk with the participant. Participants who have unusual scheduling conflicts or miss/reschedule run-in visits multiple times may not be good prospects for randomization, as most of the BARD study visits cannot be missed. If counseling by the site coordinator during the run-in period does not seem to improve the situation, the coordinator should consider terminating the participant from further study participation by filing a BARD Termination of Study Participation form (P5_TERM).

2.57 Withdrawals

These procedures are applicable for all three BARD age tracks.

Early Study Withdrawal

Complete BARD Termination of Study Participation form (P5_TERM)

Participants have the right to withdraw consent for study participation at any time and for any reason. In the case of a serious adverse event, either due to an asthma exacerbation or another medical condition, the study investigator may determine that it is in the best interest of the participant to discontinue participation in the trial.

When a participant is withdrawn from the study or withdraws consent after completing Visit 0A successfully, a BARD Termination of Study Participation form (P5_TERM) should be completed, entered into the database, and submitted to the DCC as soon as possible. Note that any AsthmaNet investigator at the performance site may approve and sign the P5_TERM form.

In addition to the P5_TERM form, participants who are withdrawing or have been withdrawn from BARD should be asked to complete an AsthmaNet Satisfaction Questionnaire (SATQX). This questionnaire is optional and anonymous in that no participant ID number or other identifying information is recorded on the form. The participant should be given a pre-addressed, postage-paid envelope in which to return the questionnaire directly to the DCC. The Satisfaction Questionnaire is posted on the secure AsthmaNet website appended to the single P5_TERM form and as part of the Visit 13 packet. See the Satisfaction Questionnaire discussion in this section for instructions on the administration of this questionnaire.

The specific termination procedures that should be followed are dependent on when in the trial the participant terminates his/her participation. See below for additional details.

Visit 0A Screen Failures

At any point during Visit 0A a participant may be deemed ineligible or withdraw consent. Information on such participants should be maintained at the performance site in the participant's study folder. Only those participants who pass all of the eligibility criteria at Visit 0A should have data entered into the study database and forms forwarded to the DCC.

If a participant is ineligible for a reason that may change soon, such as a recent respiratory tract infection, he/she may be able to meet eligibility criteria in the near

future. If the participant rejoins the study, he/she must be assigned a new study ID number (through the Protocol Enrollment module of the AsthmaNet database application) and repeat Visit 0A. See the Re-Enrollment discussion in this section for further details.

Withdrawals during the Run-In (Visit 0A through Visit 1)

The primary purpose of the screening and run-in visits is to identify an appropriate group of participants for randomization in the BARD trial. These visits give clinical personnel an opportunity to review eligibility criteria and adherence to study procedures for each participant before he/she is randomized. For the BARD study it is extremely important to gauge the participant's ability to maintain high levels of compliance. Participants who cannot accommodate the date/time of the visits, who take exclusionary medications, who fail to take study medications correctly and on schedule, or who fail to complete e-diaries and peak flows in their spirotel[®] devices are non-compliant. These participants should not be randomized at Visit 1, as their lack of adherence can affect the results of the study adversely and may jeopardize their safety if they cannot recognize exacerbation conditions appropriately. The run-in is the optimal time to identify and withdraw non-compliant participants.

When a participant is withdrawn from the run-in or withdraws consent prior to randomization at Visit 1, a BARD Termination of Study Participation form (P5_TERM) should be submitted to the DCC along with any study data that have been collected. If a participant withdraws between visits prior to randomization, the next run-in visit packet should be completed with as much information as is available. The P5_TERM form should include the same visit number. For example, if a participant withdraws after completing Visit 0B and prior to Visit 0C, the Visit 0C packet should be completed with as much information as is available. See below for minimum requirements.

In addition to the P5_TERM form, participants who are withdrawn after successfully completing Visit 0A and prior to randomization should also be asked to complete an AsthmaNet Satisfaction Questionnaire (SATQX). The participant's status at the time of termination should be completed by the coordinator at the top of the form as 'Run-in termination.'

Any spirotel[®] data collected between visits should be downloaded and transmitted to MedGraphics for inclusion in the BARD dataset.

