

Overview of the Pediatric Heart Network: Multicenter Studies of Congenital and Acquired Cardiovascular Disease in Children

Lynn Mahony

University of Texas Southwestern Medical Center, Dallas, TX, USA

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The Pediatric Heart Network (PHN) was established by the National Heart, Lung, and Blood Institute, a component of the National Institutes of Health in the United States in 2001. The purposes of this paper are to describe the structure and function of the PHN, and to review the ongoing studies. The PHN infrastructure is now well-developed and capable of implementing complex, multicenter protocols efficiently and recruiting subjects effectively. To date, five randomized clinical trials and three observational studies have been implemented. The results of these and other studies from the PHN will contribute to providing evidence-based medicine for, and improving the outcomes of pediatric patients with cardiovascular disease.

Introduction

Treatment of pediatric patients with congenital and acquired heart disease involves medical, surgical, and catheter-based approaches. Morbidity, mortality, and quality of life have improved greatly in the past 50 years, but these improvements may have been limited by most contemporary treatments being based on expert opinion, single institution observational studies, or extrapolated from adult cardiovascular medicine. Although the need to develop and apply evidence-based approaches to pediatric cardiovascular problems has been recognized by many caretakers, substantial barriers have often precluded studies evaluating treatments for these patients. These include 1) the number of patients with a given condition being too small for research questions to be answered by single center studies, 2) relative inexperience in designing and performing multicenter studies, 3) the absence of an infrastructure for clinical trials in many clinical centers, 4) ethical considerations involved in performing research studies in children, 5) potential lack of therapeutic equipoise and 6) the high cost of pediatric research.

In response to these concerns, the National Heart, Lung, and Blood Institute (NHLBI) a component of the National

Institutes of Health, established the Pediatric Heart Network (PHN) in 2001.¹⁾ Initially, the PHN was a cooperative network of seven core Clinical Centers in the United States and Canada, and one Data Coordinating Center (DCC). The PHN currently has eight core Clinical Centers and 22 auxiliary centers assisting with various studies (Fig. 1). The mission of the PHN is to achieve public health advances through the conduct and dissemination of collaborative research leading to evidence-based treatment options for and improved outcomes of pediatric patients with congenital and acquired heart disease. The specific objectives of the PHN are to accelerate research in the diagnosis and management of congenital and acquired pediatric heart disease, to standardize existing treatments, and to evaluate new therapies to bring evidence-based medicine to the care of children with heart disease. The purpose of this paper is to describe the structure and function of the PHN and to review the ongoing studies.

Structure of the PHN

The structure of the PHN has evolved since 2001 (Fig. 2). The main governing body of the PHN is the Steering Committee. The Network Chair heads the Steering Committee and provides, together with NHLBI, overall management

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Reprint requests to: Lynn Mahony, M.D., University of Texas Southwestern Medical Center, CMC-Cardiology, Dallas, TX, 1935 Motor Street, Dallas, TX 75235-7701, USA

