

# The Pediatric Heart Network: A Primer for the Conduct of Multicenter Studies in Children with Congenital and Acquired Heart Disease

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# The Pediatric Heart Network: A Primer for the Conduct of Multicenter Studies in Children with Congenital and Acquired Heart Disease

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## ABSTRACT

Most contemporary diagnostic and treatment strategies for pediatric patients with cardiovascular disease are not supported by evidence from clinical trials but instead are based on expert opinion, single-institution observational studies, or extrapolated from adult cardiovascular medicine. In response to this concern, the National Heart, Lung, and Blood Institute established the Pediatric Heart Disease Clinical Research Network (PHN) in 2001. The purposes of this article are to describe the initiation, structure, and function of the PHN; to review the ongoing studies; and to address current and future challenges. To date, four randomized clinical trials and two observational studies have been launched. Design and conduct of complex, multicenter studies in children with congenital and acquired heart disease must address numerous challenges, including identification of an appropriate clinically relevant primary endpoint, lack of preliminary data on which to base sample size calculations, and recruitment of an adequate number of subjects. The infrastructure is now well developed and capable of implementing complex, multicenter protocols efficiently and recruiting subjects effectively. The PHN is uniquely positioned to contribute to providing evidence-based medicine for and improving the outcomes of pediatric patients with cardiovascular disease.

**KEYWORDS** Clinical trials - Congenital heart disease - Pediatric clinical research

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**T**reatment of pediatric patients with congenital and acquired heart disease involves medical, surgical, and catheter-based approaches. Important improvements in morbidity, mortality, and quality of life [Z] may have been limited by most contemporary treatments being based on expert opinion, single-institution observational

studies, or extrapolated from adult cardiovascular medicine. Few contemporary treatment strategies in pediatric heart disease are supported by evidence from clinical trials.

Unfortunately, substantial barriers exist to conducting clinical trials for pediatric patients with cardiovascular disease. One of the most important is the heterogeneity of conditions and the small number of individuals with a particular malformation or condition that can be recruited and studied at a single clinical center. Another difficulty is the lack of suitable, clinically relevant, or so-called “hard,” endpoints in pediatric cardiology patients [12]. Additional barriers to clinical trials involving these patients include anecdotal-based treatment of particular problems both within and among centers; the absence of systematic, centralized databases; potential lack of therapeutic equipoise; the absence of an infrastructure for clinical trials; ethical considerations involved in performing research studies in children compared to adults; and the lack of resources to provide coordination of collaborative efforts at multiple study sites.

The National Heart, Lung, and Blood Institute (NHLBI), in response to the need to develop and apply evidence-based approaches to pediatric cardiovascular problems, established the Pediatric Heart Disease Clinical Research Network (PHN) in 2001. The PHN is a cooperative network of seven clinical centers and one data coordinating center (DCC). 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 network approach is an effective, flexible way to study adequate numbers of patients with uncommon diseases, such as congenital cardiovascular malformations. Efficiencies are achieved through a common infrastructure with standardized methods for recruiting, monitoring, and following subjects. The Neonatal Network [6] and the Maternal Fetal Unit Medicine Network [15] are examples of successful National Institutes of Health (NIH) networks. The purposes of this article are to describe the initiation, structure, and function of the PHN; to review the ongoing studies; and to address current challenges and opportunities.

### ESTABLISHMENT OF THE PHN

The NHLBI issued a request for applications (RFA) in 2000 to solicit applications for clinical centers and a DCC to participate in the PHN. The RFA described the general structure and requirements of the network based on others funded by NHLBI, provided budget guidance, and described review criteria for clinical centers and DCCs [9]. Each clinical center applicant was instructed to propose a research plan that included two protocols as models that could potentially be used in a network environment. DCC applicants were asked to discuss plans for coordination of research in a network, selection of procedures for core laboratories, and data management and analysis.

Peer review of applications was conducted by a special emphasis panel convened by the NHLBI and then by the NHLBI advisory council. In addition to standard criteria, applications were evaluated for evidence of an established research program in the area of congenital and acquired heart disease, experience and expertise in conduct of clinical studies, and demonstrated access to a sufficient number of patients to accomplish their portion of the proposed protocols. On the basis of priority scores and available funds, seven clinical centers and one DCC (see Appendix) were selected to participate in the PHN.

