



Pediatric Heart Network Policy Manual

Operational Procedures & Guidelines



**Pediatric Heart
Network (PHN)**

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Pediatric Heart Network Overview

1.1 Background

The Pediatric Heart Network (PHN) is a cooperative program of Clinical Centers, Data Coordinating Center (DCC), and independent Protocol Chair and PHN (Network) Chair, funded by the National Heart, Lung, and Blood Institute (NHLBI) beginning in September 2001 through the cooperative agreement award mechanism.

The PHN was established by NHLBI in recognition of the major barriers to clinical studies in pediatric heart disease, including the heterogeneity of conditions, the small numbers of patients with a particular malformation or condition at any one center, differences in treatment approaches among centers, absence of systematic centralized databases, and lack of resources and infrastructure to provide national coordination of collaborative efforts. NHLBI networks have proven to be an effective, flexible way to study adequate numbers of patients with uncommon diseases through a common infrastructure for recruiting, monitoring, and following patients. Networks also provide a platform to train junior investigators in pediatric clinical research, and serve as a vehicle for translational research.

The PHN cannot answer all scientific questions pertaining to pediatric heart disease, but many important clinical problems can be addressed within its structure. Studies undertaken to date and their associated publications can be found at the [PHN's public web site](#).

1.2 PHN Mission Statement

The mission of the PHN is to improve health outcomes in patients with pediatric acquired and congenital heart disease; disseminate collaborative findings as the basis for improved evidence-based treatment options and standards of care; train and educate new investigators, and provide support and advocacy for families during the conduct of excellent, ethical clinical research.

1.3 PHN Organization

The organization structure of the PHN is shown in [Figure 1.1](#). The roles of the collaborative components shown in this Figure are explained in this Chapter and in [Chapter 2](#).

1.3.1 PHN Chair

NHLBI has the discretion to appoint a PHN (Network) Chair, who would typically not be affiliated with any of the core clinical centers. The PHN Chair would serve as the Chair for all Steering and Executive Committee calls and meetings, and oversee the functions and conduct of the Executive and Steering Committees. With the DCC

Principal Investigators (PIs) and the NHLBI Project Scientists, the PHN Chair would contribute to overall guidance for the PHN., and work with the Protocol Chair and clinical center investigators to develop clinical research protocols.

1.3.2 PHN Protocol Chair

NHLBI has the discretion to appoint a PHN Protocol Chair. The Protocol Chair is appointed by the NHLBI and is not affiliated with any of the core clinical centers. The Protocol Chair provides overall guidance for the selection and development of new Network studies and works with clinical center investigators to develop clinical research protocols. The Protocol Chair is eligible to participate in Study and Writing Committees.

1.3.3 Clinical Centers

Clinical Centers are selected to participate in the PHN after rigorous peer review, and meet the minimum requirements for participation. These include appropriate experience and expertise to conduct clinical studies in congenital and acquired pediatric heart disease, an established research program, and demonstrated access to a sufficient number of patients to accomplish their portion of the proposed protocols. Clinical Centers must be dedicated to the standards of the PHN and demonstrate an ability to cooperate with other PHN centers in collaborative research.

NHLBI expects that PHN Clinical Centers will participate in all studies. During the proposal process, Clinical Center PIs are expected to discuss potential studies extensively with the relevant personnel at their centers to determine feasibility. Any serious issues with feasibility should be discussed with other members of the Study Committee and Steering/Executive Committees as necessary, and may be a basis for determining that a study is not feasible in the PHN. Only when it has been determined that a proposed study is feasible at all PHN sites will it be considered for formal development as a study protocol. In the rare event that a study is considered to be high priority, but a clinical center is unable to participate, NHLBI will consider this on a case-by-case basis, and determine how to proceed. If the study is implemented, it is likely that financial penalties in the form of reduced core costs would be incurred by the non-participating clinical center. Every Center's progress and contribution to PHN studies is reviewed annually by NHLBI. If any Center is consistently unable to contribute to PHN studies, their participation in the PHN may be terminated before the end of the five-year grant period.

A Clinical Center may consist of a consortium of sites, referred to as a 'main' site and 'sub-sites'. The main site is responsible for 1) disbursement of per-patient reimbursement funds to other members of the consortium (the sub-sites); 2) ensuring that all consortium members have resources to attend required study protocol trainings; and 3) making certain that the sub-site investigators and staff participate in required network conference calls (e.g., SC, Nurse Coordinator, and Protocol Committee calls). A sub-site may participate in all PHN studies or selected studies, as is deemed appropriate by the Clinical Center PI. The enrollment contribution of all institutional members of the consortium contributes towards the enrollment target of the Clinical Center.

a. Principal Investigator Responsibilities

Clinical Center PIs bear the overall responsibility for their Center's participation and performance in the PHN. To provide the expertise required to direct a PHN Clinical Center, the PI must be a pediatric cardiologist. The PI appoints all co-investigators, hires and supervises key personnel, ensures the ethical conduct of research, and represents the Clinical Center on the Executive and Steering Committees. The PI or designee is responsible for contributing to the development of new protocols, analyses and publications, monitoring the conduct of PHN studies, monitoring data collection, and ensuring adherence to quality assurance measures. This requires that mechanisms be in place at each Clinical Center to promote both formal and informal communication among all PHN study staff. NHLBI will assess the adequacy of these mechanisms during site visits. The PI is responsible for ensuring that the necessary financial arrangements, Institutional Review Board (IRB) approvals, and federal assurances are in place before participation in each study. Each center PI should have a plan for training new investigators. In addition, the PI is ultimately responsible for all regulatory and reporting requirements.

b. Change in Status of a Principal Investigator

If a PI leaves the institution or is not able to continue to provide the appropriate time and effort to direct the Center, another PI must be designated when there is no official multiple PI plan or when the PI is only one of two in a multiple PI plan. The NHLBI program office must approve all replacements. The current PI must submit a letter to the NHLBI program office, countersigned by the local business official, outlining the justification for the individual recommended to replace the PI, and should include that individual's NIH Biosketch and statement of other support. The new PI should meet the requirements outlined in the RFA for the current funding cycle, and have adequate time to devote to PHN studies. Ideally, this individual would already have PHN experience as a co-investigator.

c. Co-Investigators

Co-Investigators play an important role in PHN activities. Co-Investigators can serve as the chair of a PHN study, as the local PI of a PHN study, on protocol development committees and writing committees, and on standing PHN committees such as the Publications, Ancillary Studies, and Finance Committees. To the extent permitted by travel budgets, co-Investigators are expected to attend Steering Committee meetings and they always plan to participate in relevant conference calls.

d. Study Coordinators

Research Study Coordinators are research nurses or other individuals with comparable experience responsible for ensuring the successful conduct and coordination of PHN protocols under the direction of the PIs. Coordinators are responsible for the day-to-day management of PHN studies, including maintenance of the Center's PHN and protocol files and

ensuring adequate staffing, equipment, and supplies to support the needs of PHN studies implemented at the Clinical Center. Coordinators, together with the PIs, set up staff training systems and establish procedures to facilitate recruitment, to ensure adherence to protocols, and to assure the highest standards of protocol implementation, data collection and reporting. Study Coordinators have a significant role in determining the feasibility and estimated cost of study protocols at a given center. Study Coordinators also participate in protocol development, implementation, and abstract and manuscript writing committees as members of study committees, and can also propose ancillary studies. Study Coordinators are expected to attend Steering Committee meetings and other applicable PHN meetings and to participate in relevant conference calls.

e. Other Staff

The conduct of PHN studies requires a multidisciplinary team of professionals. Other staff members who contribute include clerical staff, research pharmacists, nurses, statistical/clinical trial specialists, physicians in related medical and surgical specialties, and other healthcare professionals. These individuals participate in protocol development and implementation as members of study committees, and in abstract and manuscript writing as appropriate and can also propose ancillary studies.

1.3.4 Data Coordinating Center

The DCC is responsible for scientific leadership in clinical research policies and procedures, study design, data analysis, dissemination of results, data management and quality control, site monitoring, and overall coordination of PHN operations.

The DCC is overseen jointly by a PI for Clinical and Statistical Science and a PI of Operations. The PIs have extensive experience in the design, conduct, and management of clinical trials according to Good Clinical Practice principles, and are responsible for the supervision and management of DCC staff to ensure the successful completion of PHN goals. The DCC Medical Co-Investigator advises DCC staff on clinical issues relevant to PHN trials and pediatric heart disease generally. The DCC PI of Clinical and Statistical Science leads the statistical team, collaborates closely with Clinical Center PIs and NHLBI staff on biostatistical issues related to the design, implementation, conduct, and analysis of PHN studies, and has reporting responsibilities to the Data and Safety Monitoring Board (DSMB) and the Protocol Review Committee (PRC). The PI of Operations has fiscal, administrative, and systems oversight of the DCC, coordinates activities performed by the DCC teams for implementation and conduct of PHN studies, and supervises non-statistical project staff, including project managers, data managers, programmers, and administrators. A PI or designee participates in every PHN committee meeting.

The DCC is primarily responsible for the following areas:

a. Study Design and Planning

The DCC advises and assists PHN investigators regarding study design including defining primary and secondary outcomes and the determination

of sample size and randomization schemes. DCC staff assists with protocol development and preparation of study materials, including identifying drug packaging and distribution contractors, identifying core laboratories, completing regulatory requirements, and preparing the final protocol, the manual of operations, and data collection forms for each study. DCC staff train and certify Clinical Center staff in study procedures and the use of the web-based database management system.

b. Study Conduct

The DCC provides and maintains secure, validated computerized data management systems, with capabilities for distributed and central data entry, editing and reporting of data. DCC staff monitors and reports on data quality, protocol adherence, and recruitment status, providing regular reports to study committees, the Steering Committee, and NHLBI. The DCC oversees subcontracts for any drug distribution facilities, specimen repositories, and core laboratories providing services for PHN studies. DCC staff will attend and assist in the coordination of site visits and other quality assurance activities.

c. Data Analysis

The DCC is responsible for all aspects of data analysis in the PHN. The DCC provides statistical consultation in planning manuscripts and ancillary studies, and conducts analyses for all publications and presentations. The DCC also will provide limited access data sets per NHLBI policy, and other limited data sets for defined types of ancillary studies (see Chapter 7). Study data reside centrally at the DCC, which is responsible for complete documentation of the study and archiving of the dataset.

d. Management of Patient Care Funds

The DCC is responsible for managing and distributing patient care funds. For each study, a site services agreement is established with each participating site, and patient care funds are distributed by the DCC according to the plan for that study.

e. Communication

The DCC is responsible for organizing regular conference calls and meetings of PHN committees, and for distributing all study documents, including meeting minutes, recruitment reports, protocols, manuals and data collection forms.

The DCC maintains two web sites. The [PHN NERI Connect site](#), which is password-protected, contains official study documents as well as meeting announcements and minutes, and complete contact information for all affiliated investigators and staff participating in the PHN. Materials for DSMB and PRC meetings and for in-person Steering Committee meetings are posted to the administrative web site. A partition of this site, which is further restricted to the medical monitor, DSMB Chair, and NHLBI staff,

contains summaries of serious adverse events subject to expedited reporting requirements.

The [PHN public web site](#) was developed and is maintained jointly by NHLBI and DCC staff. This site contains information for families and physicians, and is updated regularly as new publications are added, and study status changes.

1.3.5 NHLBI

The NHLBI, part of the National Institutes of Health (NIH) and the Department of Health and Human Services (DHHS), supports basic, translational, and clinical research in the areas of heart, lung, blood, and sleep disorders. The PHN is one of several networks funded by the NHLBI to promote collaborative investigation into pressing public health problems. The NHLBI Program Office staff consists of the Project Scientist and Deputy Project Scientist for the PHN, the PHN Coordinator, other medical officers, Executive Secretaries for the DSMB and PRC, the NHLBI Biostatistician, the Grants Management Specialist, and other staff as may be assigned.

a. Project Scientist and Deputy Project Scientist

The Project Scientist and Deputy Project Scientist are responsible for overall PHN operations, including policy development, implementation and conduct; budget formulation and resource allocation; and procedures for identifying new areas of research. They monitor and ensure the safe and effective execution of the program on a day-to-day basis. The Project Scientists are responsible for assuring the scientific merit as well as ethical performance of the research, including the option to withhold support for a participating center if performance requirements are not met. They may propose topics for data analysis leading to abstracts or papers, may lead or participate in manuscript preparation, and may propose but not lead ancillary studies. Per NHLBI publication policies, Project Scientists cannot be the first or senior author on a main results paper.

b. Executive Secretaries

The PHN Program Office, in conjunction with the Office of the NHLBI Director, will appoint Executive Secretaries for the PRC and the DSMB. The Executive Secretaries are responsible for the PRC and DSMB meetings, including monitoring the closed and executive sessions. The Executive Secretaries will contribute to the development of agendas for these meetings and will produce and distribute minutes from the meetings.

c. NHLBI PHN Coordinator

The NHLBI PHN Coordinator assists in the day-to-day management of the PHN and facilitates all PHN activities. This includes being an interface for the PHN study coordinators with NHLBI, attending site visits, reviewing all IRB-approved consent forms to insure consistency with NHLBI policy, reviewing adverse events, and assisting in protocol development and budget preparation. This individual may propose topics for data analysis

leading to abstracts or papers, may lead or participate in manuscript preparation, and may propose but not lead ancillary studies.

d. NHLBI Biostatistician

The NHLBI biostatistician provides statistical support to the Project Scientist and serves as an additional resource for PHN investigators during protocol development and data analysis. The NHLBI statistician attends the Steering Committee, PRC and DSMB meetings as the NHLBI's statistical expert.

e. NHLBI Grants Management Specialist

The NHLBI Grants Management Specialist (GMS) serves as an authority in grants management for the PHN. The GMS participates in the development and review of PHN fiscal policies and procedures. In addition, the GMS collaborates closely with the Program Office to develop per-patient reimbursement amounts for PHN protocols, reviews progress prior to issuing annual awards and periodic adjustments to awards, such as carrying funds forward from one fiscal year to the next. The GMS ensures that award recipients comply with all legal, regulatory and policy requirements, reviews and ensures that all contractual agreements are based on sound business principles, analyzes budgets and funding proposals, negotiates funding levels and terms of award with grantees, and issues finalized grant awards.

1.3.6 Auxiliary and Affiliate Sites

The fundamental structure of the PHN is established through a competitive process of solicitation of applications and peer review. Collaboration with other academic centers is encouraged, however, to foster broader research efforts in pediatric cardiovascular disease. Collaboration can take the form of joining a PHN study as an auxiliary or as an affiliate site, or participating with a PHN investigator on an ancillary study. (The process for participation in ancillary studies is described in detail in [Chapter 7](#) of this Manual.)