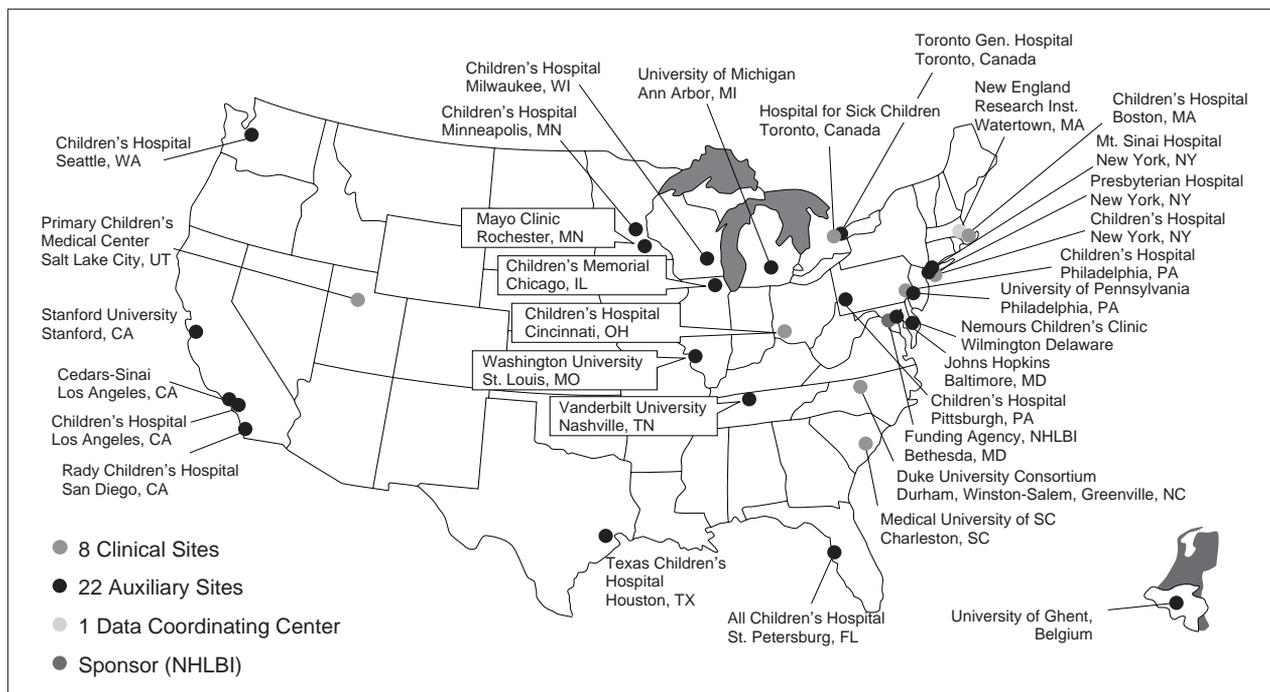


Fig. 1 Geographical depiction of Clinical Sites (core Clinical Centers), auxiliary enrolling sites, and Data Coordinating Center comprising the Pediatric Heart Network.
NHLBI: National Heart, Lung, and Blood Institute

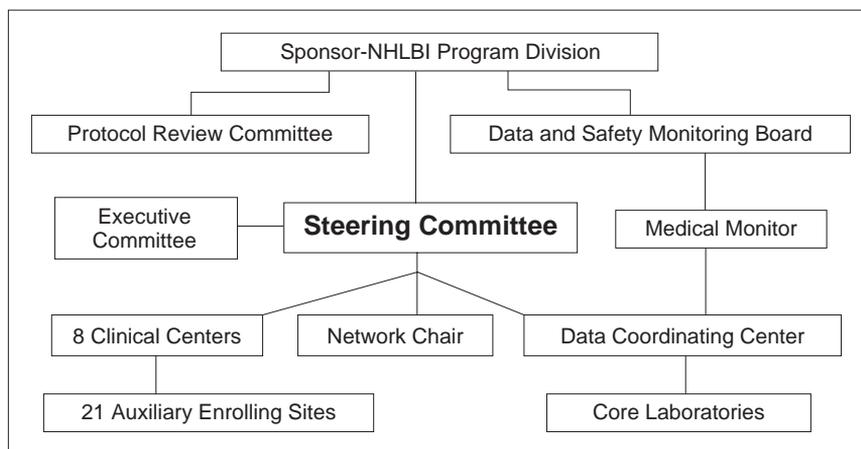


Fig. 2 Organization of the Pediatric Heart Network (see text).
The Medical Monitor assists the Data Coordinating Center in evaluating adverse events. Core laboratories are responsible for centralized interpretation of specific study measures.

and direction of PHN activities. Membership on the Steering Committee is open to investigators from the core Clinical sites and all auxiliary enrolling sites, and personnel from the DCC and NHLBI. The voting members of the Steering Committee, who are the Network Chair, the Principal Investigator from each participating Clinical Center and the DCC,

and the NHLBI Program Officer from the Executive Committee. The Executive Committee, which also includes the chairs of other standing committees (described below), is responsible for developing all policies and procedures in consultation with the Steering Committee.

Clinical Center investigators as well as investigators from

outside the PHN provide the intellectual leadership for developing proposals for new studies. For approved proposals, these investigators write the formal protocol with biostatistical consultation from the DCC. The Clinical Centers and auxiliary enrolling sites are responsible for subject recruitment and conduct of required tests for the approved studies. Members of the Clinical Centers, auxiliary enrolling sites, the Network Chair, the DCC, and the NHLBI staff collaborate in disseminating information that reports the results of the clinical studies through presentations, abstracts, and manuscripts.