### STRUCTURE OF THE PHN

The steering committee functions as the main governing body of the PHN and is responsible for developing all policies and procedures. The steering committee consists of the principal investigator from each participating clinical center and the DCC and also the NHLBI program officer. The network

chair, who is not affiliated with any of the seven clinical centers, heads the steering committee. The steering committee selects topics for investigation and then oversees the design of study protocols, the implementation of studies, the analysis and interpretation of data, and the dissemination of study findings.

The DCC is responsible for overall coordination of operations and protocols. This includes (1) all phases of protocol development and implementation; (2) training of clinical center staff to conduct each protocol; (3) preparation of protocol manuals of operation; (4) design, testing, and maintenance of data collection and management systems; (5) ensuring data safety and confidentiality; (6) implementation of systems and procedures for quality assurance including site visits; (7) conduct of data analyses and collaboration on manuscripts; and (8) setting up systems for electronic communications, administrative management, and coordination. To accomplish these tasks, the DCC has a multidisciplinary staff led by an experienced clinical trialist. The team is composed of biostatisticians, project directors, a clinical investigator and clinical/regulatory research associate, administrative research coordinators, data managers, research assistants, technical programming staff, and consultants necessary to manage multiple, concurrent studies.

Clinical center investigators 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 are responsible for subject recruitment and conduct of required tests for the approved studies. This includes completing the required human subjects education certification process, obtaining local institutional review board (IRB) approval, setting up the research pharmacy if needed, and educating clinical staff about what to expect with each study. Once recruitment of subjects begins, the nurse coordinators are primarily responsible for communication with families, coordination of the study visits and tests, completion and submission of standardized study forms, and preparation of adverse events reports following NHLBI and Food and Drug Administration guidelines. Members of the clinical centers, the network chair, the DCC, and the

NHLBI staff collaborate in disseminating information that describes the network and reporting the results of the clinical studies through presentations, abstracts, and manuscripts.

## STANDING COMMITTEES

Standing committees are necessary to support the complex operations of a multicenter clinical research program.

- The Publications, Presentations, and Ancillary Studies Committee facilitates and supervises preparation of all abstracts, presentations, and manuscripts before submission to ensure timely preparation of high-quality presentations and publications on behalf of the PHN.
- Each protocol may require one or more core laboratories for centralized interpretation of specific study measures. The Core Laboratory Selection Committee reviews submitted proposals, with the assistance of expert technical consultants if needed.
- The Nurse Coordinators' Committee consists of the 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.

## OVERSIGHT COMMITTEES

The PHN has two oversight committees: the Protocol Review Committee (PRC) and the Data and Safety Monitoring Board (DSMB) (see Appendix). Both committees were established by NHLBI and consist of individuals who do not have close professional relationships to PHN investigators. The PRC, which is analogous to a standing NIH study section, assesses the scientific merit of all proposed protocols. The DSMB reviews protocols, data forms, and consent forms after PRC approval is obtained and all protocol amendments once studies are under way. In addition, PHN study

data, including adverse events by study arm, are reviewed to ensure the safety of study subjects. The DSMB also advises NHLBI on data quality and analysis and ethical and human subject issues.

## DEVELOPMENT OF STUDY PROTOCOLS

The first studies the PHN investigators considered were the two protocols included in each clinical center's grant application. Subsequently, other ideas for studies were developed. All proposed studies are presented at steering committee meetings and evaluated on the basis of scientific rigor, feasibility within the network structure, and clinical relevance. In considering studies, the steering committee has found that some scientifically meritorious but technically demanding studies are not appropriate for all centers in the network, and that some less complex studies could easily be performed at all centers but may lack clinical importance. The goal has been to design studies with high clinical importance that can be performed at all PHN centers.