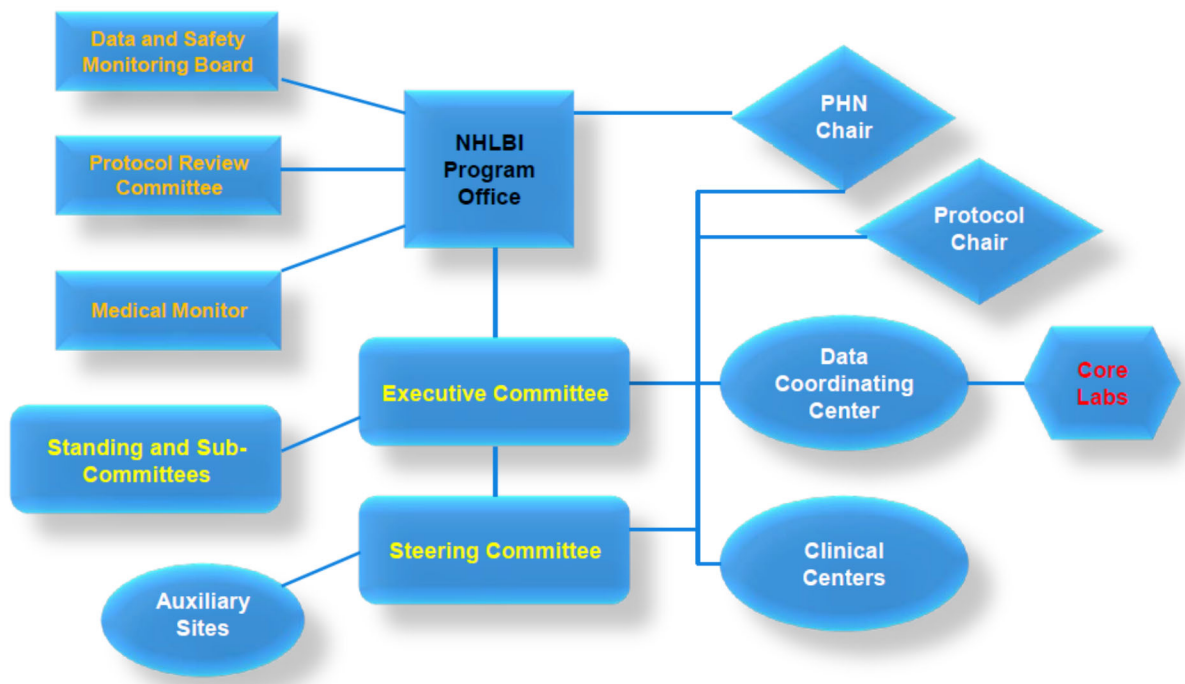
Auxiliary sites are institutions participating in the PHN because they proposed a study that the PHN decided to conduct, or were added to assist with subject recruitment in a particular study. Auxiliary sites undergo a review of their clinical research experience and infrastructure by NHLBI and the DCC; they are asked to provide data on the number of eligible patients for the particular study at their site, and also to provide detailed information about pertinent imaging capabilities. Only sites that are deemed to be able to participate successfully are invited to do so. Auxiliary sites are added to the PHN under site services agreements with the DCC, which stipulate the payment structure for patients recruited as well as the regulatory requirements that must be met before enrollment can begin.

Auxiliary site investigators and staff are encouraged to participate in Steering Committee meetings and calls, and a representative from each auxiliary site is expected to participate in conference calls that relate to the study in which the auxiliary site is participating. Auxiliary site study staff undergoes centralized training for study

procedures either at the main training sessions at the beginning of a study, or later in individual sessions with DCC staff if the site does not join at the beginning of a study. Site visits and periodic site status calls are conducted by the DCC and NHLBI as for the Clinical Centers.

Affiliate sites are institutions or groups of physicians in practice who collaborate with the PHN by identifying patients who might be eligible for enrollment in a PHN study. A limited amount of screening is done by the Affiliate site and then selected patients are referred to an enrolling PHN site for complete screening. Affiliate site staff are welcome to participate in PHN activities such a monthly study conference calls relevant to the PHN study. A small payment is provided to partially compensate the time and effort involved in patient screening. The participation of Affiliate sites in a PHN study is recognized formally in all study publications.

FIGURE 1.1: NETWORK ORGANIZATIONAL OVERVIEW



2 PHN Operational Components

The operational components are designed to ensure the smooth functioning of the PHN, and may change from time to time to meet changing needs.

2.1 Steering Committee

The Steering Committee includes all participants in the PHN. Steering Committee calls and meetings form the backbone of the PHN, and provide a forum for discussion of all aspects of PHN operations by study staff at all sites. A calendar of meeting dates is available on the [PHN NERI Connect site](#).

2.1.1 Meeting Structure, Agendas, and Attendance

The Steering Committee meets twice a year in person, and has monthly conference calls. Steering Committee calls and meetings are chaired by the DCC PI of Operations and the Protocol Chair, as appropriate, or by the NHLBI Project Scientist in the Chair's absence.

The Program Office and the DCC prepare agendas collaboratively. The DCC distributes the agenda to all investigators electronically before each call or meeting.

Participation of a representative from each primary PHN site on calls and at meetings is essential to the efficiency and productivity of the PHN. PHN PIs are also encouraged to include fellows and junior faculty in Steering Committee activities as a means of educating the next generation of pediatric cardiovascular clinical investigators. Special consultants and guests may be invited to attend Steering Committee meetings or participate in calls, with the approval of the Program Officer and DCC PIs.

2.1.2 Minutes

Draft meeting minutes are prepared by the DCC within seven working days of Steering Committee calls or meetings, and forwarded to NHLBI and others, as applicable, for comment. Those commenting have four business days in which to respond. The completed minutes are then posted on the PHN website within two and one half weeks of the meeting.

2.2 Executive Committee

Formal decision-making for the PHN is vested in the Executive Committee, which consists of the following members:

- Voting Members
 - PHN Protocol Chair
 - DCC PIs (1 vote)
 - Clinical Center PIs (one representative from each Center)
 - NHLBI Project Scientists (1 vote)
 - Chair, Study Coordinator Committee
- *Ex officio* members
 - Chair, Publications and Presentations Committee
 - Chair, Ancillary Studies Committee
 - Chair, Finance Committee
 - DCC Co-Investigator
 - Other NHLBI staff

2.2.1 Responsibilities

The Executive Committee meets quarterly by conference call or in person. With input from members of the Steering Committee, activities of this Committee include:

- Setting the overall scientific agenda for the PHN
- Determining which studies will be conducted
- Developing PHN policy and procedures
- Ensuring compliance with PHN policies
- Determining which auxiliary sites will be added
- Reviewing study protocols before they are sent to the PRC and DSMB
- Resolving identified conflicts that affect the conduct of studies or dissemination of results
- Making recommendations to the NHLBI about major changes in study design if needed

2.2.2 Meeting Structure, Agendas, and Attendance

The Executive Committee meets in conjunction with all in-person Steering Committee meetings, and holds quarterly conference calls. Executive Committee calls and meetings are chaired by the DCC PI of Operations or the NHLBI Project Scientist.

DCC staff circulates a request for agenda items in advance of each meeting. The final agenda is reviewed and approved by the DCC PIs and the NHLBI Project Scientist.

The participation of all Executive Committee members is strongly encouraged; if a member cannot participate, an alternate should be designated.

2.2.3 Minutes

Draft meeting minutes are prepared by the DCC PI within seven working days of Executive Committee calls or meetings, and forwarded to the NHLBI Project Scientists, and others, as applicable, for comment. Those commenting have four business days in which to respond. The completed minutes are then posted on the PHN website within two and one half weeks of the meeting.

2.3 Publications and Presentations Committee

The primary purpose of the Publications and Presentations Committee (PPC) is to ensure timely preparation of high-quality presentations and publications on behalf of the PHN. The PPC reviews all abstracts, presentations and manuscripts in accordance with PHN publication policies (see [Chapter 6](#), Publications and Presentations Policy). The PPC solicits recommendations for policy revisions and presents them to the Executive Committee. The PPC Chair is further responsible for adjudicating any conflicts that arise in writing committees such as inadequate investigator participation or changes in writing committee membership. PPC membership is determined by the PPC Chair, DCC PIs, and NHLBI Project Scientist, and consists of:

- PPC Chair
- Protocol Chair
- A representative from each Clinical Center
- DCC PI of Statistical Science (or biostatistician designee)
- DCC Co-Investigator
- NHLBI Staff (ex officio)
- Study coordinator

Participation of **7 members** in any publication review will constitute a quorum.

2.4 Ancillary Studies Committee

The primary purpose of the Ancillary Studies Committee (ASC) is to facilitate the conduct of appropriate ancillary studies. The ASC conducts reviews of ancillary study proposals in accordance with PHN policies (see [Chapter 7](#), Ancillary Studies Policy). ASC membership is determined by the DCC PIs and NHLBI Project Scientist, and consists of:

- ASC Chair
- A representative from each Clinical Center
- A representative from the DCC
- NHLBI Staff (ex officio)

Participation of **5 members** in any ancillary study review will constitute a quorum.

2.5 Study Coordinators Committee

The Study Coordinators Committee consists of the Coordinators from each of the clinical centers, the DCC Project Managers who work closely with the Study Coordinators, and the NHLBI PHN Coordinator. This Committee meets in conjunction with Steering Committee meetings and conducts interim monthly conference calls. The Committee Chair, who is selected from within the group on a periodic basis, is responsible for making a report at each in-person Steering Committee meeting and on some Steering Committee calls. The Study Coordinators Committee reviews the progress of ongoing studies and participates in developing implementation plans for new studies, including the development of patient education materials and other materials as needed. The goal of this Committee is to facilitate sharing of information and collaboration in problem solving on issues related to the day-to-day conduct of the studies. Topics to be discussed include issues related to the Health Insurance Portability and Accountability Act (HIPAA), IRBs and informed consent; patients' concerns; techniques for maximizing recruitment and for optimizing protocol adherence and data quality;

and budget and staffing. The Committee may make proposals to the Steering Committee for PHN policy changes or enhancements to improve PHN functioning. The Coordinators may also propose topics for PHN protocols, for ancillary studies, or for analysis of existing study data for the purpose of abstracts and peer-reviewed publications.

2.6 Finance Committee

The Finance Committee was formed during the second grant cycle to provide systematic input into study budgets, to assist in framing overall PHN fiscal priorities, and to help investigate the costs of pediatric research. The mission of the Finance Committee is to provide timely financial information about individual study costs and the overall PHN budget to assist in planning and prioritizing PHN activities. In addition, the Committee will use information obtained from PHN studies to help estimate the true costs of pediatric cardiovascular research. Members of this Committee are selected by the Finance Committee Chair, DCC PI of Operations, and NHLBI Project Scientist from among nominees submitted by each PHN Clinical Center. The Committee is chaired by one of the Clinical Center PIs, and includes Clinical Center Investigators, Study Coordinators, and budget staff; the DCC PI of Operations, and NHLBI staff.

The Finance Committee meets at all Steering Committee meetings, conducts quarterly conference calls, and meets more frequently as needed during protocol development.

2.7 Core Laboratory Selection Committee

Each protocol may require one or more core laboratories. A standing Core Laboratory Selection Chair will be appointed, and Core Laboratory Selection Committees will be formed to assist in the selection of core laboratories for each PHN protocol (see [Section 4.3](#)). The Committee will typically be composed of up to 5 members, including but not limited to representatives from the Study Committee, Finance Committee, Executive Committee and outside experts as required. Nominations will be solicited by the DCC Project Manager. The Committee members will be selected by the Core Lab Selection Chair, in consultation with the Study Chair, the NHLBI Project Officer, and the DCC PIs.

The Committee will review responses to the Requests for Proposals (RFPs) prepared by DCC staff.

2.8 Biospecimen Committee

The Biospecimen Committee is responsible for oversight of all biospecimens collected and stored during PHN studies. Committee membership includes PHN Investigators with expertise in relevant assays and cardiovascular genetics in addition to study expertise, a DCC Investigator, a representative of the NHLBI Program Office, a member of the Pediatric Cardiac Genomics Consortium, and a member of the Ancillary Studies Committee (ASC) who will serve as the liaison to facilitate ASC review. Review from experts outside the Committee will be obtained as needed. The Committee will review proposals that include use of biospecimens (see [Chapter 9](#)) to ensure that the use and testing of these specimens is appropriate.

3 Oversight of PHN Activities

3.1 Introduction

The PHN has two oversight committees: the Protocol Review Committee (PRC), and the Data and Safety Monitoring Board (DSMB). Both are established by NHLBI following NHLBI policy, and consist of individuals with no close professional relationships to PHN investigators. PRC and DSMB members make recommendations to the Director, NHLBI concerning the initiation and conduct of research protocols in the PHN. Members of the PHN PRC and DSMB have expertise in pediatric cardiology, pediatric cardiac surgery, pharmacology, clinical trials design and analysis, ethics, genetics, and other specialties as needed. One layperson serves on the DSMB. A complete listing of the current members of the PRC and DSMB is on the PHN administrative website.

3.2 Protocol Review Committee

The PRC is appointed by, and responsible to, the NHLBI to provide independent scientific peer review for protocols developed by PHN investigators. The membership of the PRC includes a chairperson and scientists with expertise in the areas enumerated above. Additional experts are added on an ad hoc basis if necessary to evaluate protocols.

The PRC will assess the scientific merit of each protocol based on:

- Importance of the question to be addressed;
- Need for a multi-center design to meet objectives;
- Merit of experimental design;
- Availability of adequate resources, including medications or devices;
- Adequacy of patient population and number of patients, including appropriate representation of minorities and women;
- Appropriate recruitment strategies.

PRC meetings are held when protocols require review. When members cannot attend the meeting, they are expected to submit written comments to the Chair 24 hours before the meeting. Input from 3/4 of the members is considered a quorum. At that session, the Study Committee chair presents an overview of the protocol to the PRC members, and answers questions. A discussion period follows, with the PHN investigator(s), DCC staff, and NHLBI staff available to answer questions. When the PRC is ready to conduct an Executive Session, everyone except the PRC members and the PRC Executive Secretary is excused from the session. After the PRC members have formulated their recommendations, PHN investigators and NHLBI staff return to the session to hear the recommendations and to ask and respond to questions as needed. The minutes, which incorporate key concerns and a summary of the recommendations, are prepared by the Executive Secretary, and sent to the PRC Chair for

review. The final minutes are sent to the Office of the Director, NHLBI for review and approval, and are then distributed by the DCC.

3.3 Data & Safety Monitoring Board

The primary objective of the DSMB is to ensure the safety of study subjects and to provide NHLBI with advice on the ethical and safe conduct of PHN studies. When the DSMB meets, participation of 4 members, one a biostatistician, is considered a quorum. The DSMB advises NHLBI on study design, data quality and analysis, and ethical and human subject aspects of studies. The DSMB reviews all ongoing trials and studies, newly developed protocols after PRC approval has been obtained and before study implementation, and all protocol amendments. The DSMB also reviews all ancillary study proposals after review by the Ancillary Studies Committee is complete, and once outside funding, if required, is assured. A full discussion of the role and responsibilities of the PHN DSMB is found in the DSMB Charter.

Minutes of each meeting are prepared by the Executive Secretary, and sent to the DSMB Chair for review. Final minutes with the DSMB's recommendations are submitted for review and approval to the Office of the Director, NHLBI. After approval, they are distributed to the DCC.

Reports to IRBs: Because this DSMB is convened to supervise multi-center studies, the NHLBI program office will prepare a memo documenting Board recommendations and submit it to the relevant study chair(s) and DCC within 21 days of each meeting. The DCC will forward the memo to each participating research site. It is expected that all sites and the DCC will forward the memo to their IRB.

If the DSMB does not identify any safety or other protocol-related concerns the NHLBI Program Office will prepare a Summary Report stating that:

- A review of outcome data, adverse events, and information relating to study performance (e.g., data timeliness, completeness, and quality) across all centers took place on a given date;
- The observed frequency of adverse events did not exceed what was expected and indicated in the informed consent;
- A review of recent literature relevant to the research took place and;
- The DSMB recommended that the study continue without modification of the protocol or informed consent.

If concerns are identified, the report to the clinical centers will outline the concerns, the DSMB's discussion of the concerns, and the basis for any recommendations that the DSMB has made in response to the concerns.

3.3.1 Medical Monitor(s)

As part of the overall data and safety monitoring plan, the PHN established the position of Medical Monitor, whose services are retained through the DCC. NHLBI has the discretion of appointing one or more as needed. This individual is independent of any PHN site, and is selected by NHLBI based on clinical and research expertise in pediatric cardiovascular disease. The Medical Monitor reviews all serious adverse events, and consults the Chair of the DSMB for additional input as needed. The

Medical Monitor also advises the PHN on strategies for improving adverse event reporting.

Protocol Development and Implementation

4.1 Study Proposals

Development of research concepts is an integral part of the PHN as this process introduces innovative topics for collaborative research and stimulates intellectual discussion concerning the direction and scope of patient care. The NHLBI PHN team and the PHN Protocol Chair can provide guidance regarding the general nature of topics appropriate for investigation by PHN. Proposals for studies funded through investigator-initiated grants or in collaboration with industry, foundation, or other entities are encouraged.