The DCC is responsible for overall coordination of operations and protocols. This includes 1) maintaining systems for electronic communications, administrative management, and coordination, 2) all phases of protocol development and implementation, 3) design, testing, and maintenance of data collection and management systems, 4) ensuring data safety and confidentiality, 5) systems and procedures for quality assurance, and 6) conduct of data analyses and collaboration on manuscripts.

1. Standing committees

Standing committees are necessary to support the complex operations of a multicenter clinical research program. The Publications and Presentations Committee facilitates and supervises preparation of all abstracts, presentations and manuscripts. The Study Coordinators' Committee consists of the study coordinators from each of the Clinical Centers and the DCC project managers. The goals of this Committee are to facilitate sharing of information and to collaborate in solving problems related to subject recruitment and the day-to-day conduct of the studies.

Ancillary studies are defined as investigations that are not part of a main NHLBI-funded PHN protocol, but use PHN participants, samples, or data collected by the PHN. The Ancillary Studies Committee has developed policies for the conduct and review of ancillary studies and reviews applications for ancillary studies.

2. Oversight committees

The PHN has two oversight committees: the Protocol Review Committee and the Data and Safety Monitoring Board. Both committees were established by NHLBI and consist of individuals who do not have close professional relationships to PHN investigators and who have expertise in pediatric cardiology, pediatric cardiac surgery, pharmacology, clinical

trials design and analysis, ethics, and genetics. The Protocol Review Committee assesses the scientific merit of all proposed protocols. The Data and Safety Monitoring Board reviews protocols, data forms, and consent forms. In addition, PHN study data, including adverse events by study arm, are reviewed to ensure the safety of study subjects. Furthermore, this committee advises the NHLBI on data quality and analysis, and ethical and human subject issues. If the trial design includes interim looks at the data, the Data and Safety Monitoring Board also reviews interim study results to assess treatment efficacy.

PHN Studies

The PHN has implemented 8 studies since 2001 (Fig. 3). Data collection is complete for 5 studies. Four of these studies involve drugs and one is a surgical procedure study. Details of each study are summarized below:

1. The relationship between functional health status and laboratory parameters of ventricular performance after the Fontan procedure

For children born with only one functional ventricle, the optimal current surgical palliation culminates in the Fontan procedure. The fact that little information is available regarding the correlation of laboratory measures such as measures of ventricular function and exercise performance and overall functional or health status in these patients makes it difficult to plan a clinical trial likely to answer important management questions. The goal of this cross-sectional study was to identify a quantifiable measure of cardiovascular performance that correlated with clinical outcome as measured by a validated health-related quality of life assessment in patients after the Fontan procedure.²⁾ This study enrolled 544 patients between the ages of 6 and 18 years of age, which illustrates the power of the multicenter approach. Subjects underwent maximal exercise testing, echocardiography, cardiac magnetic resonance imaging, and measurement of brain natriuretic peptide. Parents and subjects completed a questionnaire evaluating health status. Reports describing 1) outcomes in this cohort,³⁾ 2) the relationship between outcome and abnormalities in heart rate and rhythm,⁴⁾ 3) exercise performance,⁵⁾ 4) health status and its sociodemographic and medical determinants,⁶⁾ and 5) comparison of outcomes in subjects with and without heterotaxy⁷⁾ have been published. Further analysis of the data and preparation of additional manuscripts is ongoing. In addition, a study

