

Designing clinical trials to address the needs of childhood and adult asthma: The National Heart, Lung, and Blood Institute's AsthmaNet

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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. This review will discuss the organization of 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 to update the global asthma community regarding the progress and processes of the network. (*J Allergy Clin Immunol* 2014;133:34-8.)

Key words: *AsthmaNet, asthma, treatment, clinical trials, proof of concept, mechanistic studies, asthma management*

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

Abbreviations used

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
BADGER:	Best Add-on Therapy Giving Effective Responses
BARD:	Best African-American Response to Asthma Drugs
DCC:	Data coordinating center
ICS:	Inhaled corticosteroid
INFANT:	Individualized Therapy for Asthma in Toddlers
NHLBI:	National Heart, Lung, and Blood Institute
NIH:	National Institutes of Health
OCELOT:	Oral Corticosteroids for Treating Episodes of Significant Lower Respiratory Tract Symptoms in Children
PRC:	Protocol Review Committee
RTI:	Respiratory tract illness
SC:	Steering Committee
STICS:	Step-up Yellow Zone Inhaled Corticosteroids to Prevent Exacerbations
VIDA:	Vitamin D Add-on Therapy Enhances Corticosteroid Responsiveness in Asthma

management questions and identify new treatment approaches in pediatric and adult populations." By 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 AsthmaNet, discuss 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.

NETWORK OPERATION AND PROTOCOL DEVELOPMENT

AsthmaNet consists of 9 clinical centers and 1 data coordinating center (DCC).² Each clinical center is comprised of a partnership between at least 1 principal investigator and research team with expertise in adult asthma and 1 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,

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*A list of AsthmaNet principal investigators can be found in [Appendix E1](#) in this article's Online Repository at www.jacionline.org.

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some clinical centers have subcontracted with additional performance sites, yielding a combined total of 30 performance sites across the United States. The AsthmaNet 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 with identifying core constructs for developing a clinical asthma history and phenotype ascertainment instruments, standardizing procedures and outcome measures,⁴ and, when possible, harmonizing phenotypes to facilitate translational science.

AsthmaNet has adopted formal processes, codified in manuals of procedure, to ensure that research concepts are thoroughly evaluated for clinical effect, scientific integrity, and human subject 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's project scientist staff. This group is charged with evaluating feasibility, clinical effect, 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 by using National Institutes of Health (NIH) study section guidelines. Proposals with sufficient scientific merit are then further developed by a Protocol Writing Committee, which is composed 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 nonacceptance of the protocol to the NHLBI. Once accepted by the PRC, the protocol is submitted to an independent, NHLBI-convened data and safety monitoring board 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 data and safety monitoring board, who liaises with the DCC on financial negotiations with external partners (eg, pharmaceutical companies and 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, 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 to protect the integrity of network activities. This policy, its definitions, and 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 (adult asthma studies) and the Childhood Asthma Research and Education Network (CARE). As reviewed elsewhere,^{5,6} trials conducted over the lifespans of these networks resulted in seminal advances in asthma care. In the field of adult asthma, Asthma Clinical Research Network studies (1) evaluated and identified predictors of inhaled corticosteroid (ICS) dose response with regard to lung function and airway hyperresponsiveness⁷⁻⁹; (2) further defined the role of β -adrenergic agonists in the treatment of asthma with particular regard to efficacy, safety, and pharmacogenetics¹⁰⁻¹⁵; (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 ICSs are disease controlling but not disease modifying²³; (2) determined that ICSs are more efficacious than leukotriene modifiers in mild-to-moderate childhood asthma, both alone and in combination with long-acting β -adrenergic agonists^{24,25}; (3) investigated intermittent and acute intervention strategies^{26,27}; (4) determined optimal approaches for therapeutic escalation²⁸; (5) examined corticosteroid-sparing approaches to treating severe asthma²⁹; 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 AsthmaNet is to address important clinical management questions in the field of asthma, principally by conducting phase II and phase III clinical trials. The request for applications indicated the AsthmaNet SC would collectively decide which specific research questions to address and noted the overall expectation that 1 or more of the total protocols to be conducted should be targeted to children 0 to 4 years of age, 1 should be targeted to children 5 to 11 years of age, and 1 should be targeted to patients with severe asthma and that protocols that address issues across age groups should also be included. After initiation of the first 2 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 and definitive studies and smaller proof-of-concept studies were solicited from all partnerships, with the goal of prioritizing and initiating studies

TABLE I. 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 therapy)?
- Can anticholinergic agents replace β -agonists in patients with 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?

believed 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/long-acting β -agonist step-down therapy and 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 and the effect 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 importance. After completing internal deliberations, the AsthmaNet SC engaged 5 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 (ie, 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 I and II). 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 by 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) trial

The VIDA trial (ClinicalTrials.gov NCT01248065) is a randomized, double-blind, parallel-group trial that has completed

