Published in final edited form as:
J Allergy Clin Immunol. 2014 January ; 133(1): 34–38.e1. doi:10.1016/j.jaci.2013.10.025.

Designing Clinical Trials To Address the Needs of Childhood and Adult Asthma: NHLBI AsthmaNet

E. Rand Sutherland, MD, MPH, **William W. Busse, MD**, and **for the NHLBI AsthmaNet***

Abstract

In 2008, the National Heart, Lung and Blood Institute announced its intent to support a new asthma network, known as AsthmaNet. This clinical trials consortium, now in its fifth year, has been charged with developing and executing clinical trials to address the most important asthma management questions and identify new treatment approaches in pediatric and adult patients. In order to update the global asthma community regarding the progress and processes of the network, this review will discuss the organization of the AsthmaNet and the scientific context in which the network was developed and began its work, report the results of an internal priority-setting exercise designed to guide the network's scientific strategy, and highlight the portfolio of clinical trials, proof-of-concept studies and mechanistic studies planned for the 7-year period of the network.

Keywords

AsthmaNet; asthma; treatment; clinical trials; proof-of-concept; mechanistic studies; asthma management

Introduction

In 2008, the National Heart, Lung and Blood Institute (NHLBI) issued a funding opportunity announcing a new asthma clinical research network, known as AsthmaNet. As described in the request for applications,[1] the goal of the NHLBI was to develop "…a clinical research network that will develop and conduct multiple clinical trials to address the most important asthma management questions and identify new treatment approaches in pediatric and adult populations." Using an organizational scheme designed to promote cooperation and coordination, facilitate scientific exchange, provide training opportunities and leverage resources, AsthmaNet has focused its energy and efforts on designing clinical trials to evaluate existing and new therapeutic approaches to asthma management, while also conducting a limited number of proof-of-concept studies to advance the development of novel therapies, as well as studies to investigate the mechanistic bases for interventions examined in the network's major protocols. This article will review the organization of the AsthmaNet, discuss the scientific context in which the network was developed and began its work, will report the results of an internal priority-setting exercise designed to guide the

Correspondence: 1400 Jackson Street, Denver, CO 80206, 303-398-1655, sutherlande@njhealth.org.
*A list of AsthmaNet principal investigators in contained in the online supplement

network's scientific strategy, and will highlight the portfolio of clinical trials, proof-of-concept studies and mechanistic studies planned for the 7-year period of the network.

Network Operation and Protocol Development

AsthmaNet consists of nine clinical centers and one data coordinating center.[2] Each clinical center is comprised of a partnership between at least one principal investigator and research team with expertise in adult asthma and one principal investigator and research team with expertise in pediatric asthma. To broaden recruitment efforts, particularly with regard to enhancing the racial, ethnic and socioeconomic diversity of study participants, some clinical centers have subcontracted with additional performance sites, yielding a combined total of 30 performance sites across the United States. The AsthmaNet data coordinating center (DCC), a group of statistical and data scientists, provides expert assistance in concept development and feasibility assessment, protocol design and data analysis, database development, quality control, financial management and coordination of the implementation of collaborative studies in adult and pediatric populations with asthma.[3] Working together, the members of the network have also been charged to identify core constructs for developing clinical asthma history and phenotype ascertainment instruments, standardize procedures and outcome measures,[4] and, when possible, harmonize phenotypes to facilitate translational science.

The AsthmaNet has adopted a formal process, codified in manuals of procedure, to ensure that research concepts are thoroughly evaluated for clinical impact, scientific integrity and human subjects protection, and a series of reviews must be completed before a study has full clearance to begin. First, brief study concept proposals are invited from all AsthmaNet participants by the Steering Committee (SC), which is comprised of the AsthmaNet clinical center and DCC principal investigators. In response, working groups formally present new protocol concepts for consideration and approval by all members of the SC and the NHLBI project scientist staff. This group is charged with evaluating feasibility, clinical impact, whether the proposed study addresses an unmet need and whether it has overall potential to move the science of asthma forward. Scoring and ranking are then performed using NIH study section guidelines. Proposals with sufficient scientific merit are then further developed by a Protocol Writing Committee, comprised of investigators who elaborate scientific and budgetary aspects of the proposal, subsequently presenting the expanded concept for further discussion and approval by the SC in a second round of scoring. Those proposals with the highest scores and a majority vote of approval by the SC are then developed into full-scale study protocols with detailed budgets and submitted to an external, NHLBI-convened Protocol Review Committee (PRC). The PRC provides scientific review and commentary similar to an NIH scientific review group and recommends either revision, acceptance, or non-acceptance of the protocol to the NHLBI. Once accepted, the protocol is submitted to an independent, NHLBI-convened Data and Safety Monitoring Board (DSMB) for review of patient safety, informed consent forms, and data monitoring plans. Once these reviews have been addressed in a satisfactory manner, the NHLBI authorizes the SC to initiate the protocol.