In addition to standard studies involving all PHN Clinical Centers, we will also consider proposals for pilot studies. The purpose of a pilot study is to collect preliminary data for and/or to determine feasibility of a fully-developed study. In contrast to standard PHN studies, there is no expectation that all PHN sites will participate in pilot studies. A sufficient number of subjects should be available for recruitment within a reasonable time period from the proposed participating centers. If practice variation or certain feasibility issues are being assessed in a pilot study, then including centers with differing practices will strengthen the proposal.

The PHN proposing investigator and Center principal investigator will be responsible for ensuring that all PHN policies concerning proposals are followed. A PHN investigator who proposes a study should always consult with the Center principal investigator. A non-PHN investigator who proposes a study must work with a PHN Center investigator to bring the proposal forward. Consultation with the Center principal investigator is also recommended. Proposers should also seek guidance from the PHN Protocol Chair, the NHLBI PHN team, and/or the DCC Statistical PI as this will facilitate understanding of whether the proposed study fits into PHN goals.

4.1.1 Sources of Study Proposals

The PHN will solicit proposals from the pediatric cardiovascular community twice a year on a schedule that will permit the proposals being presented at in-person Steering Committee (SC) meetings. Emails soliciting proposals will be sent in December for the April SC meeting and in May for the September SC meeting. One-page proposals (see below) for the April SC meeting will be due to the PHN Data Coordinating Center (DCC) two weeks before the February Executive Committee (EC) call, and proposals for the September SC meeting will be due two weeks before the July EC call.

Proposal submitted at other times will also be considered, and will be scheduled to be discussed at the next available EC call or meeting.

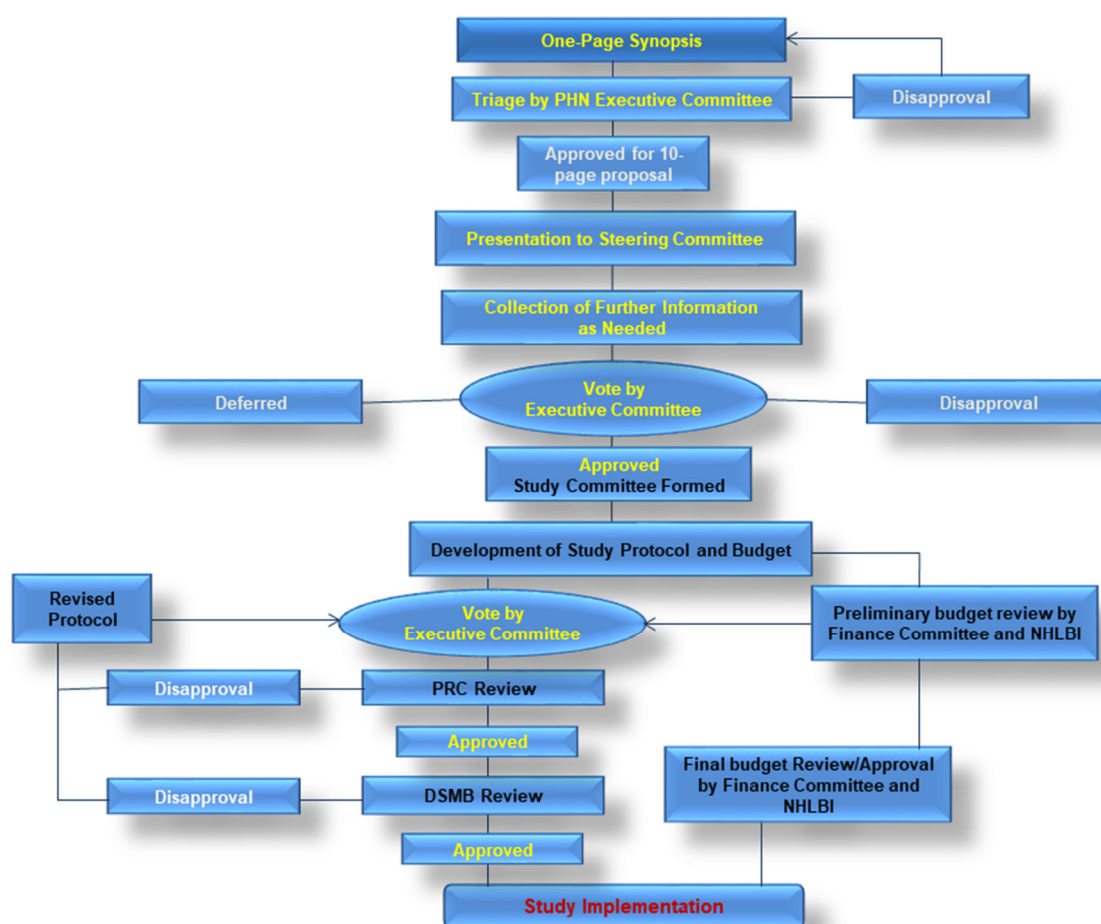
New ideas for collaborative research emerge from formal and informal discussion among PHN investigators, the Nursing Research Committee, and from outside

investigators who wish to propose an idea for the PHN's consideration. Proposals may include studies that will require funding by the PHN, those that are supported by PHN nursing research funds, or studies ([Section 4.1.2](#)) that have other sources of partial or full funding. The Center PI(s) should review any proposals emanating from his or her site before submission to the DCC).

4.1.2 Proposals for PHN-funded Studies

The proposal process starts with one-page synopsis, described below, and triage of the proposed study by PHN leadership at a scheduled EC call or meeting. This can be done with a proposal or a one-page synopsis as described in [Section 4.1.2.a](#). The steps are depicted in **Figure 4.1**.

FIGURE 4.1 DEVELOPMENT OF NEW STUDIES



a. One-page Synopsis

The one-page synopsis will be reviewed by PHN EC to determine if the proposed study is of interest to the PHN before a more detailed proposal is prepared. Consultation with the PHN Protocol Chair, the NHLBI PHN team, the DCC Statistical PI, and/or other PHN investigators may be helpful at this stage. The synopsis should include the study aims, hypotheses or research questions, a brief description of study design and population, study duration, and a rough estimate of total study costs. If approved by PHN leadership, the next step is development of a proposal, described below.

b. Proposal

If approved by the EC, the next step is to develop a proposal not exceeding 10 pages (11 pt Arial), excluding title page and references, that includes the following. At the discretion of the PHN leadership, proposals already in the format for a grant application may be submitted for review in the format required by the granting entity. Proposal template available [here](#).

1. *Abstract*: Include a brief summary with the primary hypothesis and research questions
2. *Study Aims and Hypotheses*: State the Primary Aim and all Secondary Aims, with any hypothesis(es) and study outcomes for each Aim.
3. *Background*: Include prior studies, rationale for study, and brief rationale for study outcomes.
4. *Study/Trial Design*: Include a brief overview, possibly a study schematic diagram, procedures to minimize bias if relevant, measures for all outcomes, and a schedule of measurements and visits.
5. *Selection of Subjects*: Include inclusion and exclusion criteria; data regarding subject availability; and an estimate of the accrual period. List participating institutions for pilot studies and collaborating institutions, if relevant.
6. *Treatments*: If applicable, describe the treatments to be administered. Treatments can include drugs, biologics, surgery, devices or diagnostic procedures. Describe the regulatory (FDA) status of the proposed treatment, if applicable.
7. *Safety Considerations and Assessments*
8. *Statistics*: Include a sample size calculation as well as a preliminary analysis plan. For Phase III trials, calculate sample sizes based on a minimum of 85% power. Assumptions used for the calculation of target sample size should be provided, including but not limited to the Type I and II error rates, magnitude of treatment crossover, the detectable effect size, and inflation for loss to follow-up, incomplete evaluation, and interim looks at the data.
9. *Limitations*
10. *Budget*: Include a general description of budget items and an estimate of the costs. The DCC should be included in the budget estimation process if the study is PHN-funded.
11. *Disclosures*: Include disclosure of any significant financial interest(s) that might be related to the proposed area of research.

12. References

c. Review and Prioritization Process

i. One-Page Synopsis

At the EC meeting, members will consider the scientific merit, importance of the topic, and feasibility of the synopsis. Any EC member directly involved with the proposal will be recused from the discussion, other than to answer clarifying questions about the synopsis.

The EC will take a vote to either approve the synopsis to present to the SC, or to disapprove the synopsis. The decision and rationale will be provided to the proposer(s) by the PHN Protocol Chair, or the NHLBI PHN team.

Once the EC approved the one-page study synopsis, the 10-pager proposals are presented by the lead proposer to the Steering Committee (SC), at either an in-person meeting or on one of the monthly SC conference calls. The purpose is to familiarize the PHN with the proposal and to obtain input. The discussion will focus on the primary study endpoint, significance, investigator equipoise about the research question proposed for study, and numbers of potential subjects available. Details of the study design such as specific inclusion and exclusion criteria, measurement schedule, and secondary endpoints will be considered but may change during full protocol development.

At any point during the review of study proposals, PHN EC may ask for written answers to specific questions posed to the lead writer of the study proposal, input from the Finance Committee, detailed reviews of clinical center databases to assess subject availability, consultation from outside experts in the field, and/or any other information deemed necessary for complete review.

All such information will be submitted to the DCC for distribution to the EC. At the discretion of PHN leadership, interim votes may be taken by the EC to assess interest in further review of any proposal.

After SC review of a study proposal, the EC will discuss it. During this discussion, the EC member from the proposer's site will be recused.

Each proposal is assessed according to the following criteria:

- *Scientific merit*: overall design; meaningful, valid endpoints; reliable measurements
- *Relevance and importance of topic*: potential impact on morbidity and mortality; degree of controversy in the field; public health importance
- *Feasibility*:
 - Ability to identify a clinically relevant and feasible primary study endpoint,
 - Willingness among PHN investigators to accept random assignment of patients to the proposed treatments (if a trial is proposed),
 - Availability of supplier support for study drugs or devices, if applicable,

- Likelihood that patient populations of sufficient size will be available within the PHN, and
- Cost of proposed study and availability of adequate funds for study conduct.

After the meeting, EC members will receive a confidential electronic ballot and will vote on whether the proposal should move on to development as a PHN study. EC members will also provide comments. The vote and comments should reflect a consensus opinion of the clinical site voting, not just the view of the site EC member. The PI of a Center proposing a new study will abstain from voting on that proposed study. The lead writer of the study proposal will receive aggregate feedback, prepared by the PHN Protocol Chair, from the DCC on the voting results. If a proposal receives a majority of “No” votes, the proposal will not progress to the next stage of development regardless of priority ranking. If a proposal is considered to be valuable to the PHN but needs major revision, the comments will identify the revisions requested. If there are multiple proposals that receive “Yes” votes, development of protocols will be prioritized based on ranking after the voting and will depend on available PHN resources and whether additional funds will be provided through grants or outside collaborations.

ii. Submitting a Revised Proposal

The EC may recommend resubmission of a revised proposal. A letter (2-page maximum length) describing the revisions made in response to the specific review comments or questions should accompany the revised proposal. The revised proposal will be reviewed at a subsequent EC meeting.

d. Study Committee Formation

After the EC votes to pursue development of a protocol, or after external funding is received for a study, a Study Committee is formed. The Study Committee Chair usually will be the individual who proposed the study. A PHN co-chair is required if the study was proposed by a non-PHN Investigator, and is customary otherwise to spread the workload. Co-chairs will be approved by the PHN Leadership.

The DCC will solicit nominations for membership on each Study Committee from the participating clinical sites. Final membership will be determined by the Committee Chair and approved by the PHN leadership, and will typically consist of:

- At least one representative from each participating clinical site,
- More than one representative from each site may be appropriate if additional expertise is required,
- At least one clinical research pharmacologist for any study involving drugs,
- At least one Study Coordinator,
- A statistician and Protocol Lead from the DCC
- A representative of the Pediatric Cardiac Genomics Consortium
- Core laboratory directors or designees for the proposed study if defined, and
- NHLBI staff.

For studies where PHN partners with pharmaceutical or other outside sponsors, a representative from the relevant sponsor may also participate in the study committee as an *ex officio*, non-voting member.

Once a Study Committee is formed and approved, calls will be scheduled by the DCC to occur at least monthly during protocol development and during the study. The Study Committee Chair assumes leadership responsibility, but must work collaboratively with the other members of the Committee. These responsibilities include working with the DCC to convene meetings and conference calls and monitoring the overall progress of the protocol and the study. Minutes of each call and meeting are prepared by DCC staff, approved by the Committee Chair, and then distributed via email and posted on the PHN administrative web site.

The primary objectives of the Study Committee are to:

- Produce a concept protocol (see [Section 4.2.2](#)), if applicable, for review by the PRC
- Write the full study protocol, consent forms, and appendices
- Prepare presentations of the study for the PRC and DSMB
- Modify protocols as recommended by the SC, PRC, and DSMB
- Assist the DCC with information necessary to develop the manual of operations,
- Assist the DCC with details of drug donation, formulation and distribution, as required
- Assist the DCC in obtaining equipment and supplies, specifications for core laboratories, and other logistics necessary to begin the study
- Interface with patient advocacy groups as applicable to create study materials for patients, including study brochures and study close-out letters
- Create materials and presentations for sites to use in publicizing the study locally
- Monitor implementation, conduct, and performance of the study in conjunction with the DCC and NHLBI
- Advise the Steering and Executive Committees, via the PHN Protocol Chair, DCC, or NHLBI, about special problems or concerns that arise during study implementation or conduct and that may require protocol amendment
- Prepare abstracts, make presentations and write manuscripts on the primary and major secondary study results
- Conduct other activities to disseminate study findings widely

The importance of having each site (PHN and auxiliary) participate in the Study Committee calls cannot be overstated. These calls allow investigators to share problems and concerns, and learn from others about effective solutions. They also facilitate standardization of protocol conduct while the study is underway. For these reasons, attendance will be taken on each call. The PIs from each Clinical Center will be responsible for ensuring that their Center is represented during and contributes to all Committee activities. If, in the opinion of the Committee, a Committee member is not participating fully, that member will be replaced with another investigator from the Clinical Center in question. Committee members who do not actively participate will

be replaced at the discretion of the Study Chair; the Study Chair will be replaced by the EC.

The Study Committee can invite non-PHN investigators from PHN Clinical Centers, or in special circumstances from outside clinical centers, to assist in the protocol development process when special expertise is required or the need for additional centers for a specific protocol is anticipated. If the PHN agrees to add auxiliary centers for a study, representatives of centers identified during the protocol development process are expected to work on the Study Committee with PHN investigators to develop the protocol. Once a study is approved by the DSMB, additional auxiliary sites and core laboratories can be added to the Study Committee as needed. Non-PHN investigators will be considered full members of the Study Committee, and may participate in any votes that are taken on the Committee. Partners in specific protocols, such as foundations or industry, will be invited to have a representative on the Study Committee.

e. Grant Application for Full Review

If the synopsis is reviewed favorably by the EC, the applicant(s) will be asked to follow the same process as above. In lieu of a 10-page proposal, however, applicants can submit a draft grant application if already in preparation. At the next convenient SC meeting or call, the applicant(s) will be invited to present the proposal. After the SC discussion, the EC will act as above. If the application is from a Core Center, the Center PI is recused from voting on that proposal. The Protocol Chair will notify the applicant(s) of the decision. If the vote is favorable, a letter in PDF format on PHN letterhead from the Protocol Chair indicating PHN support for the proposal will be provided to the applicant(s) to include in the grant application.

f. Reconsideration of Proposals

If a grant application is not funded and a revised application is planned, the applicant should notify the Protocol Chair at least 6 weeks before the next grant submission date.

The EC will conduct an expedited review (at the next scheduled meeting or electronically) of the proposal to determine if the study is still a priority for the PHN. The decision will be conveyed to the applicant(s) by the NHLBI Project Scientist. If favorable, a letter will be provided to the applicant(s) to include in the grant application.

4.2 Protocol Development and Review

4.2.1 Study Protocol Formats

Two protocol formats have been defined: the concept protocol and the full study protocol. The protocol format for each new study proposal approved by the EC will be determined by PHN leadership. In general, proposals for fairly well-developed studies from outside investigators, straightforward studies, and follow-up studies will be developed immediately into a full study protocol. Less well-defined proposals will generally be first developed into a concept protocol.