The steering committee rapidly developed a structure for presentation of proposed studies so that discussion would first focus on design features such as primary endpoint selection and sample size. After discussion, the steering committee votes on study proposals by secret ballot. A subcommittee is then formed to develop an approved proposal into a full study. Protocol subcommittees are chaired by the investigator who initially proposed the study and are composed of physicians representatives from each clinical center, scientists and staff of the DCC, and several nurse coordinators. Ongoing communication between the protocol development subcommittees and the investigators and nurse coordinators at the individual clinical centers is essential to ensure that the protocol is feasible and has the support of the local practitioners. After approval by the PRC and the DSMB, the final protocol is distributed to all participating clinical centers and to the DCC for submission to local IRBs.

As part of their grant award, each clinical center receives a core budget to support general PHN operations. Budgets for each study are developed after the protocol and forms are finalized, and they reflect the average per-patient cost of study-related

procedures. All centers receive the same per-patient amount. Each center apportions the money as needed to execute the protocol at its institution.

### ANCILLARY 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. Investigators are encouraged to propose and to conduct ancillary studies, particularly multicenter ancillary studies. Such studies can enhance the value of the main PHN studies and ensure the continued interest of a diverse group of investigators. Ancillary studies provide an exceptional opportunity for investigators, whether within or outside of the PHN, to conduct additional research at minimal cost.

### PHN STUDIES

To date, the PHN has implemented four randomized clinical trials (Table 1). Enrollment in the Kawasaki disease trial is complete and data analysis is under way. Enrollment is ongoing in the other three trials. The Trial of Right Ventricular vs. Modified Blalock–Taussig Shunt in Infants with Single Ventricle Defect undergoing Staged Reconstruction is an example of a study that was originally conceived by investigators outside of the PHN who then approached the PHN about the possibility of collaboration because of the need for additional subjects to power the study adequately. If successful, this study will establish a model by which other operative interventions for patients with congenital and acquired pediatric heart disease can be evaluated.

**Table 1** Pediatric Heart Network randomized clinical trials

Title	Objective	Hypothesis	Primary outcome	Secondary outcomes
Trial of Pulse Steroid Therapy in Kawasaki Disease	Randomized, double-blind, placebo-controlled trial to evaluate 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	Addition of methylprednisolone will result in less dilation of coronary arteries and fewer aneurysms	The larger of the BSA-adjusted dimensions (z scores) of the proximal right coronary artery or proximal left anterior descending artery, measured 5 weeks after randomization	Duration of fever after completion of IVIG, CRP 1 week after randomization, and incidence of adverse events
Trial of Ace Inhibition in Infants with Single Ventricle	Randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of enalapril administration to infants with a functional single ventricle	Weight at age 14 months will be greater in infants receiving enalapril therapy compared to those infants receiving placebo	Weight-for-age z score at age 14 months	Other measures of somatic growth, signs, symptoms of congestive heart failure, neuro developmental outcome at 14 months, and echocardiographic measures of ventricular mass, volume, and function
Trial of Ace Inhibition Therapy in Children with Mitral Regurgitation after Repair of an Atrioventricular Septal Defect	Randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of enalapril administration to children of age less than 18 years who have at least moderate mitral regurgitation after repair of an atrioventricular septal defect	The change in left ventricular size will differ for patients receiving enalapril the rapyvs placebo	Change in left ventricular end diastolic dimension BSA-adjusted z score	Changes in echocardiographic measures of left ventricular geometry and hemodynamics, change in level of neurohormonal activation evaluated by measurement of B-type natriuretic peptide, and the incidence of adverse effects

Trial of Right Ventricular Modified Blalock–Taussig Shunt in Infants with Single Ventricle Undergoing Staged Reconstruction	Prospective trial to compare outcomes in patients with hypoplastic left heart syndrome or other single right ventricle anomaly randomized to either a modified Blalock–Taussig or the right ventricular-to-pulmonary artery shunt as part of the Norwood procedure	Placement of a right ventricular-to-pulmonary artery shunt in infants with hypoplastic left heart syndrome or similar single right ventricular anomaly will be associated with a lower composite event rate when compared with the standard modified Blalock–Taussig shunt.	Death or cardiac transplantation 12 months after randomization	Postoperative morbidity following the Norwood procedure and stage II palliation (bidirectional Glenn anastomosis or hemi-Fontan procedure), right ventricular function and pulmonary artery growth at the time of the stage II palliation, neurodevelopmental outcome at 14 months, and the incidence of adverse events
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IVIG, intravenous immune globulin. BSA, body surface area

The PHN has also implemented two observational studies (Table 2). Data collection is complete for the Fontan Cross-Sectional Study and manuscript preparation is in progress. The information gained

from this study will provide a basis for subsequent randomized clinical trials in this and other cohorts of patients with functional single ventricles.