Minimum data requirements for individuals terminated at Visit 0A1 include:

- ICS Step-Down Assessment form (P5_STEPDOWN_ASSESS)
- Participant Compliance Report (P5_COMPLY)

-
- Spirotel[®] Quality Control (SPIROTELQC)
 - Spirotel[®] Reports (except P5_PEF_REF)
 - Termination of Study Participation form (P5_TERM)

Minimum data requirements for individuals terminated at Visit 0B include:

- Randomization Eligibility Checklist (P5_RAND_ELIG)
- Participant Compliance Report (P5_COMPLY)
- Spirotel[®] Quality Control (SPIROTELQC)
- Spirotel[®] Reports (except P5_PEF_REF)
- Termination of Study Participation form (P5_TERM)

Minimum data requirements for individuals terminated at Visit 0C/0D include:

- Randomization Eligibility Checklist (P5_RAND_ELIG)
- Participant Compliance Report (P5_COMPLY)
- Spirotel[®] Quality Control (SPIROTELQC)
- Spirotel[®] Reports (except P5_PEF_REF)
- Termination of Study Participation form (P5_TERM)

Minimum data requirements for individuals terminated at Visit 1 include:

- Eligibility Checklist 5 (P5_ELIG5)
- Randomization Eligibility Checklist (P5_RAND_ELIG)
- Participant Compliance Report (P5_COMPLY)
- Spirotel[®] Quality Control (SPIROTELQC)
- Spirotel[®] Reports (except P5_PEF_REF)
- Termination of Study Participation form (P5_TERM)

Early Withdrawals after Randomization

The intention-to-treat principle applies to the BARD study. Once a participant has been randomized, all efforts must be made to follow the participant and to collect data on his/her progress for the duration of the study. This principle applies even for participants who are discovered to be ineligible (unless the reason for ineligibility presents a safety concern) or who fail to comply with study procedures following randomization. Once a participant leaves the performance site with his/her randomly assigned Diskus[®] at Visit 1, he/she *must* be followed. Any losses in participant follow-up can lead to bias in the study results. Participant withdrawal during the post-randomization period is permissible only in the following situations:

- Withdrawn Consent (i.e., participant refusal to continue)

- Pregnancy
- Participant is considered a treatment period drop-out during treatment period 4. See the discussion of Drop-Out Status (Treatment Period) in this section for further details.
- Participant meets treatment (arm) failure criteria during treatment period 4. See the discussion of Treatment (Arm) Failure in this section for further details.
- Serious Adverse Event or Severe Asthma Exacerbation

A serious adverse event, either unrelated to asthma or due to a significant asthma exacerbation, may prompt the study investigator to terminate the participant from further study participation because it is in the participant's best interest for safety reasons.

- Loss to Follow-up

Participants who cannot be contacted for an extended period of time qualify as lost to follow-up. Clinic staff should continue to attempt to contact the participant until the time he/she would have completed the trial. At this point, a BARD Termination of Study Participation form (P5_TERM) should be completed, entered into the database, and sent to the DCC.

Once randomized, participants cannot be terminated from the study solely for non-compliance with attendance at study visits, e-diary and peak flow completion, dosing with study medications, or any other form of non-compliance. Non-compliance may be stated as a secondary reason for participant termination on the P5_TERM form; it may not be used as the primary reason for termination.

Withdrawal at a regular visit (2-13)

If a randomized participant withdraws consent during a post-randomization visit, any data already collected at that visit should be reported on the data collection forms and forwarded to the DCC. A BARD Termination of Study Participation (P5_TERM) form should be submitted. The participant should be asked to complete the BARD Participant Study Treatment Questionnaire (P5_PARTTXQX) and the coordinator should complete the BARD Coordinator Study Treatment Questionnaire (P5_CTXQX). If termination is occurring at visits other than 4, 7, 10 or 13, these forms should be submitted as single forms with the current visit number on them. The participant should be given an

AsthmaNet Satisfaction Questionnaire (SATQX) with pre-addressed, postage-paid envelope to complete and return at his/her leisure.