The concept protocol provides an opportunity for the investigators to obtain feedback from the PRC. It is typically 8-12 pages long and focuses only on scientific background, rationale for the study, the primary endpoint, and feasibility of recruitment and study execution. The PRC may recommend to the NHLBI that the protocol not be developed further. If the concept protocol is accepted, then the PRC feedback provides the PHN investigators with valuable advice to help guide final protocol development. This approach hopefully will avoid the PHN having a fully developed study protocol rejected, an outcome that is inefficient and detrimental to group morale. Note that the DSMB does not review concept protocols.

4.2.2 Preparation of the Study Protocol

Development of the study protocol, whether a concept protocol or the full study protocol is a large task that requires great effort on the part of many PHN members. The framework of the protocol document is a function of a protocol template provided by the DCC and should reflect the most recent protocol developed by the PHN. The Study Committee is expected to work out major protocol issues, and to present the results of these discussions to the SC during regularly scheduled SC calls and meetings. The Study Committee should obtain input from relevant core lab personnel. The Study Committee also may form specialized subgroup committees for the duration of protocol development, which focus on areas such as core lab/imaging or neurodevelopmental assessment. Any materials that the Study Committee wants to discuss with the SC should be provided in a timely fashion to the DCC to be distributed as background materials for the pertinent call or meeting.

Estimates of available potential subjects are critical to both concept and full study protocols. The statistical representative from the DCC provides preliminary sample size calculations based on any available data early in the process, possibly even during EC review of the study proposal. Feasibility estimates are also done based on availability of subjects as reported by the clinical centers or through registry data. As the primary outcome, analysis, and inclusion and exclusion criteria sections of the protocol become more defined, these estimates are refined and updated.

4.2.3 Planning for Protocol Review

The completed protocol must be approved by vote of the Study Committee, which must be documented in the Study Committee meeting minutes. The protocol must be prepared in final formatted form before review can take place. As the Study Committee approaches this endpoint, scheduling of review meetings by the PRC and DSMB should take place. The length of time between EC, PRC and DSMB review must be estimated and will depend in part on the complexity of the proposal. A timeline for each protocol should be developed in collaboration with the Study Chair, DCC personnel, Protocol Chair, and NHLBI personnel.

4.2.4 Formatting Requirements

The PI who is submitting the protocol should work with DCC personnel to get the protocol as close to a final version as possible. The protocol should be single-spaced, in 11 point font.

The DCC will prepare final formatting including placing the version number and version date in the footer and on the title page, preparing the table of contents, and assuring that the protocol is free of split tables and images.

The study PI should give the DCC at least two business days to format the final protocol before submission to the EC.

4.2.5 Cover Letters

- **PRC**

A cover letter for the PRC should be prepared and submitted to the EC for review with the protocol. The purpose of the cover letter is to introduce the broad concept of the study to the reviewers and to discuss any design issues that do not fit conveniently into the protocol document (e.g. choice of primary outcome, why there is no placebo group, etc.). Statements about details of the protocol that are readily available in the protocol document should NOT be repeated in the letter.

In general the letter should be no longer than 3 pages- the shorter the better. Examples of cover letters for PRC review are available on the PHN NERI Connect home page under [Network Policies and Templates](#).

- **DSMB**

Once the protocol has been approved by the PRC, a new cover letter should be prepared for submission with the protocol to DSMB. The letter can be exactly the same as that submitted to the PRC with an additional paragraph added towards the end as follows:

The PHN Protocol Review Committee met on {date}, and voted unanimously to approve the protocol. A copy of minutes of this meeting is enclosed for your review. The PHN has the following responses to the PRC's recommendations:

- ☐ The PRC recommended that
- ☐ The PRC was concerned that...

Examples of cover letters for DSMB review are available on the PHN NERI Connect home page under [Network Policies and Templates](#).

4.2.6 Protocol Review by the EC

Both concept and full study protocols are reviewed by the EC before being submitted to the PRC. Protocols are sent to the EC 14 days before votes are due. Protocols are sent to the entire EC, but only voting members provide approval/disapproval and comments. The votes and comments are submitted to the Protocol Chair who will prepare the final EC review within 5 days. As described below (Sections [4.2.8](#) and [4.2.11](#)), in the event of PRC or DSMB disapproval of a protocol, the EC will re-review

the revised protocol prior to resubmission to the disapproving body. This re-review typically will be handled electronically, and the review time may be less than 14 days.

4.2.7 Preparation of Presentation Slides

Slides for presenting the protocol to the PRC and DSMB via conference calls should be prepared by the Study PI in collaboration with the Study Committee and Protocol Chair. In general, there should be no more than 20 slides as the PRC and DSMB members will have all read the protocol. Examples of PRC and DSMB slide sets are available on the PHN NERI Connect home page under Network Policies and Templates, at the links below.

[PRC Slide Set Examples](#)

[DSMB Slide Set Examples:](#)

A version that has been approved by the Study Committee should be sent to the Protocol Chair at least one week before the PRC call. After review is completed, these slides are posted on the PHN NERI Connect website at least 3 days before the call.

The slides for the DSMB conference call can be essentially the same as those for the PRC call with the addition of 1-2 slides as needed to review PRC recommendations. A version that has been approved by the Study Committee should be sent to the Protocol Chair at least one week before the DSMB call.

4.2.8 Protocol Review by the PRC

The PRC meeting should be scheduled at least 6 weeks after EC review to give the Study Committee time to respond to EC feedback. If a concept protocol was reviewed by the PRC, the cover letter for the full study protocol should include responses to PRC comments about the concept protocol. See [Chapter 3.2](#) for further information about the conduct of the PRC meeting.

If the PRC does not approve a concept (if applicable) or a full study protocol, this likely means that major substantive revisions are required. Therefore, review and approval of the revised protocol by the EC is required prior to submission to and re-consideration by the PRC. The need for re-review can be waived in the rare circumstance that it is not considered necessary by the PHN Leadership and the Protocol Chair.

4.2.9 Preparation of Case Report Forms (CRFs)

This is a demanding task that requires meticulous attention to detail and involves close collaboration between Committee members and DCC staff. The Committee is encouraged to obtain input from relevant core lab personnel and additional study coordinators.

4.2.10 Budget

The study budget should be developed while the protocol is being prepared. This is a collaborative effort between the DCC, applicable PHN investigators, and NHLBI staff. A budget template is developed for each study to include the costs of any patient care

or diagnostic testing that are not part of routine clinical care, drug costs if applicable, costs to cover the study-related expenses of patients and families, and similar items. Templates are sent to each participating site and sites will enter line item costs.

DCC and NHLBI program office review the returned templates and develop an average per-patient cost that will be applied to all PHN sites. In the case of auxiliary sites participating in only a single protocol, the per-patient budget can include a small amount for infrastructure expenses, such as study coordinator time. The per-patient budget will be posted on the PHN Web Site.

A final estimated budget with site cost estimates should be submitted to the Finance Committee for review and approval before being submitted to the EC along with the study protocol.

4.2.11 DSMB Review

After PRC review and NHLBI approval, any recommended changes are addressed, and the protocol is submitted to the DSMB for review accompanied by a cover letter that includes a summary of changes recommended by the PRC and draft Informed Consent and Assent Forms. See [Chapter 3.3](#) for further information about the conduct of the DSMB meeting.

If the DSMB does not approve a study protocol, this may mean that major substantive revisions are required. Review and approval of the revised protocol by the EC is required prior to submission to and re-consideration by the DSMB. The need for re-review can be waived in the rare circumstance that it is not considered necessary by the PHN Leadership and the Protocol Chair.

For clinical trials, once the DSMB has approved a new trial, the DSMB charter will be amended to include statistical monitoring guidelines for the new trial, including stopping early for safety, futility, and efficacy as appropriate. Details on timing and content of interim analyses will be provided, including detail on which analyses will be presented to the DSMB blinded vs. unblinded.

4.2.12 FDA Review

For studies being conducted under FDA regulation, the protocols can either be submitted to the DSMB and the FDA simultaneously, or to the FDA after DSMB review, depending on time constraints.

4.3 Study Implementation

After final protocol approval, the DCC circulates a timeline for pre-recruitment activities, and final arrangements are made for any necessary supplies or services, such as study drug manufacture, special equipment or diagnostic testing. Selection of any auxiliary (including international) sites occurs at this time through a formalized application and vetting process.

After final revision, draft CRFs are distributed to Study Coordinators at 2-4 clinical centers for pilot testing using existing patient charts. The Coordinators return detailed comments (but not the completed CRFs) to the DCC on a standardized feedback form. After revisions are made

in response to the piloting feedback, the CRFs are finalized and the complete CRF set, along with a standardized Form Approval Signoff form is sent to the Study Chair, the PHN Protocol Chair (if appropriate), the DCC PI of Statistical Science and one or two additional members of the Study Committee. After signed approval of the CRFs is received, Study Committee members work with the DCC to provide relevant validation ranges for study data fields and to develop detailed definitions of data fields for inclusion in the study Manual of Operations. The DCC also uses this information to program the web-based data management system and randomization system (if applicable).

After a protocol is final, a Request for Proposals (RFP) for any new core lab(s) necessary for the study is distributed to the PI at each center, and to any other investigators the Study Committee may want to include for specific expertise. The Study Committee will help the DCC to draft the scientific details and selection criteria for the RFP(s). PHN clinical centers may apply to be a core lab, but the proposed core lab director cannot be the center or study PI (unless the study is research stemming from core laboratory activities). The typical deadline for submission of proposals is six weeks after an RFP is distributed. Submitted proposals are reviewed by the Core Laboratory Selection Committee, which may add outside expert technical consultants if necessary. Reviewers use a standardized rating form that assigns points in the areas of facilities and equipment; managerial coordination plans; qualification, experience, and availability of proposed personnel; and ability to perform testing and quality control procedures. If none of the submitted proposals is deemed acceptable, then the RFP will be re-competed. After selection of a core lab the Core Laboratory Selection Committee Chair communicates the results of the review to applicants.

4.3.1 IRB/REB Approval

After DSMB approval, the final protocol and patient-related materials are distributed by the DCC to all participating clinical centers for the local or single IRB. IRB/REB approval of the protocol and related documentation (e.g., patient education materials, study brochures, questionnaires, HIPAA forms) is required before recruitment can begin. PIs may need to devote time to educating the IRB/REB Chair about the need for consistency in study documents for multi-center studies to avoid unnecessary editing of consent forms and other study materials. NHLBI policy requires that all consent forms in multi-center studies be reviewed by the DCC and/or the NHLBI program office before submission to the local IRB and again after IRB/REB approval to ensure that required content has not been revised incorrectly.

4.3.2 Training and Certification

One or more training sessions are held for the Study Coordinators, investigators, and other research staff. These sessions are coordinated and conducted by the DCC. Before the study starts, each center must complete certification requirements, which include demonstration of familiarity with study procedures, methods for endpoint measurement, use of the database management system, and designation of staff to conduct the study. The DCC will work with each center on certification and notify NHLBI when it is achieved. Each study will require different types of training which may include database system training, demonstration of randomization processes, and completion of a post-protocol training quiz. In addition, dedicated training sessions are

held, as applicable, for technical echo/imaging site staff, developmental specialists, and for pharmacists.

4.3.3 Study Registration

All PHN studies will be registered with ClinicalTrials.gov to fulfill journal requirements for subsequent publication and to meet FDAAA requirements. The DCC will work with NHLBI to oversee this process.

5 Quality Assurance

5.1 Overview

A number of measures have been established to assure standard administration of all study protocols and procedures by all data collectors across all PHN sites; these range from weekly editing of the data by the DCC to on-site visits by NHLBI and DCC staff to review and evaluate research procedures and organization. Several routine reports are generated and distributed to the Steering Committee by the DCC that report the quality of study procedures and data.

5.2 Routine Study and Data Quality Checks

Data management activities that the DCC performs to maintain data integrity and quality include:

1. A system check to identify data forms not completed within the specified study windows. If a data form is not completed within its window, then the form is considered overdue. The window is defined specifically for each protocol.
2. A system check to identify data fields that have pending validation edits or missing values and data discrepancies. Monitoring of these edits is done by re- running the report until no edits are produced. Validation edits identify missing or incongruent information within and across data fields. These edits are provided in real-time to the clinical site at the time of data entry. DCC checks on outstanding edits are additionally conducted on a periodic basis to notify sites of any backlogs.

Clinical sites are routinely notified and requested to review and take action on items identified per the above procedures.

In addition, a Quality Control Double Data Entry (QC DDE) process is established for each study to help ensure accurate data entry and to alert the DCC of high levels of discrepancies in data entry. Approximately 5% of data entry forms entered into the data management system are randomly selected to be re-keyed. The QC DDE system uses a self-adjusting algorithm to select an additional percentage of forms for double data entry when a data entry person fails to maintain an acceptable error rate. The system also blocks data entry when QC DDE is not completed in a timely manner.

5.3 Protocol Training

The DCC provides training at study start up to study staff based on their role. Anyone performing randomization procedures will receive randomization training (i.e., study coordinators, PIs), anyone working with the database will receive database system training, and all study coordinators and a designated center investigator will receive and must successfully complete protocol training. The DCC monitors the clinical sites' adherence to

randomization and protocol procedures and violations and deviations from the protocol, including enrollment of ineligible patients, which are reported to the Steering Committee at least quarterly. The DCC also monitors recruitment for all PHN studies. Recruitment reports emphasize the numbers recruited per month by clinical center, the numbers screened, and the numbers eligible and consenting. These reports are submitted to the SC and study committees.

5.4 Site Visits

5.4.1 Clinical Centers

Clinical Center site visits are evaluations conducted by the DCC and NHLBI staff, and additional PHN representatives if needed. Site visits occur in person at least once during each protocol, and additional site visit conference calls may be scheduled.

- **Site Initiation Calls or Visits**

The purpose of a site initiation conference call or visit is to ensure that sites are initiating protocols effectively, to help with any procedural issues, and to share information learned at other sites. Site initiation calls are used primarily for auxiliary sites that may not be familiar with PHN procedures, but also may be conducted at all sites for a particularly complex protocol. They are scheduled by the DCC in conjunction with NHLBI. A standard agenda is provided to each site prior to the call, and the site PI is asked to review staffing and procedures for the protocol. If concerns are identified, a follow-up call or visit may be needed.

- **Quality Assurance Site Visits**

The purpose of a quality assurance site visit is to:

- Review PH with the clinical center's PI and relevant staff
- Assess the clinical center's proficiency in executing PHN protocols
- Assess data quality and completeness
- Provide consultation in identifying and solving problems
- Transfer effective approaches from one clinical center to others

Considerable detail and planning are undertaken to conduct a site visit. The clinical site PI will be contacted in advance to set up a suitable date. The DCC and NHLBI will establish a specific Site Visit Agenda in conjunction with site investigators; the Agenda will be distributed to the clinical center before the site visit.

During a quality assurance site visit, the team will evaluate the following areas:

- Overall performance of the clinical center and the conduct of PHN protocols, including ability to meet enrollment targets
- Data quality, to include a chart audit of select data variables
- Regulatory documentation
- Facilities and records
- Research procedures and organization

- Pharmacy (if applicable)
- Any PHN Core Laboratories at that particular clinical center

- **Site Visit Objectives and Procedures**

The site visit will be conducted in accordance with the following objectives and procedures. Some of these procedures, such as touring the facilities, will only be required at the first site visit:

- a. **Research Setting: Staff and Facilities**

- Objectives
 - Evaluate adequacy of facilities
 - Evaluate adequacy of staffing in relation to required tasks to conduct PHN protocols
- Procedures
 - Walking tour of the facilities, including: clinic space, offices, data entry site(s), files, pharmacy, echo lab, MRI suite, and other areas as applicable
 - Meet study personnel, including the principal investigator, study coordinators, pharmacists, data entry personnel, grants management administrator, and other staff involved with the conduct of PHN protocols.