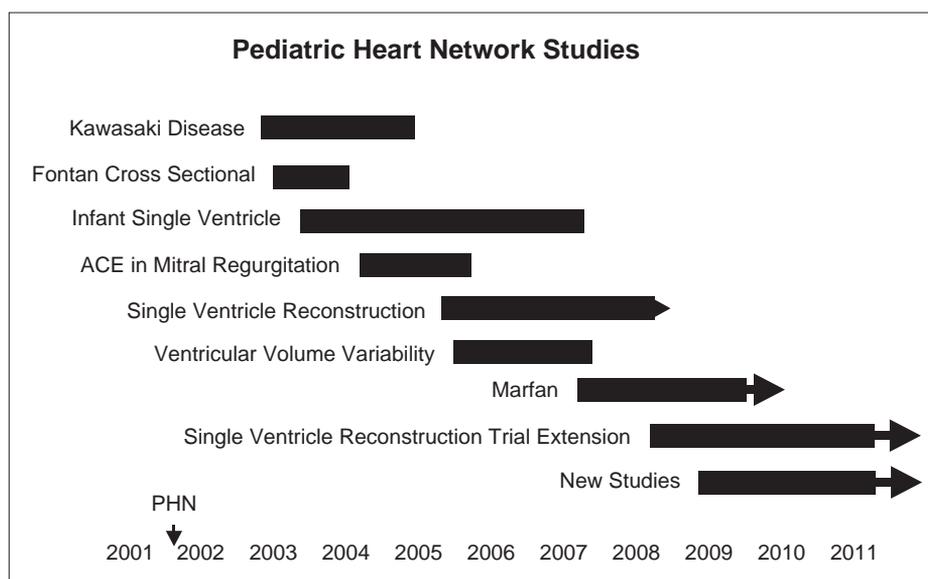


Fig. 3 Timeline for Pediatric Heart Network studies.

designed to obtain longitudinal data on subjects in this cohort is being developed.

2. Trial of Pulse Steroid Therapy in Kawasaki Disease

Treatment with high-dose intravenous gamma globulin (IVIG) and aspirin is the standard of care for children with acute Kawasaki disease. This multicenter, randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of pulse steroid therapy, when added to conventional treatment with IVIG plus aspirin, for treatment of children with acute Kawasaki disease. The hypothesis was that the addition of methylprednisolone would result in less dilation of coronary arteries and fewer aneurysms. The primary endpoint was coronary artery z-score measured five weeks after randomization. The results of this study in 199 subjects showed that addition of methylprednisolone to conventional therapy for acute Kawasaki disease was associated with more rapid resolution of serum inflammatory markers. Despite this, methylprednisolone did not improve coronary outcomes, adverse events, or total hospital or fever days.⁸⁾

3. Trial of ACE Inhibition in Infants with Single Ventricle

Angiotensin converting enzyme (ACE) inhibitors are widely used in the treatment of infants with severe congestive heart failure to improve cardiac function and somatic growth. This randomized, double-blind, placebo-controlled trial will evaluate the efficacy and safety of administering the

ACE inhibitor, enalapril, to infants with a functional single ventricle.⁹⁾ Infants up to age 45 days with single ventricle physiology and stable systemic and pulmonary blood flow were eligible. The hypothesis is that growth at age 14 months will be greater in infants receiving enalapril therapy compared with those infants receiving placebo. The primary endpoint is weight-for-age z-score at age 14 months. Secondary aims include comparison of other measures of somatic growth (height- and head circumference-for-age z-scores), signs and symptoms of congestive heart failure, developmental indices, and echocardiographic measures of ventricular mass, volume and function in the subjects in the two groups. Enrollment of the target 230 subjects and all study procedures have been completed; data analysis has just begun.

4. Trial of ACE Inhibition Therapy in Children with Mitral Regurgitation after Repair of an Atrioventricular Septal Defect

ACE inhibition therapy may decrease the severity of mitral regurgitation and, thus, decrease left ventricular size in asymptomatic patients. However, studies performed in animals and humans have shown conflicting results regarding efficacy of these medications. This randomized, double-blind, placebo-controlled trial was designed to evaluate the efficacy and safety of enalapril therapy initiated 6 to 18 months after repair of an atrioventricular septal defect in children under age 5 years who had at least moderate mitral

regurgitation. The hypothesis was that the change in left ventricular size will be decreased in patients receiving ACE inhibition therapy. The primary endpoint was the change in left ventricular end-diastolic dimension body surface area (BSA)-adjusted z-score. This study was begun in mid-2004 but was stopped because of lack of enrollment. Enrollment was limited by the small number of available patients with moderate mitral regurgitation (defined by left ventricular end-diastolic dimension BSA-adjusted z-score ≥ 2.0 and either a proximal regurgitant jet area $\geq 6 \text{ mm}^2/\text{m}^2$ or a regurgitant fraction $\geq 30\%$) and lack of equipoise by some investigators at the enrolling sites.

