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

E. Rand Sutherland, MD, MPH,[a] and William W. Busse, MD,[b] for the National Heart, Lung, and Blood Institute's AsthmaNet* *Denver, Colo, and Madison, Wis*

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*

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

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." 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,

From [a]the Department of Medicine, National Jewish Health, the University of Colorado School of Medicine, Denver, and [b]the Department of Medicine, University of Wisconsin, Madison.

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

Supported by National Institutes of Health grants HL098075, HL098098, HL098102, HL098107, HL098090, HL098112, HL098103, HL098096, HL098177, and HL098115.

Disclosure of potential conflict of interest: E. R. Sutherland has consultancy arrangements with Forest Laboratories; is employed by National Jewish Health; has received one or more grants from or has one or more grants pending with Boehringer Ingelheim, Novartis, the National Institutes of Health (NIH), and Janssen Research and Development; and has received one or more payments for the development of educational presentations for Genentech (activity ended in 2011). W. W. Busse is a board member for Merck; has consultancy arrangements with Amgen, Novartis, GlaxoSmithKline, MedImmune, Genentech, Boston Scientific, and ICON; has received one or more grants from or has one or more grants pending with the NIH/National Institute for Allergy and Infectious Diseases (NIAID) and the NIH/National Heart, Lung, and Blood Institute (NHLBI); and has received royalties from Elsevier.

Received for publication September 3, 2013; revised October 9, 2013; accepted for publication October 14, 2013.

Corresponding author: E. Rand Sutherland, MD, MPH, 1400 Jackson St, Denver, CO 80206. E-mail: sutherlande@njhealth.org.

0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2013.10.025

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 hyperresponsiveness[7-9]; (2) further defined the role of β-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 ICSs are disease controlling but not disease modifying[23]; (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 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 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