**Table 2** Pediatric Heart Network observational studies

Title	Goals	Variables measured
The Relationship between Functional Health Status and Laboratory Parameters of Ventricular Performance after the Fontan Procedure	Cross-sectional study seeks to identify a quantifiable measure of cardiovascular performance that correlates with clinical outcome as measured by a validated quality of life assessment in patients after the Fontan procedure	Maximal exercise testing, echocardiography, cardiac MRI, measurement of brain natriuretic peptide, and parental report and child report child health questionnaires
Variability of Echocardiographic Left Ventricular Mass, Volume, and Ejection Fraction in Pediatric Patients with Congestive Cardiomyopathy	Observational study to provide quantitative longitudinal data concerning indices of ventricular function in pediatric patients with congestive cardiomyopathy. Interstudy variability in echocardiographically determined left ventricular end diastolic volume z score, mass z score, and ejection fraction z score will be quantified	Interstudy variability of other echocardiographic indices of ventricular function, and quantification of the relative contribution of definable sources of interstudy variability

The limited availability of quantitative longitudinal data concerning indices of ventricular function in pediatric patients with cardiomyopathy 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. The Variability of Echocardiographic Left Ventricular Mass, Volume and Ejection Fraction in Pediatric Patients with Congestive Cardiomyopathy study was designed with the aim of providing such data.

## Challenges

### SELECTION OF PRIMARY ENDPOINT

The primary endpoint selected for a prospective trial should be clinically meaningful; that is, it

should measure how a subject survives, feels, or functions [1, 16]. Such endpoints are often difficult to evaluate in pediatric cardiology patients [11, 12]. Discrete events such as death and major complications are relatively rare. This often makes performing an adequately powered study using these endpoints difficult within a reasonable time frame. Outcomes such as neurodevelopmental status are difficult and costly to measure reliably, and they require a long follow-up period with repeated assessments for maximal validity, thus prolonging the time necessary to evaluate the study intervention. Quality of life measures are often used as primary endpoints in adult studies of heart failure [10], but there are few validated instruments for pediatric cardiology patients, and before the PHN, no studies were available correlating quality of life measures with other patient outcomes. The lack of knowledge regarding these correlations and the

variance of outcome measures in pediatric cardiology populations led to the PHN developing two observational studies (Table 2) that are intended to obtain data to support the selection of meaningful and properly powered endpoints in future studies. Because of the difficulties in identifying clinically relevant primary endpoints, investigators in other fields have turned to surrogate markers as outcome measures [2, 5, 13]. These measures are usually laboratory measurements or physical signs, and they are expected to predict a clinically meaningful endpoint. The use of surrogate outcome measures allows all subjects in the trial to contribute to the study endpoint, which may decrease the number of subjects needed and thus may reduce the length of the study necessary to achieve statistically significant results. Research based on surrogate endpoints, when the surrogate is a valid predictor of clinical outcome, can bring treatment benefits to patients years before information on long-term outcome becomes available, and at a relatively low cost. However, reliance on a surrogate when the surrogate does not predict clinical benefit can lead to the adoption of futile or even harmful therapies. For most trials in pediatric cardiology, it may be unrealistic to define survival benefit, but it may be possible to use an intermediate endpoint, such as exercise tolerance or ventricular function, as an outcome measure. Evaluation of outcome measures as potential study endpoints is an important function of the PHN.

### ESTIMATION OF SAMPLE SIZE

Determining an accurate estimate of the outcome rate in the control group is required to calculate the sample size necessary for adequate statistical power. We have found it necessary to conduct formal chart reviews to estimate current event rates rather than relying on historical data because event rates for many conditions of interest change relatively rapidly.