5. Variability of Echocardiographic Left Ventricular Mass, Volume and Ejection Fraction in Pediatric Patients with Congestive Cardiomyopathy

Cardiomyopathy is an important cause of chronic disability and death in pediatric patients. These patients currently account for approximately 50% of cardiac transplants performed during childhood. The limited availability of quantitative longitudinal data concerning indices of ventricular function in this patient population is a major impediment to developing trials of therapy for ventricular dysfunction in children. Knowledge of the longitudinal variation in these indices is essential for study endpoint selection, sample size calculations, and determining study feasibility. This observational study will provide these data and will also quantitatively evaluate the relative contribution of several potentially controllable sources of intra- and interstudy variability. The primary aim is to quantify interstudy variability (that is, the variance of change in measurements over time) in echocardiographically-determined left ventricular end-diastolic volume z-score, mass z-score, and ejection fraction z-score. Secondary aims include evaluation of interstudy variability of other echocardiographic indices of ventricular function and quantification of the relative contribution of definable sources of interstudy variability. Enrollment of the target 131 subjects is complete and data analysis will begin after follow-up echocardiographic examinations have been obtained for all subjects 3–18 months after the baseline study.

6. Trial of Right Ventricular vs. Modified Blalock-Taussig Shunt in Infants with Single Ventricle Defect Undergoing Staged Reconstruction (Single Ventricle Reconstruction Trial)

Patients with hypoplastic left heart syndrome and other

single right ventricle conditions constitute the highest-risk group of patients with congenital cardiovascular malformations. The Norwood procedure transformed care of these patients but hospital mortality remains as high as 24%. Recently, a few small, non-randomized studies have reported short-term improvements in survival with placement of a right ventricle-to-pulmonary artery shunt to provide pulmonary blood flow after the Norwood procedure instead of the standard modified Blalock-Taussig shunt.^{10, 11)} The right ventricle-to-pulmonary shunt has the theoretical advantage of eliminating aortic diastolic run-off and coronary arterial steal. The long-term outcome of these patients is unknown and no data are available comparing their outcome to contemporary outcomes in patients after the Norwood procedure with Blalock-Taussig shunt. This multicenter, randomized trial will compare outcomes in patients with hypoplastic left heart syndrome or other single right ventricle anomalies who are randomized to the Norwood procedure with either a Blalock-Taussig shunt or the right ventricle-to-pulmonary artery shunt.¹²⁾ The hypothesis is that placement of a right ventricle-to-pulmonary artery shunt will be associated with a decrease in the combined endpoint, mortality, or transplantation, when compared with the standard Blalock-Taussig shunt. The primary endpoint is the rate of death or cardiac transplantation 12 months after randomization. Secondary aims include post-operative morbidity after the Norwood and stage II palliation procedures, right ventricular function and pulmonary artery growth at the time of the stage II palliation, and neurodevelopmental outcome at 14 months. The incidence of adverse events will also be compared between the treatment groups. Enrollment of the target 554 subjects was begun in May, 2005. Enrollment by 15 clinical sites was completed in July, 2007. Publication of the results of this trial is anticipated in late 2009, after all subjects have completed the study procedures at age 14 months.

This is an example of a study that was originally conceived by investigators outside of the PHN who approached the PHN about the possibility of collaboration because of ability of the PHN infrastructure to provide the number of subjects needed to adequately power the study. This trial represented an important milestone for the PHN because it is the first active collaboration with cardiovascular surgeons and the first randomized surgical trial. This collaborative effort has established a model by which other operative interventions for patients with congenital and acquired pediatric heart disease can be evaluated.

7. Single Ventricle Reconstruction Trial Extension

The Single Ventricle Reconstruction Trial cohort provides a valuable database of surgical morbidity and mortality, cardiac, and neurodevelopmental outcomes. However, the design of this trial included a minimum follow-up of only 14 months after the first surgery. The primary aim of the extension study is to compare transplant-free survival at 6 years for subjects assigned to one of the two surgical strategies. All subjects who were randomized in the Single Ventricle Reconstruction Trial will be included in analysis of this endpoint. Secondary outcome variables will include measures of right ventricular function; clinical status including the incidence of heart failure and arrhythmias; the operative and post-operative course at the Fontan completion; and measures of neurodevelopmental outcome, behavior, health-related quality of life, and family function. This study will also collect biological specimens for storage in a central repository for future genetic and biomarker studies.