Recognizing that network-based team science is dependent on the effort of multiple partners, the AsthmaNet SC determined that, as part of full protocol development, a formal leadership plan should be developed for each protocol and approved by a subset of the SC. This plan identifies who represents the SC during deliberations with the PRC and DSMB, who liaises with the DCC on financial negotiations with external partners (e.g. pharmaceutical companies, external laboratories), who has primary responsibility for various aspects of protocol development and initiation, and who has responsibility for oral presentations and manuscript authorship. Additionally, to protect the integrity of network activities, all

investigators operate under a conflict of interest policy that conforms to NIH policy and requires review both annually and with the initiation of any new protocol. This policy, its definitions, as well as the existence of any financial or other significant interest are public information.

Scientific Context: Prior NHLBI Network Studies of Asthma

A significant component of the AsthmaNet scientific agenda grew out of observations made by NHLBI-supported research networks, in particular the Asthma Clinical Research Network (ACRN, adult asthma studies) and the Childhood Asthma Research and Education Network (CARE). As reviewed elsewhere,[5, 6] trials conducted over the life spans of these networks resulted in seminal advances in asthma care. In adult asthma, ACRN studies: 1) evaluated and identified predictors of ICS dose-response with regard to lung function and airway hyperresponsiveness,[7-9] 2) further defined the role of ß-adrenergic agonists in the treatment of asthma, with particular regard to efficacy, safety and pharmacogenetics,[10-15] 3) determined approaches by which therapeutic escalation (step-up) should occur,[12, 13, 16] 4) tested intermittent and biomarker-based ICS treatment strategies,[17, 18] and 5) assessed novel immunomodulatory and bronchodilator therapeutic approaches,[19-21] as well as treatment approaches in specific patient subsets.[22]

From a pediatric standpoint, CARE studies made a number of specific contributions to our understanding of pediatric asthma therapy. CARE studies: 1) identified that ICS are disease-controlling but not disease-modifying,[23] 2) determined that ICS are more efficacious than leukotriene modifiers in mild-moderate childhood asthma, both alone and in combination with long-acting ß-adrenergic agonists,[24, 25] 3) investigated intermittent and acute-intervention strategies,[26, 27] 4) determined optimal approaches for therapeutic escalation,[28] 5) examined corticosteroid-sparing approaches to treating severe asthma,[29] and 6) evaluated strategies to prevent exacerbations.[30] This scientific output, along with innumerable studies performed by investigators across the global asthma clinical research community, provided the context for AsthmaNet investigators to define the network's scientific agenda.

Priority-Setting for AsthmaNet Protocols

As noted previously, the primary goal of the AsthmaNet is to address important clinical management questions in asthma, principally by conducting Phase II and Phase III clinical trials. The RFA indicated the AsthmaNet SC would collectively decide which specific research questions to address, and noted the overall expectation that of the total protocols to be conducted, at least one should be targeted to children 0-4 years of age, one to children 5-11 years of age, one to patients who have severe asthma, and that protocols that address issues across age groups should also be included. After initiation of the first two AsthmaNet protocols (see below), the network undertook a formal planning exercise to identify top priority research questions and potential protocol ideas. Additionally, specific ideas for large, definitive studies and smaller “proof-of-concept” studies were solicited from all partnerships, with the goal of prioritizing and initiating studies felt by the group to be most informative and responsive in light of the priorities identified by the network.