- b. **Organizational Procedures and Study Administration**

- Objectives
 - Evaluate communication among research staff
 - Evaluate staff training
 - Evaluate organization, maintenance and security of subject research records
 - Evaluate organization and process of data collection
- Procedures
 - Review established methods of communication among clinical site investigators and staff
 - Review maintenance and storage of regulatory documentation and official PHN correspondence (Operations Memos)
 - Assess organization and process of data collection, transmission, and storage by reviewing subject research record organization, methods and maintenance

- c. **Regulatory Review**

- Objectives
 - Evaluate regulatory binder for completeness consistent with good clinical practice guidance.
 - Evaluate completeness and dates of informed consents
- Procedures
 - Review completeness of regulatory binders

- Review the informed consent of every randomized patient for signatures and dates to ensure the documents were current and within the IRB approval window

d. Trial/Study Patients: Data Quality & Protocol Compliance

- Objectives
 - Evaluate site-specific procedures for protocol implementation
 - Evaluate completeness of study documentation
 - Evaluate accuracy of records
 - Evaluate accuracy and completeness of adverse event reporting
 - Evaluate accuracy and completion of data collection and recording
 - Evaluate delays responding to data edits and form completion
- Procedures
 - Review completeness of screening and actual vs. expected enrollment numbers
 - Review a sample of randomized patient medical records for accuracy and completeness of adverse event reporting
 - Review eligibility violations, loss to follow-up, and protocol violations
 - Review randomization procedures, location and maintenance of back-up randomization materials, pharmacy records, and completeness of pharmacy drug log and comparison of drug log with patient chart. (If applicable)
 - Review charts requested for chart audit. The DCC will identify patient charts to be audited in advance. The clinical center should prepare for this audit by providing the required charts and ensuring that the charts and protocol study nurses and coordinators are available for the site visit team. Charts will be examined for agreement between medical record and submitted PHN data for key study outcomes, eligibility, and treatment variables. Additional review occurs to identify a signed copy of the informed consent, data completion procedures, and protocol violations
 - Review timeliness of data entry, data transmission, and response to and documentation of date.
 - Review quality of screening/randomization logs and mail-in data forms
- **Oral and Written Recommendations**

The site visit team will convey an assessment of the site with regard to the objectives outlined above at the end of the visit. Areas of excellence as well as any recommendations for improvement will be noted. In addition, a formal written report will be prepared for the site PI by NHLBI and the DCC, and forwarded to the center following the site visit. The written report will detail the site visit team's overall assessment of the clinical center with

specific emphasis on problem areas. The written report will provide a formal assessment of the following areas:

- Research Setting: Staff and Facilities
- Organizational Procedures and Study Administration
- Data Management
- Adverse Event Reporting
- Trial/Study Patients: Data Quality
- Summary of Recommendations

The Center PI will have 10 days to challenge any item in the report. If significant concerns are noted, the site PI will be asked to reply in writing, usually within 30 days. In this case, a follow-up site call will be scheduled within 3-6 months.

5.4.2 Data Coordinating Center

Site visits will be conducted by NHLBI to the DCC at least once in each grant cycle. The purpose of such visits initially is for NHLBI staff to become familiar with DCC staff and processes. On subsequent site visits, the purposes may include resolving problems, refining PHN procedures, and other issues. The verbal and written reporting format will be similar to those used for the Clinical Center site visits.

5.4.3 Site Visits To Address Problems (audit)

Site visits to clinical centers can be initiated by NHLBI if concerns arise about ability to recruit, adherence to the protocol, data quality, or patient safety. The purpose of such a site visit is to assess reasons for the problems identified, and to work together to develop a plan to improve performance. The site visit team may include additional members depending on the nature of the problem, and the site principal investigator may be asked to include additional personnel, including Division and Department chairs. At the conclusion of this type of site visit, a verbal report will be provided, with a formal written report to follow, focusing on problem areas and recommended solutions. A written response to the recommendations, with a timeline for implementing them, will be required from the clinical site within 30 days of receipt of the NHLBI formal written report.

Site visits to the DCC can be initiated by NHLBI if concerns arise about the ability to provide appropriate support to PHN studies. The purpose of such a site visit is to assess reasons for the problems identified, and to work together to develop a plan to improve performance. The site visit team will include NHLBI staff, and may include senior investigators from other data coordinating centers or contract research organizations. A verbal report will be provided at the end of the site visit, and a written report focusing on problem areas and recommended solutions will follow. A written response will be required from the DCC within 30 days of receipt of the NHLBI formal written report.

5.5 Performance Reports

5.5.1 Clinical Center Reports

Performance reports will give Clinical Centers and the NHLBI an objective measure of performance. They will be generated periodically and will be available to NHLBI peer reviewers upon re-competition of the PHN.

Evaluation will focus on overall Center participation in PHN activities, and for each study protocol will consider:

- Recruitment
- Protocol Adherence
- Study Completion
- Data Quality
- Timeliness of data entry
- Citizenship

5.5.2 DCC Reports

Performance reports will give the DCC and NHLBI an objective measure of performance at the DCC. A tool developed by NHLBI is used to solicit input about the performance of the DCC from the Clinical Center PIs and Study Coordinators in the following areas, including timeliness of DCC responses:

- Staff and administrative operations
- Organization and conduct of site visits, conference calls and meetings
- Protocol development, training, and forms development
- Data management and statistics

Summary scores as well as detailed comments are generated and provided to the DCC, usually before a site visit by NHLBI staff.

5.6 Unblinding Procedures for Trials

5.6.1 Request for Unblinding

Unblinding of individual patient treatment assignment during the conduct of the overall trial has the potential to introduce bias into screening procedures and determination of trial endpoints for future and currently enrolled patients. A request for unblinding of treatment assignment should only be made in situations where knowledge of the treatment assignment will actually affect the subsequent care or decision-making process for care of the trial subject. Typically such a request is made in a rare life-threatening situation or where the outcome of the index event prompting the need for unblinding has other permanent consequences. However, such situations do not always require knowledge of the treatment assignment to provide proper care. In some instances, holding study drug administration for a short period of time may be sufficient to assess patient condition and response to cessation of study drug as an alternative to unblinding. It should be assumed that the trial subject will remain in the trial if study visits are not yet completed and will continue adherence to the trial protocol after the

event is resolved. Therefore, every effort should be made to maintain trial participation in a blinded nature.

5.6.2 Initial Steps

1. All considerations of unblinding should be discussed in detail with the *PHN clinical center PI* before a formal request is made, and the PI should assess whether the situation truly requires an official unblinding request.
2. The primary 24-hour verbal contact for an unblinding request is the *Trial Chair*. Contact information for the trial chair for each active study can be found on the [NERI Connect web site](#).
3. The request for unblinding of treatment assignment must also be made in writing to the Trial Chair and to the DCC PI of Statistical Science by the PHN clinical center PI, or that center's designee.

5.6.3 Permissions

1. Permission/acknowledgement for unblinding will be provided in writing by the Trial Chair (or designee) or the DCC. Whenever possible, contact of the local pharmacist should not occur prior to receipt of permission.

5.6.4 Rare life-threatening or emergency situations

In rare life-threatening or emergency situations, patient welfare may necessitate unblinding before the PHN Trial Chair or DCC can be contacted for discussion. In such cases, the local pharmacist for medication trials, or the provider with knowledge of the study intervention administered for other trials should be contacted per local guidelines, but ideally only after full discussion with the PHN center PI. Such unblinding that occurs without PHN Trial Chair or DCC involvement should be reported the first working day after the event.

5.6.5 Procedures

1. After receiving written permission for unblinding, the treatment assignment should be obtained from *the local pharmacist* for medication trials, *or the provider* with knowledge of the study intervention administered for other trials.
2. The assignment information should be provided *only to the physician who is directly responsible for the care of the subject* to resolve the index event. The treatment assignment should not be revealed to trial staff or specialists unless critical to the decision-making process of care. The number of persons to whom the treatment assignment is revealed should be kept to a minimum, regardless of involvement in the PHN trial.
3. If the approved unblinding request is for a patient who has completed all trial requirements/study visits, the local pharmacist (or, for a non-drug trial, the appropriate provider) should provide the treatment assignment in writing to the primary cardiologist (who may be part of or outside the PHN clinical center) and send a copy of the letter to the DCC PI with the patient's identifying information omitted.

- **Documentation Considerations**

The treatment assignment should not be recorded in the research record or study file of the subject. In addition, if possible, the recording of information regarding treatment assignment in the medical record should occur only after/if the subject withdraws completely from the trial (due to death or request of the family/physician) and the conduct of the entire trial is completed. Every effort should be made to separate the recording of information regarding treatment assignment in the medical record from the research records and files.

- **Communication Considerations**

If unblinding is considered necessary after a patient has completed the trial, it is the responsibility of the PHN clinical center PI or investigator involved in the care of the patient to speak directly with the primary cardiologist to request that physician notes forwarded to the PHN center avoid reference to the patient's actual treatment received during the period of time that the trial is ongoing.

- **Post-Trial Completion Unblinding**

Unblinding guidelines apply equally to patients who have completed all trial requirements/study visits while the study is still active. At the end of all patient follow-up for the trial for all enrolled patients, treatment assignments will be provided to Clinical Center PIs by the DCC.

6.1 Introduction

The PHN undertakes unique scientific investigations impacting knowledge of the pediatric cardiology patient population and its care. Because of the great effort that goes into PHN studies and the large amount of resources used, study investigators have the right and responsibility to communicate their findings to the scientific community and to the public at large.

To minimize the possibility of inaccurate data in published materials, it is the policy of the PHN that all data and text considered for all papers, abstracts, and materials for presentation at scientific meetings be submitted to the Publications and Presentations (PPC) Committee for review and approval prior to presentation or publication. Also, the DCC shall review these materials to verify that they are accurate and consistent with data used in other PHN documents and papers.

PHN centers are not permitted to write papers on local data and experience related to PHN protocols. Investigators may lead or join a writing committee to prepare a manuscript on a topic of interest using data from the entire study.

6.2 Objectives

The objectives of the PHN Publications and Presentations policy are:

1. To ensure orderly and timely dissemination of all pertinent data resulting from PHN studies;
2. To ensure the scientific accuracy of PHN presentations and papers;
3. To ensure that all investigators, particularly those of junior rank, have the opportunity to participate and be recognized in PHN presentations and publications;
4. To ensure that press releases, interviews, presentations, and publications of PHN materials are accurate and objective, and do not compromise the scientific integrity of these collaborative studies;
5. To establish procedures which allow the PHN PPC and Executive Committee (EC) and the NHLBI to exercise review responsibility in a timely fashion for PHN publications and presentations; and
6. To maintain a complete up-to-date list of PHN presentations and publications, and to make this information readily available to all PHN investigators and the PHN DSMB.

6.3 Definitions

6.3.1 Main Papers and Presentations

Main papers and presentations are those reporting results dealing with the main hypotheses of the PHN study (e.g., primary and secondary endpoints, the design of the study) as well as papers and presentations using the complete study data set. In general, main papers and presentations refer to use of study data from all sites.

6.3.2 Abbreviated Communications

Abbreviated communications, typically in the form of a letter to the editor, may be appropriate from time to time for clarification of previously published work, response to critiques, or dissemination of important negative results that would not be publishable in a full paper.

6.3.3 Other Papers and Presentations

Other papers and presentations are those not encompassed by the above categories. Examples include those related to work done in ancillary studies or by a single center or a limited number of centers (i.e., using data from a subset of all the sites), or papers related to PHN operations.

6.3.4 Content

1. PHN study design, screening and baseline data may be used for preparation of abstracts and presentations prior to the planned end of the study.
2. Observational studies with complete data on an intermediate time point may be used for preparation of abstracts and presentations prior to the planned end of the study, either by agreement of the Study Committee or for Study Aims that were pre-specified in the protocol.
3. With the exceptions listed in points 1 and 2 above, PHN trial data involving randomized patients will not be analyzed for purposes of publication or presentation outside the PHN until the planned end of the study.

6.3.5 PHN Investigator

A PHN investigator is any physician or coordinator at a main or auxiliary clinical center or core lab, or statistician or project manager at the data coordinator center, or NHLBI scientist or coordinator who is involved in conducting a PHN study.

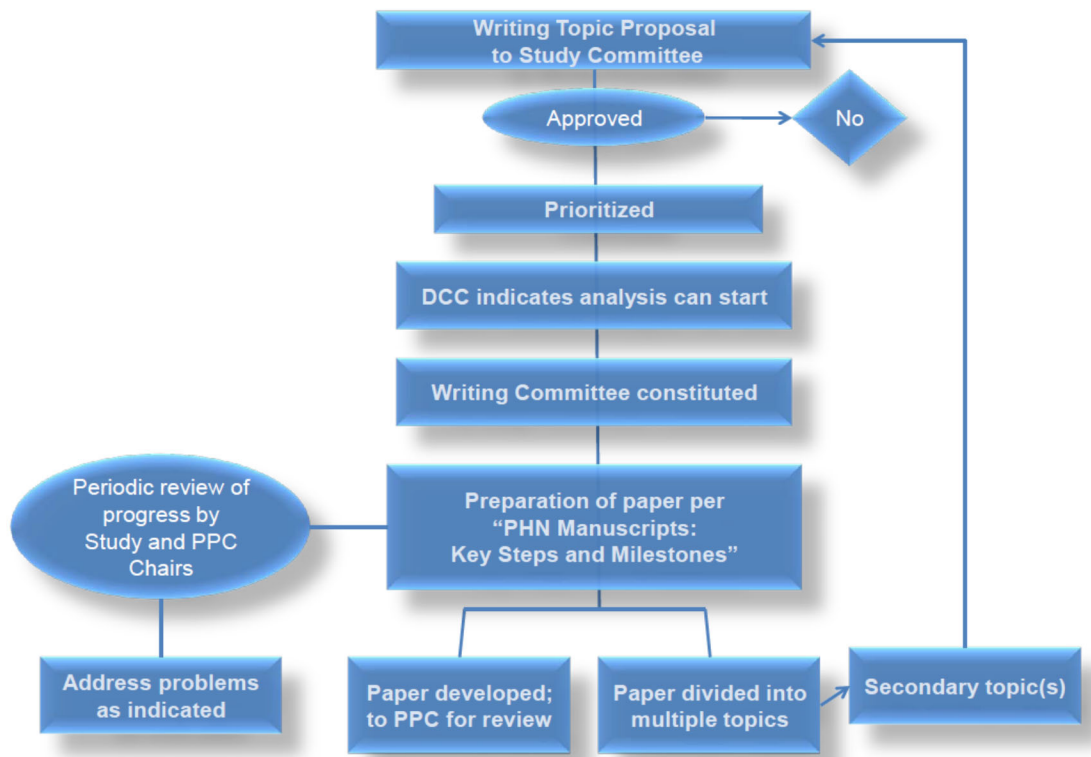
6.3.6 Quorum

All materials and decisions requiring approval by the PPC rather than just the PPC Chair require a quorum of 7 PPC members. In all instances, the waiting period for PPC member response is the stated deadline for the review/decision in question, even if 7 members reply before the deadline.

6.4 Proposal and Approval Process for Papers, Abstracts and Presentations

For each PHN study, the Study Committee plays an important role in identifying and prioritizing writing topics for development of papers and abstracts. Although the Study Committee will generate most proposals for abstract and paper topics, any PHN investigator can propose a writing topic to a Study Committee. An overview of the steps in this process is displayed in Figure 6.1.

FIGURE 6.1 STEPS FOR PREPARATION OF PAPERS



The Study Committee is charged with evaluating and prioritizing all proposals for abstracts, presentations, and manuscripts related to the main study.

1. Writing topic proposals must be submitted in writing to the Study Committee Chair. The proposal should clearly state the research question or hypothesis and include a brief background statement to clarify the purpose and importance of the research question using the [Writing Topic Proposal Form](#).
2. Writing Topic Proposals should be written with the understanding that only one paper will be prepared if the proposal is approved (see also #5 below).
3. Writing Topic Proposals should also be written with the understanding that the proposed paper can be completed using the existing study dataset. Although additional measurements may enhance the depth or breadth of a study dataset, priority will be given to writing topics that utilize existing study data,

which will facilitate the Network's mission of rapid dissemination of research findings.