8. Trial of Beta Blocker Therapy (atenolol) vs. Angiotensin II Receptor Blocker Therapy (Losartan) in Individuals with Marfan Syndrome (Marfan Trial)

Marfan syndrome is a systemic disorder of connective tissue involving the ocular, musculoskeletal, and cardiovascular systems. This syndrome is caused by mutations of the *FBNI* gene that encodes fibrillin-1, the major glycoprotein component of extracellular microfibrils. Cardiovascular pathology, including aortic root dilation and dissection, is the leading cause of mortality. Beta-blocker therapy is commonly administered to patients with Marfan syndrome to delay or prevent aortic aneurysm and dissection. The majority of published studies have demonstrated that aortic root growth may be slowed with beta blockade, but not stopped or reversed.

Dietz and colleagues have developed a fibrillin-1 deficient mouse model that demonstrates many of the phenotypic features of Marfan syndrome in humans.¹³⁾ This group has shown that administration of the angiotensin II type 1 receptor blocker (ARB), losartan, to fibrillin-1 deficient mice completely arrests abnormal aortic growth and appears to promote aortic wall remodeling.¹³⁾ On the strength of the animal data, PHN investigators and Dietz designed a clinical trial to determine if these findings are applicable to humans with Marfan syndrome.¹⁴⁾

The primary aim of the study is compare the effect of atenolol therapy to that of losartan therapy on the rate of

aortic growth and progression of aortic regurgitation. Secondary endpoints include incidence of the following cardiovascular events: aortic dissection, aortic root surgery, and death; progression of mitral regurgitation; left ventricular size and function; echocardiographically-derived measures of central aortic stiffness; skeletal and somatic growth; and incidence of reported adverse drug reactions. The total sample size target of 604 participants will be recruited over approximately 36 months. As of 31 October 2008, the 8 core Clinical Centers and 22 auxiliary enrolling sites have enrolled and randomized 316 subjects in this trial. The results of this study will make an important contribution to the management of a relatively common and often devastating disorder, and may also be applicable to other disorders predisposing to aortic dilation.

Challenges and Opportunities

Design and conduct of complex, multicenter studies in children with congenital and acquired heart disease must address numerous challenges. Identification of an appropriate clinically-relevant primary endpoint is often difficult because of the lack so-called “hard”, endpoints such as mortality or life-threatening morbidity in pediatric cardiology patients.^{1, 15)} Quality of life is clinically relevant, but age- and disease-specific measures are limited. Surrogate endpoints such as laboratory measurements or physical signs may not be correlated with a clinically meaningful endpoint. Evaluation of outcome measures as potential study endpoints is an important function of the PHN.

An accurate estimate of the outcome rate in the control group of a clinical trial is required to calculate the sample size necessary for adequate statistical power. Preliminary data on which to base these sample size calculations are often not available. Data from registries may provide current information on the frequency and distribution of specific morbidities that can be used to generate hypotheses and facilitate the design of prospective trials. The PHN expects that longitudinal data collected for patients with specific conditions will provide data to plan intervention trials.

Recruitment of an adequate number of subjects with relatively rare conditions such as protein losing enteropathy is often difficult if not impossible. The PHN has worked to increase the number of potential subjects by recruiting auxiliary enrolling sites for certain studies such as the Single Ventricle Reconstruction Trial and the Marfan Trial.

Recruitment of patients to a clinical trial may also be lim-

ited by lack of investigator equipoise. Equipoise means that the investigators are not certain which treatment is best. Some physicians feel strongly that certain therapies are effective (“true belief”), thus making it difficult to randomize patients. These concerns or “beliefs” can easily be transferred to other staff and to patients and families. Other issues that affect recruitment include the complexity of the informed consent process, concern about potential effects on the doctor-patient relationship, loss of autonomy, mistrust of clinical research, and discomfort with open discussion about uncertainties in medical practice.¹⁶⁾ These issues can deter families from enrolling their children in studies, and also can deter physicians from encouraging enrollment. The PHN assists in educating the medical community caring for pediatric cardiology patients about the benefits of randomized clinical trials.

Despite these challenges, the PHN is uniquely positioned to perform rigorous, efficient, and cost-effective studies in pediatric patients with congenital and acquired heart disease. Since 2001, PHN efforts have contributed to the science of pediatric cardiology and have provided insights into the design and conduct of complex multicenter studies in children with complex defects. The results of PHN studies will permit those taking care of children with heart disease to evaluate clinical practice critically and will provide data for an evidence-based rationale to support decisions in clinical practice.

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