In initial deliberations, the network identified specific overarching knowledge gaps; pediatric asthma investigators identified primary prevention, disease modification, treatment of wheezing and mild asthma, identification of optimal strategies for ICS or ICS/LABA step-down, strategies to prevent exacerbations and personalization of asthma therapies as the most important general areas of focus. Adult asthma investigators highlighted the identification of strategies for phenotypic refinement, improved understanding of disease biology, the impact of obesity on prognosis and response to therapy, development of strategies to predict exacerbations, improved understanding of the role of the microbiome

and questions related to asthma in older adults as being of significant import. After completing internal deliberations, the AsthmaNet SC engaged five external experts in clinical asthma research to provide general input on important directions for AsthmaNet research and specific critiques of study concepts identified as above. Furthermore, the NHLBI released a Request for Information in the NIH Guide (HL-11-125: Ideas for Clinical Trials to be Conducted by the NHLBI Asthma Network (AsthmaNet)) to provide a public forum for a broad spectrum of asthma stakeholders - medical, patient, and scientific community members alike - to submit their ideas for AsthmaNet clinical trials.

Collectively, these discussions generated numerous areas deemed important for study, from which the SC identified priority questions to drive protocol development (Tables 1 and 2). In this light, the network reviewed a number of proposals for clinical trials, associated mechanistic studies and proof-of-concept studies, and advanced the studies outlined below for further development, review, approval and initiation, using the protocol development processes described above.

AsthmaNet Clinical Trials and Associated Mechanistic Studies

Vitamin D add-on therapy enhances corticosteroid responsiveness in asthma (VIDA): the VIDA trial (ClinicalTrials.gov NCT01248065) is a randomized, double-blind parallel group trial that has completed enrollment of individuals 18 years and older who have vitamin D insufficiency and asthma, along with persistent symptoms despite low-dose ICS. In this trial, participants on low-dose ICS are randomized to add-on therapy with either placebo or high-dose vitamin D (100,000 IU load followed by 4,000 IU/day) for a 28-week period. During an ICS-stable phase, participants remain on low-dose inhaled corticosteroid. During an ICS taper phase, participants taper their inhaled corticosteroid by 50% at two time points post randomization, with the ultimate research aim of determining if the addition of vitamin D reduces the likelihood of treatment failure when compared to placebo during both the inhaled corticosteroid-stable and inhaled corticosteroid-taper phases of the study. Concurrent with the parent protocol, an associated mechanistic study is being performed to evaluate the hypothesis that Vitamin D deficiency in patients who have asthma results in a pro-inflammatory state that contributes to the lack of response to ICS. This mechanistic study will also assess if treatment with vitamin D increases the number and function of dendritic and T regulatory cells while also decreasing pro-inflammatory cytokine secretion by CD4+ T cells.

Azithromycin for preventing the development of upper respiratory tract illness into lower respiratory tract symptoms in children, and Oral corticosteroids for treating episodes of significant lower respiratory tract symptoms in children (APRIL-OCELOT): the APRIL and OCELOT trials (ClinicalTrials.gov NCT01272635) are two ongoing separate but linked studies that target preschool aged children with recurrent severe episodes of lower respiratory tract symptoms. Participants initially enter APRIL, a prevention study, to examine the efficacy of azithromycin versus placebo administered at the early signs of respiratory tract illness (RTI), and then continued for 5 days, in attenuating the progression of an upper RTI into clinically significant lower respiratory tract (LRT) symptoms. The primary outcome measure for APRIL is the number of RTIs that do not progress to treatment failure. If and when an APRIL treatment failure occurs, the participant then proceeds to OCELOT, a study designed to evaluate the efficacy of prednisolone versus placebo in treating significant LRT symptoms. The primary outcome measure of OCELOT is the Pediatric Respiratory Assessment Measure (PRAM) score,[31] measured 36-72 hours after the initiation of OCELOT therapy.

Individualized therapy for asthma in toddlers and Acetaminophen Vs. Ibuprofen in children with asthma (INFANT-AVICA): the INFANT and AVICA trials (ClinicalTrials.gov NCT01606306 and NCT01606319) are two separate but linked clinical trials that target preschool children 12-59 months of age who meet criteria for treatment with Step 2 asthma controller therapy.[32] The INFANT trial utilizes a cross-over study design to test the primary null hypothesis that in preschool children 12-59 months of age with persistent asthma, the following therapies will provide similar degrees of asthma control: 1) regularly-scheduled daily inhaled corticosteroid (ICS) treatment used with intermittent (as-needed) SABA, 2) daily leukotriene receptor antagonist (LTRA) treatment, and 3) intermittent ICS and intermittent SABA used as needed for asthma symptoms. The primary outcome is a composite variable of asthma control encompassing domains of risk and impairment, similar to the measure used in the CARE Network's BADGER trial.[28] At the time of randomization into the INFANT trial, participants will also be randomized as participants in the AVICA trial, which will test the primary hypothesis that, in preschool children with persistent asthma, the number of asthma exacerbations requiring systemic corticosteroids will be more frequent in children receiving acetaminophen as compared to those receiving ibuprofen on an as-needed basis for fever and/or pain. Both INFANT and AVICA will follow participants for a 48 week study period.