Additional data collection and system modification requires resources at both the PHN sites and the DCC, and may divert resources from existing studies. Therefore, a strong justification for a request for additional data must be provided. If additional data are essential to a paper topic, then approval is required. The first step is for the request for additional data collection to be reviewed and approved by the Study Committee. If the Study Committee agrees, then the proposer must submit a request to the PHN EC using the [Request for Additional Study Data form](#).

4. The Study Committee will review the proposal within the context of other proposed and approved writing topics. If approved, the topic will be prioritized for development. If approved with modifications, the Writing Topic Proposal must be revised before it is sent out for WC member nominations.
5. If, during the course of developing a paper, the Writing Committee (WC) determines that the original topic is best addressed in multiple papers, the WC must choose the specific paper they will write and provide the Study Committee Chair with a brief explanation. The Study Committee Chair will determine the suitability and priority of the chosen subtopic, and has the discretion to involve the Study Committee as a whole in this assessment. Writing Topic Proposals will then need to be developed for topics not included in the chosen paper and these must be submitted, approved, and prioritized following the procedures herein. A WC(s) will be constituted for the approved topic(s) per the procedures in [Section 6.5](#).
6. In general, an individual should not be Chair of more than one actively working WC at a time. A WC is considered to be "actively working" from formation until a manuscript is submitted to a journal. With appropriate justification, the PPC Chair will approve exceptions to this rule.
7. The DCC will inform the Study Committee when data analysis for an approved writing topic can begin, and will assign a statistician to the topic.
8. From time to time it may become apparent, before a writing committee is convened, that there are negative or other minor results from a PHN or ancillary study that merit reporting, for example in the form of a letter to the editor. In this circumstance, the lead investigator—either the PHN study committee chair or the ancillary study PI—should notify the PPC chair of the intent to submit an abbreviated communication, along with the proposed author list. The PPC chair has the discretion to decide whether or not additional PHN authors need be identified.

6.5 Selection of Writing Committee Chair and Members for Papers and Abstracts

1. A WC will be constituted when the DCC indicates that data analysis for a topic can begin within two months. On behalf of the PPC Chair, the DCC will invite nominations from PHN principal investigators at each main and auxiliary site and the DCC, the study chair(s), core lab principal investigators for the study, Protocol Chair, and NHLBI. The Study Coordinator Chair will be similarly notified, and Study Coordinators interested in a writing topic should contact their respective Principal Investigators for consideration of nomination. The PI must provide the rationale for each nominee (such as level of participation in the development or implementation of the study protocol, or the nominee's specialty area of expertise). Most WCs will have one representative from each PHN site. However, in some instances it may be appropriate for a site to nominate more than one representative, and in others none, depending on the topic. A PI can propose more than one nominee, under exceptional circumstances, with appropriate justification. Nominations received by the stated deadline will be forwarded to the PPC Chair and to the Study Chair(s) and copied to the NHLBI.
2. In most cases, the proposer of a writing topic will chair the WC. The PPC Chair and WC Chair will determine the membership of the WC. All WCs for main papers, abstracts, and presentations will have DCC representation. Any disagreements about the membership of a WC will be addressed first by the PPC. If resolution is not possible, the matter will be referred to the EC.
3. It is the intent that selection of WC members is equitable and fair to all groups and individuals participating in this collaborative program, including encouragement of participation by younger professional colleagues and Study Coordinators, with due regard paid to exceptional efforts of groups or individuals.
4. The PPC Chair will send the list of approved WC members to the DCC. The DCC will then notify the members by email and send them the [PHN Writing Committee Responsibilities](#) and [PHN Manuscripts: Key Steps and Milestones](#). The DCC will post the writing topic, the WC members, and the approved writing topic proposal on the PHN website. The final analysis outline will be re-posted once the WC has met and finalized the plan.

6.6 Preparation of Papers

The steps listed below should be followed in the preparation of PHN manuscripts.

6.6.1 Responsibilities of the Writing Committee Chair

The Chair of the WC should first review the PHN Publications and Presentations Policy and then should:

1. Contact each WC member and review the specific charge to the WC and the timeline for developing the paper based on [PHN Manuscripts: Key Steps and Milestones](#).

2. Communicate with the WC to develop a detailed manuscript outline, specify research hypotheses, and draft dummy tables. The Writing Topic Proposal form is to be modified by the WC Chair to document all WC decisions.
3. Submit the finalized Data Analysis Request form and dummy tables to the DCC statistician and collaborate with the statistician to identify needed data and analyses. The WC was formed with the knowledge that the DCC is ready to perform needed analyses but all should be aware that the DCC will process all requests for data analysis according to the overall priorities of the PHN as determined by the EC. Analysis requests will be triaged by the DCC PI according to this principle and where necessary, if there are competing priorities across PHN studies, the EC will provide guidance.
4. Assume a leadership role in writing the paper. Obtain input from every member of the WC and make every effort to accommodate the expression of differing interpretations and alternate analyses within the body of the manuscript, so that all points of view are represented to the satisfaction of every member. The WC Chair is responsible for tracking and documenting the contributions of the members of their WC with regard to input provided on all draft documents.
5. Monitor the progress of development of the paper in relation to the [PHN Manuscripts: Key Steps and Milestones](#). Report the status of the paper development to the Study Committee Chair monthly, and present this report on the monthly Study Committee calls.
6. Communicate with the Study Committee Chair if the WC decides that the original writing proposal is too broad and should be divided into two or more papers rather than the one paper originally approved (see [Section 6.4.3](#)).
7. Monitor the participation of the WC members. Members of each WC should participate actively in the writing and review of the paper assigned to that group. The following process will be used for addressing non-performing WC members:
 - a. The WC Chair will first contact the individual directly and indicate concern over lack of participation. Defining this will be at the discretion of the WC Chair but, in general, would include failure to attend WC meetings or conference calls, failure to read and respond substantively to working drafts, and/or repeated failure to meet response deadlines.
 - b. If there is still no or inadequate response from the individual, the WC Chair will notify the Study Committee Chair and the PPC Chair and copy the respective center PI (in the event that the non-performing individual is a center PI, the WC Chair will then instead copy the NHLBI Project Scientist). The center PI (or PPC Chair) will then speak directly with the individual.
 - c. If reasonable participation is still not forthcoming, as determined by the WC Chair in consultation with the Study Committee Chair and PPC Chair, the individual will be removed from the WC and excluded from co-authorship. Whether the center PI can appoint a substitute will be considered on a case by case basis in consultation with the WC Chair and the PPC chair.

8. Draft a brief (3-5 sentences) summary of the manuscript for the PHN public website that addresses the following: background/reason for undertaking the study, overview of method, key findings, and implications.

6.6.2. Responsibilities of Writing Committee Members

Inclusion on a WC carries responsibilities that must be met in order to be included as an author for the paper or abstract (see [Section 6.7](#)). Each WC member is expected to:

1. Participate in all WC conference calls. If unable to attend a call, the member is expected to notify the WC Chair and the DCC and provide input to the Chair before the call.
2. Review the analysis summary before the call.
3. Review all drafts within the stated time frame (typically two weeks) and to provide commentary and/or edits to the WC Chair. If the topic of a conference call is to discuss a draft manuscript, members are expected to have read the manuscript before the call.
4. Review the final draft before its submission to the PPC and submit the approval signoff to the DCC.
5. Voluntarily withdraw from a WC if unable to participate fully in the WC process. This will not preclude future participation in other WCs.

6.6.3 Responsibilities of the Study Committee Chair

The Study Committee Chair is responsible for:

1. Leading the Study Committee in the identification of potential writing topics, followed by approval and prioritization.
2. Reviewing WC member nominations for appropriateness with the PPC Chair and finalizing the WC.
3. Reviewing the status and progress of approved papers and abstracts in relation to [PHN Manuscripts: Key Steps and Milestones](#) on at least a monthly basis.
4. Assist the WC Chair and PPC Chair in addressing non-performing WC members.

6.6.4 Responsibilities of the PPC Chair

The PPC Chair is responsible for:

1. Reviewing WC member nominations for appropriateness with the Study Committee Chair and finalizing the WC.
2. Performing a periodic systematic review of the work of all WCs.
3. Assisting WCs as appropriate or requested.
4. Collaborating with the Study Committee Chair to address non-performance issues related to an individual WC member or the entire WC, including revising the membership or reconstituting the entire WC when indicated.

5. Assisting the DCC in prioritizing work if DCC resources cannot accommodate all simultaneous analysis requests.
6. Summarizing PPC review of abstracts, presentations, and manuscripts, adjudicating PPC comments, and issuing a final PPC decision for approval or disapproval of submission for presentation and/or publication.

6.7 Authorship of Papers and Abstracts

1. For main papers and presentations, the names of members of the WC shall be listed as authors in the masthead, followed by the phrase "for the Pediatric Heart Network Investigators." The WC Chair, with the concurrence of WC members, should determine the order of authorship. The Chair may choose to add PHN investigators to the authorship who are not initially in the WC, with prior approval from the PPC Chair. A major criterion for order of authorship shall be the effort and contribution made by each member of the writing committee in preparation of the manuscript. Membership in a WC without substantive contribution to the manuscript does not justify authorship. In general, "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" ([NEJM 1991; 324: 424-428](#)) shall be adhered to with regard to authorship. Disagreement about the order of authors which cannot be resolved by the chair of the WC will be resolved by the PPC Chair or the full PPC if necessary.
2. The list of authors may not be exactly the same on the abstract and corresponding paper.
3. The phrase "for the Pediatric Heart Network Investigators" added after the names of the authors in the masthead is optional in papers reporting local data, or ancillary studies using local data.
4. Regardless of source of funding, papers produced from ancillary studies must acknowledge the use of PHN subjects in the Methods or Support section of the paper.
5. Acknowledgement of support from the NHLBI and any other sponsors must be included in all PHN papers and presentations. Acknowledge financial support (including the grant number) from the PHN and NHLBI/NIH with the following text: *"This work was supported by Grant Number(s) _____ from NHLBI" and "Its contents are solely the responsibility of the authors and do not necessarily represent the official views of NHLBI or NIH."* Study-specific text is posted on the PHN website on the home page for each study.
6. Disclosures of significant financial interest must be reported by all authors as required by the journal.
7. A credit roster of all major committees, core laboratories, the DCC, and PHN centers with their members (generally no more than ten persons from each center) is to appear at the end of each main paper (printed as an appendix). Each site PI, the DCC PI, and the NHLBI Project Scientist will be responsible for designating investigators from his/her center who are to be listed in this appendix. It is the responsibility of the DCC to solicit, obtain and prepare the final list for inclusion in each PHN study.

8. If an NHLBI staff member is listed as an author on a PHN manuscript, approval of the manuscript must be obtained by the NHLBI. To expedite approval, it is recommended that the article be submitted simultaneously to the PPC and the NHLBI.
9. If a coauthor of a PHN manuscript has a change in institutional affiliation between the time research was performed and the time of publication, the affiliation of the coauthor will be listed as the institution where the research was performed, regardless of whether the new affiliation is a PHN center. If the first author has a change, then the author's current institutional affiliation and address will be listed separately from the research affiliation section of the title page, for correspondence purposes.

6.8 Clearance and Submission of Papers

1. The final manuscript draft and summary for the PHN public website should be submitted to the DCC. The DCC will distribute this to each co-author for review with a form for final electronic sign-off. After this has been accomplished, the DCC will submit the manuscript and summary for the PHN public website to the PPC for review, with a specified deadline.
2. Submission to the PPC should be treated as if the manuscript is absolutely ready to be submitted to a journal, so drafts should be clean, with figures labeled appropriately, and references in proper format.
3. Journal requirements for length and other formatting should be followed.
4. Members of the PPC will prepare comments on the manuscript and a recommendation for approval, modification, or disapproval of the manuscript on the electronic form provided. These forms should be submitted to the DCC and to the WC Chair simultaneously by the deadline. If the WC Chair is simultaneously a member of the PPC, he/she will be recused from participation in PPC decision-making related to that manuscript (other members of the WC who are also on the PPC should still participate).
5. The DCC will forward all comments received by the deadline to the PPC Chair. The PPC Chair will prepare a summary letter indicating approval or disapproval, proposing a resolution to any conflicts among reviewers' recommendations, and indicating whether PPC review of the revised manuscript is required. This letter will be sent electronically to the DCC.
6. The DCC will then send the summary letter and copies of the comments from individual PPC members electronically to the WC Chair and members.
7. If only minimal revisions (as indicated by the PPC Chair in the summary letter) are requested, the manuscript may be submitted for publication without additional PPC review. A copy of the submitted manuscript should be sent electronically to the DCC and to all co-authors by the WC Chair.
8. If substantial revisions (as indicated by the PPC chair in the summary letter) are required, the revised manuscript will require formal re-approval by the co-authors, and then will be submitted to the DCC for distribution to the PPC for review and approval before submission to the journal.

9. If revisions to a manuscript are requested by a journal, the manuscript will be revised with input from all co-authors, at the discretion of WC chair, depending on the extent of the revisions and need for certain expertise among the WC members. All co-authors will confirm that they agree with the revisions. The revised manuscript and the letter to the editor will be sent to the DCC and forwarded to the PPC Chair for approval before resubmission to the original journal or to a new journal. If major revisions (with 'major' determined by the PPC Chair) were requested by the journal, the PPC will review the manuscript again.
10. If responses to published commentary are requested by a journal editor, the WC Chair will prepare and distribute the document to coauthors and PPC Chair for review with cc: to the DCC. The WC Chair will determine authorship of the commentary based on contributions, journal requirements/limitations, subject matter, and time frame. Distribution and documentation of published commentary will follow step number 10 above.
11. Since all circumstances that might cause disagreement among PHN investigators on the content and conclusions of a given paper cannot be foreseen, these disagreements will be resolved by the PPC. If resolution is not possible within the PPC, the matter will be referred to the EC.

6.9 Submission of Manuscripts to Pub Med Central

When a manuscript is accepted for publication, it must be submitted to the National Library of Medicine's Pub Med Central as required by the [NIH Public Access Policy](#).

1. The lead author is responsible for submission of any manuscript arising from a project with direct funds from NIH to the National Library of Medicine's PubMed Central. Assistance from the DCC with the submission process is available; however, the final responsibility for submission remains with the lead author.
2. Prior to submitting a manuscript to a journal, the lead author must ensure that all agreements with the journal publisher permit: 1) submission of the accepted manuscript to Pub Med Central; and 2) archiving the manuscript in the PHN central repository.
3. When a manuscript has been accepted for publication, the lead author must submit the manuscript to Pub Med Central using the [NIH Manuscript Submission System \(NIHMS\)](#). A final manuscript includes manuscript revisions resulting from the peer review but not necessarily copyediting changes from the publisher. This submission fulfills the requirement to submit a copy of a publication with a grant progress report.
4. The lead author should indicate when the manuscript should be made public, i.e., from publication date to 12 months later.
5. If the manuscript is accepted by a journal that submits all NIH-funded final published articles to Pub Med Central, then no further action is required by the lead author. Journals that do this are listed at http://publicaccess.nih.gov/submit_process_journals.htm.
6. The lead author should send the initial NIHMS ID and then the PMCID to the DCC. When preparing an application, proposal, or progress report, papers that resulted from NIH funding must be cited by including the Pub Med Central reference

number (PMCID) at the end of the citation. When a PMCID is not yet available, then include the NIH Manuscript Submission System reference number (NIHMS ID) and state "PMC journal -- in process".

- Note: PubMed (PM ID) and PMC (PMC ID) numbers are different numbers.

6.10 Preparation, Submission, and Presentation of Abstracts at National and International Meetings

The PHN website contains a current list of all relevant meetings and their deadlines for submission of abstracts, including but not limited to the American Heart Association, the American College of Cardiology, the American Academy of Pediatrics, the American Society of Echocardiography, the Society for Pediatric Research, World Congress of Pediatric Cardiology, Heart Rhythm Society, and the Society for Clinical Trials.