Any urine samples that are collected during the participant's termination visit should be processed and forwarded to ADx Labs in Denver as outlined in this manual.

Data on the spiroteI[®] should be downloaded following normal procedures.

Withdrawal between regular post-randomization visits

If a randomized participant withdraws consent by contacting performance site personnel between visits, he/she should be asked to return to the clinic for a brief termination visit, if possible. The purpose of the visit is to collect study materials and to ensure that the participant has plans for his/her asthma care. At a minimum, the BARD Termination of Study Participation form (P5_TERM) must be completed and should specify the number of the last regular visit the participant completed as the visit number. In addition, a BARD Coordinator Study Treatment Questionnaire (P5_CTXQX) should be completed using the visit number of the last visit completed.

If the participant refuses to return to the performance site for even an abbreviated visit, arrangements must be made to have the participant ship his/her spiroteI[®] device and study medications back to the site. Data on the participant's spiroteI[®] device should be downloaded as soon as the device is returned. Compliance should be estimated as best possible from the returned Diskuses[®] and recorded on the BARD SpiroteI[®] Participant Compliance Report (P5_COMPLY). This form should be entered as a single form using the number of the last visit the participant completed. The participant should be mailed an AsthmaNet Satisfaction Questionnaire (SATQX) with return envelope and instructions for completion.

For participants who are unwilling to come to the performance site for an exit visit, the study coordinator may administer the BARD Participant Study Treatment Questionnaire (P5_PARTTXQX) over the phone, if the participant is agreeable. No source documentation will be available on the form in this case. This form would be entered as a single form with the number of the last visit completed under these circumstances.

General Note:

After a participant has been terminated from the BARD trial, no additional data and/or specimens may be collected from the participant with the exception of the AsthmaNet Satisfaction Questionnaire (SATQX) referenced above. If any procedures are performed and/or specimens are collected after the participant's termination date, a protocol violation will be assigned.

It should be noted that the above rule applies only to procedure-related data and specimen collection. For example, when induced sputum is collected, the results of slide reading are not known immediately. The SPUTLAB form may be completed after the participant's termination date, but the sputum induction procedure itself may not be completed after the termination date (i.e., the SPUTUM and SPUTUM_ADD_TRT forms may not be dated after the termination date). Likewise, if a participant forgets to bring his/her spirote[®] device to the termination visit and he/she mails it back to the clinic at a later date, spirote[®] quality control (SPIROTELQC) may take place after the termination date without penalty.

If a participant is deemed to have experienced a treatment (arm) failure at the time of Visit 13, he/she should be followed until the final course of prednisone has been completed and the event has fully resolved. Under these circumstances, the P5_TERM form should not be completed and submitted to the DCC until final resolution is documented. See the discussion of Treatment (Arm) Failure in this section for further details.

2.58 Work Productivity and Activity Impairment Questionnaire

This questionnaire is applicable only for the BARD Age 12-17 and Age 18+ Tracks.

The Work Productivity and Activity Impairment Questionnaire (WPAI) assesses health-related activity and work impairment, taking into account both time lost from work (absenteeism), as well as loss of productivity while at work (presenteeism). The questionnaire uses a 7-day recall period. Generic and disease-specific versions of the WPAI have been validated for use in different populations. An allergy-specific version (WPAI:AS) was developed and tested in patients with moderate-to-severe allergic rhinitis. This version incorporated classroom impairment, as well as work and activity impairment. An asthma-specific version of this adapted questionnaire (WPAI:Asthma) was validated in a sample of patients with severe or difficult-to-treat asthma²⁰. The WPAI:Asthma is being used for the BARD study. It has been validated for and is applicable to participants ages 12 and older.

For more details on the WPAI, see <http://www.reillyassociates.net>.