Additional trials under development: at least three other major trials are under development (but not yet enrolling participants) at the time this manuscript was prepared. The first study, entitled *Best African-American response to asthma drugs (BARD)*, will address the question of the most efficacious step up therapy in African-American patients with asthma (age 5 and older) who are in adequately controlled on low-dose ICS. The study will also evaluate if participants ages 5-11 respond differently than participants 12 years of age and older. Another study, entitled *Steroids in eosinophil negative asthma (SIENA)*, will determine if symptomatic patients with mild to moderate asthma who have a persistently non-eosinophilic sputum inflammatory phenotype require a different treatment strategy than those with sputum eosinophilia. A third study, *Step-up yellow zone inhaled corticosteroids to prevent exacerbations (STICS)*, will determine whether, in children ages 5-11 years receiving low-dose ICS monotherapy or low-dose ICS + LABA combination therapy, quadrupling the dose of inhaled corticosteroids during episodes of asthma symptoms in the “yellow zone” (as reflected in a standardized symptom-based asthma action plan) reduces the rate of severe asthma exacerbations requiring treatment with oral corticosteroids. In addition, concurrently in each of these three studies, the network is developing and evaluating an index for characterizing exacerbations in order to promote harmonization of this outcome measure.

AsthmaNet Proof-of-Concept Studies

Airway Microbiome in Asthma: Relationships to Asthma Phenotype and Inhaled Corticosteroid Treatment

This bronchoscopy-based proof-of-concept study (NCT01537133) is designed to examine relationships between the lung and gut microbiome, systemic immune function, pulmonary immune function, and pulmonary function and inflammation across three populations: allergic asthmatics, allergic non-asthmatics, and non-allergic, non-asthmatics. A number of important hypotheses are to be tested: 1) that the microbiota of the bronchial airways of allergic asthmatic, allergic non-asthmatic, and non-allergic, non-asthmatic healthy subjects differ in diversity, richness, evenness, and/or taxonomic composition, 2) that clinical, physiologic, and inflammatory phenotypic features of asthma (including “Th2- vs. non-Th2” pattern of gene expression in bronchial epithelial cells, and cluster by BAL cytokine pattern) are associated with characteristic bronchial microbial community compositions, 3) that ICS treatment alters bronchial microbial community composition in asthmatic subjects, and 4)

that differences in bronchial microbial community composition at baseline or after ICS treatment are associated with differences in responsiveness to ICS treatment. Additionally, at the time of manuscript preparation, the network is in the early stages of considering additional proof-of-concept studies.