1. Abstracts should be prepared only with the prior approval of the corresponding Study Committee Chair. Abstracts involving PHN process or other more general topics not limited to a single study should instead be discussed with the PPC Chair.
2. With rare exception, abstracts must be based on a manuscript already under development in a previously convened WC, and will be prepared by that WC. The Study Committee will give priority to abstracts based on manuscripts that are near completion. If an abstract proposal does require the formation of a new WC, then the steps for Study Committee approval and WC nomination outlined in [Sections 6.4-6.7](#) should be followed.
3. In the rare event that a proposed abstract requires formation of a new WC, the proposal must be submitted to the Study Committee and then to the DCC at least 4 months prior to the meeting abstract deadline to guarantee the availability of completed data analyses, the opportunity for WC discussion and interpretation of initial findings, and completion of requests for any secondary analyses.. The initial analyses will be provided to the WC Chair of the abstract at least 7 weeks prior to the abstract deadline.
4. All WC members should have the opportunity to have input into the abstract and must approve the final draft before its submission to the PPC. WC members will be listed as co-authors only if they have reviewed the abstract and accepted authorship prior to the abstract submission deadline.
5. The final abstract must be approved by the PPC before it can be submitted to the meeting organizers for consideration. Completed abstracts and certification of co-author review must be submitted to the PPC at least 10 days prior to the abstract deadline in order to guarantee review and allow time for revision if required by the PPC. Supporting data in the form of tables and graphs should be included if these data are not contained in the abstract.
6. WCs are encouraged to have a first draft of the manuscript available for review by the entire Committee within 12 weeks of presentation of the abstract.

7. Abstracts from ancillary studies must also be approved by the PPC prior to submission to meeting organizers. For an ancillary study using only local data, as determined by the Ancillary Study Committee (ASC, see [Chapter 7](#)), permission of the PPC must be obtained before submission of results for presentation or publication if this occurs before publication of the main PHN study results. For all other single-center and multi-center ancillary studies, the ASC will determine the level of PPC review and approval required. If an abstract is submitted without prior PPC approval, and the PPC then disapproves, the author(s) will be required to withdraw that abstract immediately.
8. When an abstract is selected by the organizers for presentation at the meeting, the presentation itself—e.g. PowerPoint slides, poster, or other format—must also be reviewed and approved in advance by the PPC. Submission of the presentation for PPC review should occur no later than 10 days prior to the meeting date.
9. Presentations should:
 - Acknowledge all co-authors and the PHN
 - Include relevant financial disclosures
 - Acknowledge support from the NHLBI and any other sponsors. Acknowledgement of financial support (including the grant number) from the PHN and NHLBI/NIH should use the following text: *“This work was supported by Grant Number(s)_____ from NHLBI” and “Its contents are solely the responsibility of the authors and do not necessarily represent the official views of NHLBI or NIH.”* Study-specific text is posted on the PHN website on the home page for each study.
10. Slides or posters which either a) have been reviewed and approved previously and used again for a different presentation or b) have been prepared using only published PHN data do not need to be reviewed again by the PPC. Copies of the slides or poster along with a description of the presentation (meeting name, purpose, date) should be sent to the DCC to include in the PHN bibliography. Presentations that include a few slides with published PHN data but do not focus on PHN studies do not have to be reported to the DCC.

6.11 Preparation and Submission of Abbreviated Communications

Preparation and submission of letters to the editor and other abbreviated communications should, in general, follow the process outlined above for abstracts and manuscripts. The PPC chair may review these administratively or instead decide to refer them for full PPC review. The PPC chair should be consulted for questions of authorship on such communications.

6.12 Documentation of Publication Process

1. For each publication, a Checklist will be maintained by the DCC so that adherence to the publication process is documented for each publication.
2. The DCC will document publication status on the PHN website for all PHN publications. The author list and analysis outline for each paper will be posted on the PHN web site.

3. For the SC and Study Committee calls, a summary table of manuscripts under preparation will be provided on a monthly basis.

6.13 PHN Ancillary Studies and Presentations

1. Proposals for ancillary studies are submitted in accordance with the ASC guidelines. The [Ancillary Study Application Form](#) is available on the PHN website.
2. For single-center and multi-center ancillary studies using data or biospecimens from the main PHN study, the selection of a WC for ancillary study findings, the preparation and submission of papers, and the submission of abstracts may be required to follow the same PPC guidelines that apply to other PHN papers. The ASC will determine the level of PPC review required and inform the PPC Chair and PI of the requirements.

6.14 Dissemination of Information

Dissemination of study results is an important part of the PHN mission. Results can be distributed in manuscripts and abstracts as well as informal talks, articles, interviews, and postings to the PHN public website. When communicating with media representatives about PHN studies it is important to:

- Emphasize the importance of pediatric research in addition to the significance of the science
 - Mention the PHN specifically and refer reporters to the [PHN public web site](#)
 - Mention NHLBI and any other applicable funding sources (e.g., National Marfan Foundation, Children's Heart Foundation, FDA)
1. Prior to abstract presentation, the responsible WC is required to submit a copy of the slides or poster, including tables and graphs, to the PPC for review and approval well in advance of the particular meeting. It is also helpful to submit a copy of the presentation text if available. Templates for slides and posters that include the PHN logo, and the NIH and NHLBI logos are available on the PHN website and should be used for all presentations and on all posters. Each presentation shall be identified as the work of the PHN Study Group, be presented "for the PHN Investigators", and acknowledge NHLBI/NIH support.
 2. For an ancillary study using only local data, as determined by the ASC as presented in [Chapter 7](#), permission of the PPC must be obtained before submission of results for presentation or publication if this occurs before publication of the main PHN study results. In publications from such studies, the Methods section should specify the site of interpretation of the data, if applicable (local vs. core). These presentations need not use the PHN slide or poster template nor include the phrase "for the PHN Investigators."
 3. For presentations or publication of single-center or multi-center ancillary studies using main PHN study data or biospecimens, slides and illustrations prepared by the presenting investigator must be approved by the PPC, if so determined by the ASC.

4. Once a main paper has been presented at a scientific meeting, the slides used should be available to PHN investigators and may be used by them at other scientific meetings. However, any such subsequent presentations that will appear in published form must receive approval from the Study Committee and the PPC prior to the presentation, unless the data in the original paper are already published. This review can be expedited assuming that the same slide set is used.
5. The meeting name, date, and location for all such presentations should be forwarded to the DCC by the presenter to include in the PHN bibliography.
6. In the case of study results scheduled for presentation before an organization issuing press releases, the presenter may submit, for release to the press, the text of the presentation after it has been approved by the PPC. If the presentation is based on a manuscript not yet accepted for publication in a peer-reviewed journal, a sentence must be included on the front page indicating the preliminary nature of the results.
7. Slides that have been used at national or international meetings and illustrations or publications of the main study results must be sent to the DCC for archiving, and will be made available to PHN investigators on the PHN administrative web site by the DCC.

6.15 Invitations to PHN Investigators for Presentation of PHN-Related Information

The PHN welcomes opportunities to participate and present reports at national and international scientific meetings. When a member of the PHN receives such an invitation, PHN policies with regard to publications and presentations must be followed.

1. When a PHN investigator is invited to make a presentation about the PHN and/or its studies at a national or international meeting, the invitation shall be sent to the PPC for review and approval. If the request is relevant to a specific PHN study, the Study Committee Chair should be asked to review and approve the request before it goes to the PPC Chair.
2. The slides for presentation (PowerPoint or other format) must be reviewed and approved by the PPC in advance of the meeting date. Presentations based entirely on previously published PHN data may be approved administratively by the PPC Chair, in consultation with the respective Study Committee Chair(s) if indicated.
3. Any presentation of unpublished PHN data or data not otherwise previously presented must be reviewed and approved by the relevant Study Committee and then by the PPC prior to the date of presentation. The proposer will be required to submit a written proposal to the Study Committee, which will consider the proposal within the context of other proposals and WCs, and prioritize it. The proposal should clearly state the research question or hypothesis and include a brief background statement to clarify the purpose and importance of the question. The standard steps for presenting an abstract will be followed in this case ([Section 6.12](#))

4. Presentations of previously published PHN data by PHN investigators at local meetings (city, state or regional) need no prior clearance by the PPC if the presentation is not to be published. However, all such local presentations must be reviewed and approved by the principal investigator at the center making the presentation. PHN investigators should be encouraged to accept such invitations, and should notify the DCC so the DCC can keep record of these presentations.

6.16 Use of PHN Material for Graduate/Medical Student Theses or Dissertations

1. The PPC will review all requests for use by students of PHN data that are not available in public use datasets.
2. The student requesting PHN data must be associated with an investigator in the PHN study. The PHN investigator shall act as the student's "sponsor" with regard to the data request.
3. Students may not use PHN data if the data related to the PHN study's main paper are in progress or if the PPC deems the data necessary for a future paper.
4. If the PPC recommends approval for the use of the requested data, a review group will be established and will include the student as convener of the group.
5. In most instances the data will be analyzed by the DCC under the direction of the student with respect to research and analysis aims, and compensation to the DCC must be provided according to the terms of a consulting contract. If the data are to be analyzed by the student directly, the DCC will forward a dataset containing the specific variables required by the proposal. If the student requires significant assistance with handling the data or its analysis, a consulting contract with reimbursement to the DCC will also be required. Independent analysis by the student will be for the purpose of an institutional thesis or dissertation only and not for submission to a journal.
6. The review group will take no action regarding the paper until the student has completed and defended the thesis or dissertation, provided this occurs in a reasonable length of time. (The student's sponsor will be requested to report on the student's progress to the PPC.)
7. The students must include in the completed thesis the following:
 - a. a statement acknowledging the PHN for use of the data;
 - b. a statement indicating that opinions, ideas, and interpretations included in the thesis or dissertations are those of the student alone and not necessarily those of the PHN Investigators.
8. When the thesis or dissertation has been completed as determined by the sponsor, the dissertation review group will proceed to prepare the paper(s) for publication. A WC will be formally constituted and will be composed primarily of the review group members. The student should be given the opportunity to take the lead on the paper. If the research topic becomes a formal Writing Topic for the PHN and it was independently analyzed by the student, then analyses for journal submissions will be repeated and/or confirmed by a DCC statistician. The student will be required to submit his/her analysis program(s) to the DCC.
9. The PHN publication policy will apply to any material published from the thesis or dissertation.

10. The PHN reserves the right to proceed with preparing a paper for publication on the thesis or dissertation topic if, in the view of the PPC, the student has not made reasonable progress on completing the thesis or dissertation.

Chapter

7 Ancillary Studies Policy

Investigators are encouraged to propose and conduct Ancillary Studies, particularly multi-center Ancillary Studies. Such studies will enhance the value of main PHN studies and ensure the continued interest of a diverse group of investigators. They provide an exceptional opportunity for investigators, whether within or outside of the PHN, to conduct additional projects at minimal cost, and with greater feasibility and efficiency.

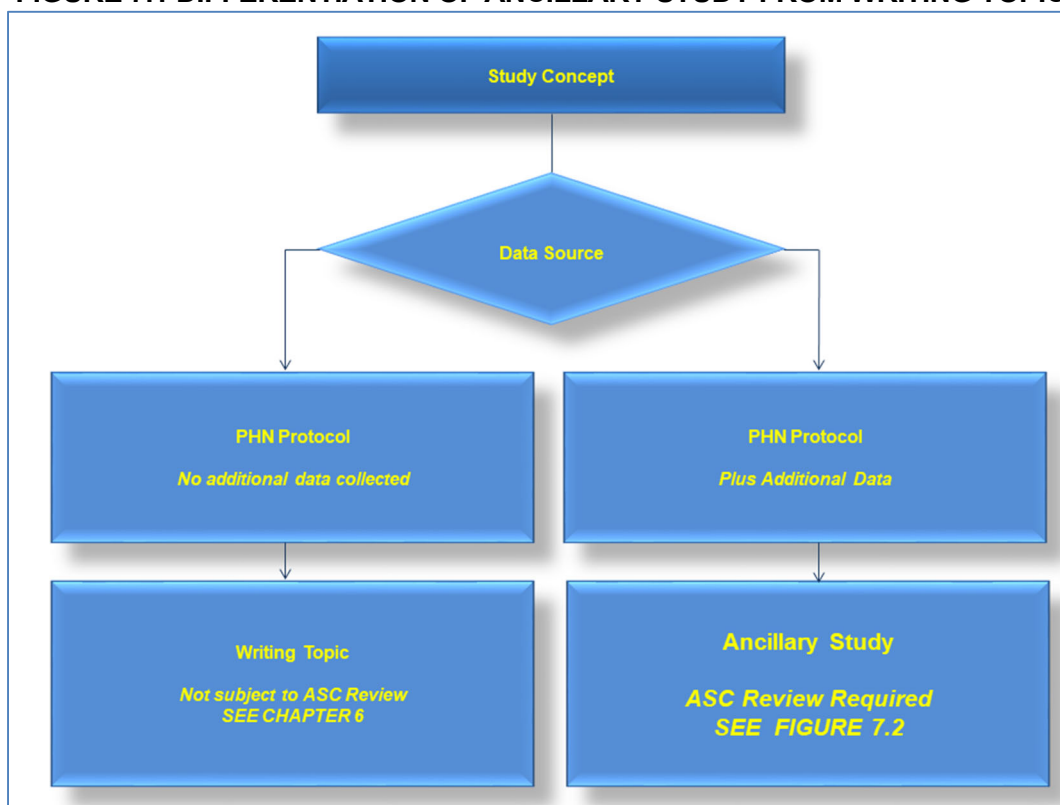
All Ancillary Studies must undergo review by the Ancillary Study Committee (ASC). This is not an administrative review but is aimed at protecting the successful completion of the main study and increasing the likelihood of successful extramural funding of the ancillary study. The review provides a thoughtful critique to address areas of the proposal that are weak, incomplete, or lack sufficient clarity in an effort to improve the application. Approval of the Ancillary Study may be accompanied by a strong Letter of Support from the PHN signed by the ASC Chair and the Data Coordinating Center (DCC) Manager.

7.1 Definitions

7.1.1 Ancillary Studies

Ancillary Studies are investigations that are not part of a main PHN protocol, but use PHN study participants, biospecimens, or data collected by the PHN. Ancillary Studies should be differentiated from Writing Topics (see [Figure 7.1](#)). Writing Topics use existing data for additional or secondary analyses to answer specific questions. All data for the proposed Writing Topic have been collected in an established PHN database. No additional data are collected and the proposal does not undergo ASC review. In contrast, an Ancillary Study involves acquisition of additional data, regardless of type or amount that were not collected as part of the main PHN protocol. A proposal that requires additional data to be combined with the existing PHN data is subject to the Ancillary Study review process.

FIGURE 7.1 DIFFERENTIATION OF ANCILLARY STUDY FROM WRITING TOPIC



7.1.2 PHN Investigators

A PHN Investigator is any member of the relevant main study team from the DCC, a PHN core center, PHN auxiliary center, or core laboratory. These centers are considered “initiating centers”.

7.1.3 Initiating Centers

An initiating center is one that has participated in the development of the main study or trial concept and protocol. NHLBI will determine which centers are considered initiating centers.

7.2 Funding

Support for Ancillary Studies is not available through PHN grant funds. Additional funding is typically required and can be sought from a variety of sources, including NIH research and career awards, grants from academic institutions, and funding from foundations, granting agencies, institutions, or other private sources. The additional demands on each participating center and study subject must be considered and accounted for in the budget. For example, if a study coordinator must retrieve and submit data, the Ancillary Study budget must address the hours needed to complete these tasks and include appropriate compensation. If support from the PHN DCC or support for an outside DCC is required, the costs must be addressed in the budget and include any fees associated with IRB submission, data use agreements, etc.

In addition to the funding needed for study execution, the budget must include funds to support the extraction of requested Main Study data from the DCC. Investigators proposing an Ancillary Study will need to provide a **complete and detailed** list of the data elements needed for their proposal. An incomplete list of the data elements leads to multiple data export requests and inflates the cost of the data export process. The list should be formatted by the study form name and question number. Study forms are available under the main study on NERICConnect. The formatted list should be sent to the [DCC](#) at least **2 weeks** prior to finalizing the Ancillary Study budget. If additional PHN DCC services are anticipated to support the proposed Ancillary Study, an additional agreement will be enacted.