Subjects in the control (placebo) group of a clinical trial tend to do better overall than comparable patients not being studied [3, 4]. This phenomenon increases the risk of a negative result or of a trial being stopped early for futility. Faced with this situation, investigators in the Maternal Fetal Medicine Units Network have concluded that the best source of data for sample size estimation is another randomized trial or a prospective

observational study of similar size and complexity [15]. Another approach to this problem is to establish a registry that provides current information on the frequency and distribution of specific morbidities [6]. The PHN is considering establishing one or more registries for patients with specific conditions with the expectation of using the data to plan prospective trials.

The required sample size for a study is also a function of the magnitude of the treatment difference investigators wish to measure. After the outcome rate in the control group is determined, the size of the minimum clinically significant treatment difference must be specified. More subjects are needed to evaluate smaller treatment differences, but a trial designed to detect only a large risk reduction may miss clinically important treatment benefits [13, 16].

### NUMBER OF POTENTIAL SUBJECTS

Accurately defining the number of potentially available subjects is challenging for several reasons. The individual clinical centers were initially asked to review their databases to determine the number of patients with a certain diagnosis. This approach resulted in an overestimation of the number of patients who would ultimately meet eligibility criteria, a phenomenon also reported by the Maternal Fetal Medicine Units Network [15]. One unforeseen issue was that the centers in the PHN have national reputations for excellence and thus attract patients from long distances. These patients are often followed by a pediatric cardiologist near their homes and do not return to the study center for routine care, making studies that require follow-up at the original PHN center impractical. Even if the study pays for transportation and lodging, logistical considerations for the family may preclude participation in the study.

### SUBJECT RECRUITMENT

The timing of a trial is critical to recruitment success. For example, the introduction of any new procedure is accompanied by a learning curve. Before a study can be implemented, time must be allowed for all clinical centers to develop sufficient experience with the new therapy so that outcomes will not reflect a learning curve. On the other hand, the trial must be started before therapeutic equipoise is lost and the treatment becomes standard of care

despite any evidence beyond anecdotal reports that it is the best approach.

Relatively few multicenter clinical studies and even fewer randomized clinical trials have been performed in pediatric cardiology patients [8]. As a result, many individual caretakers are resistant to random allocation of treatment (including the use of a placebo) and to study-imposed testing. Some physicians strongly believe 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 [3]. These issues can deter families from enrolling their children in studies and can also 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.

### PATIENT SAFETY

Effective and timely evaluation of adverse events using a standardized grading system is critical to the success of the PHN because studies are being performed in a vulnerable population. The complexity of adverse event monitoring varies by study, but it is particularly time-consuming and complex in young subjects with functional single ventricles. The presence of an underlying condition associated with a high frequency of serious adverse events makes it challenging to detect when and if a study treatment causes an increase in the frequency of an event.

### FUTURE OPPORTUNITIES

The PHN network is uniquely positioned to perform rigorous, efficient, and cost-effective studies in pediatric patients with congenital and acquired heart

disease. Since 2001, network 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 should provide clinicians with the evidence base to support decisions in clinical practice.

Developing an adequate clinical research workforce is critical to ensuring the success of clinical research [14]. Involvement in the PHN has accelerated development of a clinical trials infrastructure at the participating and collaborating institutions. The clinical centers are encouraged to involve junior faculty in PHN activities, such as conference calls and meetings of the steering committee. This exposure to the clinical trials process has resulted in some junior investigators being appointed to be the lead investigator at their own site for an ongoing network study. The clinical center principal investigators work hard to ensure that their junior colleagues receive appropriate academic recognition for their involvement in PHN trials.

### SUMMARY

The PHN was established because of the critical importance of evidence-based approaches to patient management, the need for well-designed clinical investigations, and to eliminate barriers to research studies in a vulnerable population such as pediatric patients with cardiovascular disease. Everyone involved in the PHN has collaborated energetically to overcome many of these barriers and to meet each challenge. The well-developed infrastructure now allows efficient implementation of complex multicenter protocols and effective subject recruitment. Every new study undertaken is improved by the lessons learned from previous studies. The accomplishments of the PHN will permit those taking care of children with heart disease to evaluate clinical practice critically and will provide data for an evidence-based rationale for diagnostic and therapeutic options.

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## APPENDIX

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