Conclusion

Herein, we have described the current portfolio of AsthmaNet clinical trials, proof-of-concept and mechanistic studies. These trials arise directly from the processes and scientific context described above, and additional studies are in various stages of development. In sum, the network will continue to use these approaches to address the most important asthma management questions in pediatric and adult patients with asthma, with the goal of developing new treatment approaches that will directly impact and improve the care of patients with asthma across the lifespan.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Clinical Centers for the NHLBI Asthma Network (AsthmaNet). [accessed June 25, 2013] RFA-HL-08-010 http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-08-010.html
2. AsthmaNet Web Site. [accessed June 25, 2013] http://asthmanetresearch.net/
3. Data Coordinating Center for the NHLBI Asthma Network (AsthmaNet). [accessed June 25, 2013] RFA-HL-08-011 http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-08-011.html
4. Busse WW, Morgan WJ, Taggart V, Togias A. Asthma outcomes workshop: overview. J Allergy Clin Immunol. 2012; 129(3 Suppl):S1–8. [PubMed: 22386504]
5. Denlinger LC, Sorkness CA, Chinchilli VM, Lemanske RF Jr. Guideline-defining asthma clinical trials of the National Heart, Lung, and Blood Institute's Asthma Clinical Research Network and Childhood Asthma Research and Education Network. J Allergy Clin Immunol. 2007; 119(1):3–11. quiz 2-3. [PubMed: 17141853]
6. Szefler SJ, Chinchilli VM, Israel E, et al. Key observations from the NHLBI Asthma Clinical Research Network. Thorax. 2012; 67(5):450–5. [PubMed: 22514237]
7. Martin RJ, Szefler SJ, Chinchilli VM, et al. Systemic effect comparisons of six inhaled corticosteroid preparations. Am J Respir Crit Care Med. 2002; 165(10):1377–83. [PubMed: 12016099]
8. Martin RJ, Szefler SJ, King TS, et al. The Predicting Response to Inhaled Corticosteroid Efficacy (PRICE) trial. J Allergy Clin Immunol. 2007; 119(1):73–80. [PubMed: 17208587]
9. Szefler SJ, Martin RJ, King TS, et al. Significant variability in response to inhaled corticosteroids for persistent asthma. J Allergy Clin Immunol. 2002; 109(3):410–8. [PubMed: 11897984]
10. Drazen JM, Israel E, Boushey HA, et al. Comparison of regularly scheduled with as-needed use of albuterol in mild asthma. Asthma Clinical Research Network. N Engl J Med. 1996; 335(12):841–7. [PubMed: 8778601]
11. Israel E, Chinchilli VM, Ford JG, et al. Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. Lancet. 2004; 364(9444): 1505–12. [PubMed: 15500895]
12. Lazarus SC, Boushey HA, Fahy JV, et al. Long-acting beta2-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. JAMA. 2001; 285(20):2583–93. [PubMed: 11368732]
13. Lemanske RF Jr, Sorkness CA, Mauger EA, et al. Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol: a randomized controlled trial. JAMA. 2001; 285(20):2594–603. [PubMed: 11368733]

14. Wechsler ME, Kunselman SJ, Chinchilli VM, et al. Effect of beta2-adrenergic receptor polymorphism on response to longacting beta2 agonist in asthma (LARGE trial): a genotype-stratified, randomised, placebo-controlled, crossover trial. Lancet. 2009; 374(9703):1754–64. [PubMed: 19932356]
15. Wechsler ME, Lehman E, Lazarus SC, et al. beta-Adrenergic receptor polymorphisms and response to salmeterol. Am J Respir Crit Care Med. 2006; 173(5):519–26. [PubMed: 16322642]
16. Deykin A, Wechsler ME, Boushey HA, et al. Combination therapy with a long-acting beta-agonist and a leukotriene antagonist in moderate asthma. Am J Respir Crit Care Med. 2007; 175(3):228–34. [PubMed: 16973987]
17. Boushey HA, Sorkness CA, King TS, et al. Daily versus as-needed corticosteroids for mild persistent asthma. N Engl J Med. 2005; 352(15):1519–28. [PubMed: 15829533]
18. Calhoun WJ, Ameredes BT, King TS, et al. Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma: the BASALT randomized controlled trial. JAMA. 2012; 308(10):987–97. [PubMed: 22968888]
19. Fish JE, Peters SP, Chambers CV, et al. An evaluation of colchicine as an alternative to inhaled corticosteriods in moderate asthma. National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. Am J Respir Crit Care Med. 1997; 156(4 Pt 1):1165–71. [PubMed: 9351617]
20. Peters SP, Kunselman SJ, Icitovic N, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. N Engl J Med. 2010; 363(18):1715–26. [PubMed: 20979471]
21. Sutherland ER, King TS, Icitovic N, et al. A trial of clarithromycin for the treatment of suboptimally controlled asthma. J Allergy Clin Immunol. 2010; 126(4):747–53. [PubMed: 20920764]
22. Lazarus SC, Chinchilli VM, Rollings NJ, et al. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. Am J Respir Crit Care Med. 2007; 175(8):783–90. [PubMed: 17204725]
23. Guilbert TW, Morgan WJ, Zeiger RS, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. N Engl J Med. 2006; 354(19):1985–97. [PubMed: 16687711]
24. Szefler SJ, Phillips BR, Martinez FD, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. J Allergy Clin Immunol. 2005; 115(2):233–42. [PubMed: 15696076]
25. Sorkness CA, Lemanske RF Jr, Mauger DT, et al. Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: the Pediatric Asthma Controller Trial. J Allergy Clin Immunol. 2007; 119(1):64–72. [PubMed: 17140647]
26. Bacharier LB, Phillips BR, Zeiger RS, et al. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. J Allergy Clin Immunol. 2008; 122(6):1127–35 e8. [PubMed: 18973936]
27. Zeiger RS, Mauger D, Bacharier LB, et al. Daily or intermittent budesonide in preschool children with recurrent wheezing. N Engl J Med. 2011; 365(21):1990–2001. [PubMed: 22111718]
28. Lemanske RF Jr, Mauger DT, Sorkness CA, et al. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. N Engl J Med. 2010; 362(11):975–85. [PubMed: 20197425]
29. Strunk R, Bacharier L, Phillips B, et al. Azithromycin or montelukast as inhaled corticosteroidsparing agents in moderate-to-severe childhood asthma study. J Allergy Clin Immunol. 2008; 122(6):1138–44.e4. [PubMed: 18951618]
30. Martinez FD, Chinchilli VM, Morgan WJ, et al. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial. Lancet. 2011; 377(9766):650–7. [PubMed: 21324520]
31. Ducharme FM, Chalut D, Plotnick L, et al. The Pediatric Respiratory Assessment Measure: a valid clinical score for assessing acute asthma severity from toddlers to teenagers. J Pediatr. 2008; 152(4):476–80. 80 e1. [PubMed: 18346499]
32. Guidelines for the diagnosis and management of asthma: National Heart, Lung and Blood Institute. 1997 NIH Publication No 07-4051.