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

- What are the optimal approaches for ICS/long-acting β -agonist step-down therapy?
- What are the optimal approaches for treatment of intermittent disease?
- Are symptom-based treatments appropriate in patients with 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 asthmatic patients who smoke?
- How does obesity affect the diagnosis and management of asthma?
- How do we treat comorbid gastroesophageal reflux disease, and is there benefit to doing so?
- Are tailored approaches based on race/ethnicity needed?
- Can we use phenotypes to optimize therapy and define prognosis?
- What is the pathobiology of fixed airflow limitation?

enrollment of subjects 18 years and older who have vitamin D insufficiency and asthma, along with persistent symptoms despite low-dose ICS treatment. In this trial, participants receiving low-dose ICSs are randomized to add-on therapy with either placebo or high-dose vitamin D (100,000 IU load followed by 4,000 IU/d) for a 28-week period. During an ICS-stable phase, participants continue to receive low-dose ICSs. During an ICS-taper phase, participants taper their ICSs by 50% at 2 separate time points after randomization, with the ultimate research aim of determining whether the addition of vitamin D reduces the likelihood of treatment failure when compared with placebo during both the ICS-stable and ICS-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 asthmatic patients results in a proinflammatory state that contributes to the lack of response to ICSs. This mechanistic study will also assess whether treatment with vitamin D increases the number and function of dendritic and regulatory T cells while also decreasing proinflammatory cytokine secretion by CD4⁺ T cells.

Azithromycin for Preventing the Development of Upper Respiratory Tract Illness into Lower Respiratory Tract Symptoms in Children (APRIL) and Oral Corticosteroids for Treating Episodes of Significant Lower Respiratory Tract Symptoms in Children (OCELOT) trials

The APRIL and OCELOT trials (ClinicalTrials.gov NCT01272635) are 2 ongoing separate but linked studies that target preschool-age 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 symptoms. The primary outcome measure for the APRIL trial 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 the

OCELOT trial, a study designed to evaluate the efficacy of prednisolone versus placebo in treating significant lower respiratory tract symptoms. The primary outcome measure of OCELOT is the pediatric respiratory assessment measure score,³¹ which is measured 36 to 72 hours after the initiation of OCELOT therapy.

Individualized Therapy for Asthma in Toddlers (INFANT) and Acetaminophen Vs. Ibuprofen in Children with Asthma (AVICA) trials

The INFANT and AVICA trials (ClinicalTrials.gov NCT01606306 and NCT01606319) are 2 separate but linked clinical trials that target preschool children 12 to 59 months of age who meet the criteria for treatment with step 2 asthma controller therapy.³² The INFANT trial uses a crossover study design to test the primary null hypothesis that in preschool children 12 to 59 months of age with persistent asthma, the following therapies will provide similar degrees of asthma control: (1) regularly scheduled daily ICS treatment used with intermittent (as-needed) short-acting β -agonists, (2) daily leukotriene receptor antagonist treatment, and (3) intermittent ICS and intermittent short-acting β -agonist treatment used as needed for asthma symptoms. The primary outcome is a composite variable of asthma control encompassing domains of risk and impairment, which is 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 compared with those receiving ibuprofen on an as-needed basis for fever, pain, or both. Both INFANT and AVICA will follow participants for a 48-week study period.

Additional trials under development

At least 3 other major trials were 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 years) whose symptoms are inadequately controlled with low-dose ICSs. The study will also evaluate whether participants age 5 to 11 years respond differently than participants 12 years of age and older. Another study, entitled Steroids in Eosinophil Negative Asthma (SIENA), will determine whether symptomatic patients with mild-to-moderate asthma who have a persistently noneosinophilic 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 age 5 to 11 years receiving low-dose ICS monotherapy or low-dose ICS plus long-acting β -agonist combination therapy, quadrupling the dose of ICSs 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

3 studies, the network is developing and evaluating an index for characterizing exacerbations 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 the relationships between the lung and gut microbiome, systemic immune function, pulmonary immune function, and pulmonary function and inflammation across 3 populations: allergic asthmatic patients, allergic nonasthmatic patients, and nonallergic nonasthmatic subjects. A number of important hypotheses are to be tested: (1) that the microbiota of the bronchial airways of allergic asthmatic, allergic nonasthmatic, and nonallergic nonasthmatic healthy subjects differ in diversity, richness, evenness, and/or taxonomic composition; (2) that clinical, physiologic, and inflammatory phenotypic features of asthma (including the " T_H2 - vs non- T_H2 " pattern of gene expression in bronchial epithelial cells and cluster by bronchoalveolar lavage cytokine pattern) are associated with characteristic bronchial microbial community compositions; (3) that ICS treatment alters bronchial microbial community composition in asthmatic patients; 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 and 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 affect and improve the care of asthmatic patients across the lifespan.

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