Visit 0A, at the time of an exacerbation, and at post-exacerbation study visits

Administer Asthma-Specific Work Productivity and Activities Impairment Questionnaire (WPAI_ASTHMA)

To introduce the WPAI_ASTHMA questionnaire and to establish a baseline, this questionnaire will be administered to participants ages 12 and up at the time of Screen Visit A (Visit 0A). The administration of this questionnaire is one of the early procedures performed at Visit 0A, in conjunction with the administration of the other asthma outcome questionnaires such as the ACT. Study coordinators should observe the order of procedures as they are laid out on the visit procedure checklists.

If the participant experiences an exacerbation between study visits, then he/she should complete the copy of the WPAI_ASTHMA questionnaire that resides in the Asthma Attack kit that he/she has at home (see the discussion of the Asthma Attack/Exacerbation Kit in this section for further details). This form should be returned to the performance site at the next study visit, and the visit ID should be the number of the previous completed visit (the visit date should match the date the participant supplied in the source documentation box at the time of completion). At the first post-exacerbation study visit, the WPAI_ASTHMA form should be completed again (as follow-up to the event), and the visit ID on this form should be the number of the current

²⁰ Chen H, Blanc PD, Hayden, ML, Bleecker RE, Chawla A, Lee JH. Assessing productivity loss and activity impairment in severe or difficult-to-treat asthma. *Value in Health* 2008;11:231-9.

visit. These forms will be entered as single forms. Note that these instructions also apply if the participant is seen at the performance site for exacerbation conditions between visits and he/she will start a prednisone course the same day. In that case the form may be completed and turned in to study personnel the same day.

If an exacerbation is identified at the time of a regular study visit and prednisone is prescribed and will be started the same day, then the participant should complete the WPAI_ASTHMA questionnaire at the time of the visit (rather than waiting to complete it at home). The visit ID on this form should be the number of the current visit. At the participant's next (post-exacerbation) study visit, he/she should complete the WPAI_ASTHMA questionnaire again (as follow-up to the event), using the number of the current visit as the visit ID. These forms will be entered as single forms.

At post-exacerbation visits the WPAI_ASTHMA questionnaire is not part of the normal visit procedures. It has been added to the visit procedure checklists with a prompt for completion only if the participant experienced an exacerbation at a prior study visit or between study visits. This questionnaire should be administered after the last asthma questionnaire that is part of the visit structure and prior to recording adverse events and concomitant medications. That is, this questionnaire should be administered directly after the ACT and any quality of life questionnaires at the visit.

See section 4 of this MOP for data management instructions for handling WPAI_ASTHMA questionnaires completed at various times during the trial.

Administration Instructions

The WPAI_ASTHMA is completed by the participant. When administering the questionnaire, request that the participant complete the entire form and provide answers as completely and as accurately as possible. No stated or implied time limit should be set. If the participant requests help with or clarification of any question, the study coordinator may provide the following information:

Q1/Q1000: Current employment status:

The participant should answer this question 'yes' if he/she works part-time or full-time, is self-employed, works in a family business, is on vacation from paid employment (e.g., school teachers on leave for the summer). The participant should answer this question 'no' if he/she does not work for pay, only does volunteer work, usually works but has been laid-off or unemployed during the past seven days, or is a seasonal worker not currently working.

Q3/Q1020 and Q7/Q1060: Work/class time missed due to asthma:

Include: any time taken off from work/class due to asthma itself, doctor visits for asthma, trips to pharmacy for asthma medication, side effects of asthma medications, and time taken off partly due to asthma and partly due to something else.

Exclude: time taken off from work/class the day of the clinic visit and time taken off work/class that the participant is not sure was at least partially related to asthma.

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

When the participant is finished with the questionnaire, collect it and review it for completeness before proceeding with the visit. If a question has been left blank, ask the participant to do his/her best to answer it. The answers to all of the questions are necessary to score the instrument. Check that the participant's responses are clearly marked. Complete Q1030, 1070 and 1080 with the numeric value the participant circled for each question. If the participant's intended answer is unclear, ask him/her to clarify and to make the appropriate data correction.

The participant should provide source documentation on the WPAI_ASTHMA form by providing his/her initials and the date/time in the source documentation box. Review the source documentation provided by the participant to ensure that the date and time are accurate before collecting the form.