Abbreviations

ACRN	Asthma Clinical Research Network
APRIL	Azithromycin for preventing the development of upper respiratory tract illness into lower respiratory tract symptoms in children
AVICA	Acetaminophen Vs. Ibuprofen in children with asthma
BARD	Best African-American response to asthma drugs
CARE	Childhood Asthma Research and Education Network
DCC	data coordinating center
DSMB	data and safety monitoring board
ICS	inhaled corticosteroid
INFANT	Individualized therapy for asthma in toddlers
LABA	long-acting beta-agonist
LRT	lower respiratory tract
NHLBI	National Heart, Lung and Blood Institute
OCELOT	Oral corticosteroids for treating episodes of significant lower respiratory tract symptoms in children
PRAM	Pediatric Respiratory Assessment Measure
PRC	protocol review committee
SC	steering committee
SIENA	Steroids in eosinophil negative asthma
STICS	Step-up yellow zone inhaled corticosteroids to prevent exacerbations
RTI	respiratory tract illness
VIDA	Vitamin D add-on therapy enhances corticosteroid responsiveness in asthma

Table 1

Critical pediatric asthma questions identified by AsthmaNet members during protocol planning.

- Does immunomodulation prevent asthma or improve control?
- Does treatment in childhood prevent morbidity in later life?
- What is the best approach to step 2-4 therapy in children (both step-up and step-down)?
- Can anticholinergics replace beta-agonists in suboptimally-controlled asthma?
- Does early treatment of exacerbations reduce their severity or duration?
- Which is better - intermittent or continuous therapy for exacerbations?
- Is there a role for macrolide antibiotics in acute exacerbations?
- What are the optimal objective measurements of disease in children unable to perform spirometry?
- Can we use biomarkers to predict treatment response in children?
- What are optimal drug delivery strategies for children with asthma?
- Can we enhance adherence in adolescents?
- Does parental education enhance treatment efficacy?

Table 2

Critical adult asthma questions identified by AsthmaNet members during protocol planning.

- What are the optimal approaches for ICS/LABA step-down?
- What are the optimal approaches for treatment of intermittent disease?
- Are symptom-based treatments appropriate in moderate asthma?
- What is the optimal clinical evaluation for patients with refractory asthma?
- What approaches are best when Step 6 therapy fails?
- Can we prevent exacerbations or manage them more effectively?
- What is the optimal approach to treating asthmatics who smoke?
- How does obesity impact the diagnosis and management of asthma?
- How do we treat comorbid GERD and is there benefit to doing so?
- Are tailored approaches based on race/ethnicity needed?
- Can we use phenotypes to optimize therapy, define prognosis?
- What is the pathobiology of fixed airflow limitation?