7.3 Ancillary Study Philosophy

All Ancillary Studies should adhere to the following “universal guidelines”:

1. The specific aims of an Ancillary Study must not overlap extensively with the goals of ongoing PHN studies and cannot preempt the findings of the main study.
2. The Ancillary Study cannot adversely affect either enrollment of patients into the main PHN studies or performance of testing/procedures required in the main study protocols. Required main study tests/procedures should be completed before tests/procedures are done solely for the purpose of an Ancillary Study. If this is not possible, the investigators of the Ancillary Study must provide justification for the timing of the Ancillary Study tests/procedures and provide a clear plan for minimizing the impact on the main study.
3. Ancillary Study data associated with clinical trials must never be unblinded before analysis of the main trial results is concluded and the primary results have been published.
4. Centrally interpreted data will be used for all study measures that undergo core laboratory review if more than one center is participating in an Ancillary Study.
5. Approval of the Ancillary Study is granted only for the specific testing and analysis detailed in the proposal. Data provided by the PHN cannot be used for other analyses or testing of additional hypotheses without prior approval from the ASC.
6. Partial support from the PHN must be acknowledged when Ancillary Studies include data collected or testing/procedures done solely for PHN research purposes and supported by NHLBI/NIH funds.

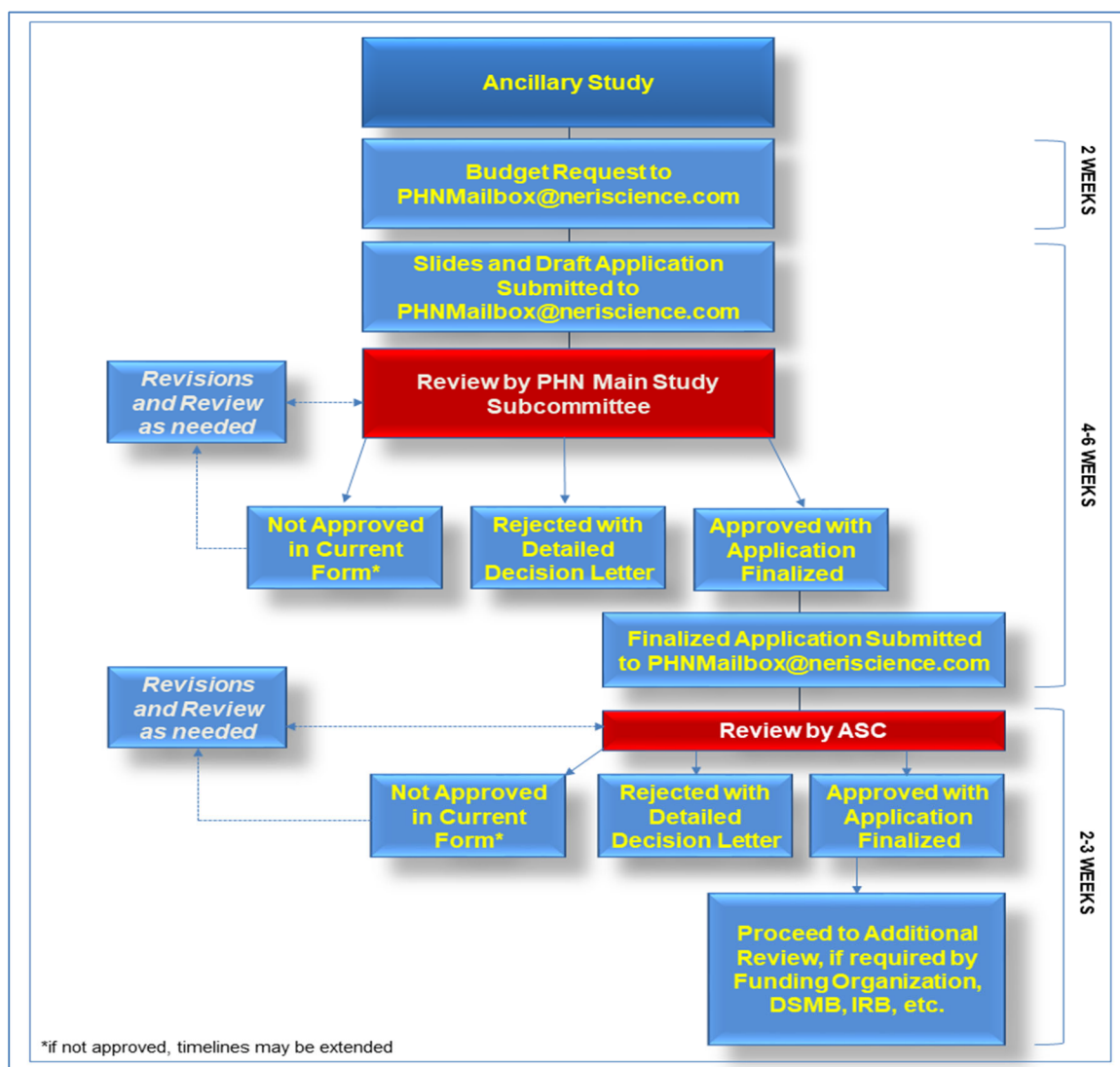
7.4 Proposal Process for Ancillary Studies

1. Any investigator can propose an Ancillary Study to the PHN, but a PHN investigator from an initiating center for the main study must be a co-investigator for every multi-center Ancillary Study.
2. Ancillary Studies that use only local data do not require a PHN co-investigator.
3. Members of the PHN Protocol Review Committee (PRC) or Data and Safety Monitoring Board (DSMB) may not propose Ancillary Studies, although researchers from a division or section different than the one with which the PRC or DSMB member is affiliated may do so. This is to avoid the appearance of a conflict of interest for PRC and DSMB members.

7.5 Application and Review Process for Ancillary Studies

1. If the proposed Ancillary Study is to be part of a grant application, **ASC approval must be obtained before the grant is submitted**. As delineated below, the anticipated total time from date of submission of the Ancillary Study to the Main Study subcommittee to final approval by the ASC is 8 weeks. Grant deadlines are published well in advance and investigators should address the timeline for the ASC review process early in the grant planning stage. If a Letter of Support (in addition to the ASC approval letter) is requested for the grant application, the Ancillary Study Principal Investigator (PI) should provide a draft of the proposed letter with the ASC application. If the study is approved, the ASC chair and the DCC manager will edit and sign the Letter of Support.
2. Proposals for Ancillary Studies must be submitted in writing to the PHN DCC, using the [Ancillary Study Application Form](#). This form can be accessed in the Policies and Templates section of the PHN Administrative website NERIScience. *Refer to [Section 7.9](#) and [Chapter 9](#) for additional information for studies requesting biospecimens.* NIH Biosketches are required *only* for the PI and the senior mentor (as appropriate). The preliminary Application Form and accompanying documents (including slides for the presentation to the Main Study Subcommittee) should be submitted to the DCC at PHNMailbox@neriscience.com. The subject line of the email should state "PHN Ancillary Study Application."
3. The Ancillary Study review process begins with a review by the PHN Main Study Subcommittee ([Figure 7.2](#)). The preliminary Application Form and slides will be forwarded to the Main Study Subcommittee. The proposal is not accepted for review by the ASC until approval is granted by the Main Study Subcommittee and the Ancillary Study Checklist (see [Section 7.8](#)) is completed. Submission of the final Ancillary Study Application that has been approved by the Main Study subcommittee, the Checklist, and appropriate Biosketch(es) triggers the process for Ancillary Study review. The DCC will track the date of successful completion of each step in the review process. The number of revisions, response time of the investigators, and additional reviews, if any, will affect the length of the review process.

FIGURE 7.2: ANCILLARY STUDY PROCESS



4. Within 2 business days of receipt of the application, the DCC will notify the appropriate Main Study chair(s) via email and attach the Ancillary Study Application and/or slide presentation and the Ancillary Study Checklist. The DCC, Main Study chair(s) and the Ancillary Study PI will set up a conference call with the Main Study subcommittee members within 4 weeks. Review of the proposal is typically added to the agenda for the next scheduled Main Study Subcommittee call. If a regularly scheduled call cannot accommodate the Ancillary Study review in its agenda, the DCC, Main Study chair(s) and the Ancillary Study PI will set up an additional conference call with the Main Study Subcommittee members within 4 weeks. ***The Checklist must be completed and the application (including revisions, if any) must be approved by the Main Study Subcommittee prior to being submitted for ASC review.***

5. Upon receiving the completed Checklist and approval by the Main Study subcommittee, the DCC will review the application for completeness. Completed applications will be forwarded to the ASC within 2 working days.
6. Within 2 business days of submission of the appropriate complete documents to the ASC, the DCC will poll members for setting a conference call for discussion. The call will be scheduled to allow 2 weeks for ASC members to review the Ancillary Study documents.
7. The ASC members will submit their written reviews via email to the DCC and the ASC Chair. The ASC Chair will determine if the Committee can conduct the review solely via email or continue with the scheduled conference call. If no call is necessary, the scheduled call will be cancelled. Otherwise, review results will be compiled by the DCC and forwarded to the ASC members at least 1 working day before the call.
8. At the ASC Chair's discretion, the PI may be asked to be available to answer questions during the discussion of their proposal.
9. The results of the ASC discussion will be summarized by the Chair and the DCC within 2 working days. A letter detailing any deficiencies and the final decision of the committee will be sent to the PI within 3 working days.
10. If the Ancillary Study is **"approved"**, the grant application can be submitted as directed by the funding agency. A letter of support from the PHN will be provided by the ASC and DCC Chairs, upon request. If the ASC review is not favorable, the Ancillary Study will either be **"rejected"** without further consideration or **"not approved in its current form"**. If the study is rejected, a detailed explanation will accompany the rejection letter. If the study is not approved in its current form, the deficiencies will be listed and the PI will be given an opportunity to respond. The revised application (with track changes) and a letter responding to each deficiency should be submitted to the [DCC](#). The subject line of the email should state "PHN Ancillary Study Application, revised" and the review process will be reinitiated. Studies that are either "rejected" or "not approved in its current form" cannot be submitted to the funding agency. Only formally approved studies can be submitted.
11. All approved Ancillary Studies must be submitted for DSMB review and approval prior to study launch.
12. After the ASC and DSMB have approved a multi-center Ancillary Study that is open to PHN centers' participation, it will be announced by email or at the next Steering Committee call or meeting, so that all centers can consider joining the study.

7.6 Review Criteria

1. In general, the ASC will consider the following elements in evaluating proposals for Ancillary Studies:
 - a. Scientific merit
 - b. Incremental burden on study subjects and personnel
 - c. Risk to study participants
 - d. Potential interference with the main PHN study
 - e. Adequacy of proposed funding

- f. Likelihood that the study will be completed successfully
- 2. At each level of review, highest priority will be given to studies that:
 - a. Do not interfere with the main PHN protocol objectives
 - b. Have the highest scientific merit
 - c. Result in the smallest burden on PHN participants
 - d. Require the unique characteristics of the PHN cohort

7.7 Publication Considerations (See also Publication and Presentations Policy in [Chapter 6](#))

1. The PI of the Ancillary Study will be responsible for meeting all the requirements outlined in the Publications and Presentations Policy (Chapter 6), unless otherwise specified by the ASC.
2. The PI of an approved Ancillary Study usually will serve as the lead for papers based on that study.
3. At the time of approval of an Ancillary Study, the ASC will determine the level of participation to be extended to initiating centers and communicate this decision in the acceptance letter to the PI.
4. If the Ancillary Study utilizes PHN primary study or core laboratory data or banked biospecimens for main outcome(s), all PHN Centers that contributed the data must be invited to participate in writing committees for all papers resulting from the study. At the earliest possible opportunity, the Ancillary Study PI should draft a list of intended writing committee members and submit it to NERI for circulation to PHN participating center/ core PIs for approval. The approved list of nominees will then go to the PPC and the PPC chair will finalize the writing committee. The Ancillary Study PI and the PHN center PIs should exercise discretion in making these nominations:
 - a. At a minimum, nominees must have contributed to the acquisition of the data and must read and revise the manuscript critically for important intellectual content.
 - b. Each participating PHN center and core laboratory will be invited but not obliged to participate in the writing committee.
 - c. In general, each center will have no more than one representative on the writing committee.
 - d. Under exceptional circumstances, the requirement for PHN co-authors may be waived by advance agreement with the ASC and PPC Chairs, in consultation with the respective main study Chair(s).
5. Based on the guidance from #1 above, the Ancillary Study PI will notify the Publications and Presentations Committee (PPC) of the intent to prepare an abstract, paper or presentation.
6. For a study reporting *only* local PHN data as determined by the ASC:
 - The PPC must concur with submission of results for presentation or publication if this occurs before publication of the main PHN study results.

If centrally interpreted data are used, the Methods section of any publication should specify that readings were performed in a core laboratory.

- An abstract request must be made to the PPC at least 3 weeks before the abstract deadline. The purpose of PPC review is to ensure that the results do not preempt the main PHN study with respect to important outcome measures, and that the abstract adheres to the PHN's ancillary study principles.
7. The letters of Ancillary Study approval will include the following statement to inform the PIs that they must acknowledge financial support for all papers, abstracts and presentations from the PHN and NHLBI/NIH with the following text:
- "This publication was made possible by Grant Number(s) _____ from NHLBI." or "The project described was supported by Grant Number(s) _____ from NHLBI" and "Its contents are solely the responsibility of the authors and do not necessarily represent the official views of NHLBI or NIH."*

7.8 Ancillary Study Checklist for the Main Study Committee

The main study subcommittee must approve all Ancillary Studies prior to submission to the ASC. This ensures protection of the conduct and results of the main study. The process for review by the main study committee should be transparent and inclusive with a detailed review of all elements of data collection, burden of data collection and testing/procedures on both the subjects and staff, and likelihood of successful completion. The timelines for main study enrollment should be considered. If the Ancillary Study is rejected, a detailed explanation will be submitted along with the rejection. If revisions are needed, these should be made and approved before the main study subcommittee completes the checklist and the revised study is submitted to the ASC. The Check List must be completed and submitted with all approved Ancillary Studies.

Ancillary Study Checklist (will accompany the submission of the application)

1. The information obtained from the Ancillary Study is important and is not included in the main study. _____
2. Ancillary Study Consent:
 - Will be obtained after the consent for the main study. _____
 - Has a statement that the patient can participate in the main study without participating in the Ancillary Study. _____
3. The Ancillary Study Protocol:
 - Specifically defines the burden of additional data collection and testing/procedures on the patient/family. _____
 - Specifically defines the burden of additional data collection and testing/procedures on the staff. _____
4. Plans to minimize the burden on both the patients/families and staff are explicit in the application. _____

5. Study coordinator time (enrollment of subjects, data collection, testing/procedures, handling of specimens, etc.) is detailed and accounted for in the budget. _____
6. An agreement with the DCC for data extraction has been completed and included in the budget. _____
7. A statement that the Ancillary Study results will not be published before the results of the main study is included in the application. _____

Approved _____

Rejected _____

Date: _____

Chair _____

7.9 Ancillary Studies Involving Biospecimens or Biologic Datasets

1. If the proposed ancillary study involves use of existing biospecimens or existing biological datasets generated from biospecimens, the proposal will first be reviewed by the PHN Biospecimen Committee for appropriate use of the specimens/data. The proposal must be submitted in writing to the PHN Biospecimens Committee using the [Ancillary Study Application Form and the supplemental Biospecimen / Biological Data Request Form](#). Both forms can be accessed in the Policies and Templates section of the PHN Administrative website NERISConnect. The results of the Biospecimens Committee review will be submitted to the ASC Chair. If the proposed study is limited to use of biospecimens or biological data only, the ASC Chair may administratively approve the proposal. If the proposed study involves use of PHN study data in addition to the biospecimens or biological data, the proposal will be reviewed by the full Committee (see [Figure 7.3](#)). Biological data is defined as sequencing, genotyping, gene expression, proteomics or metabolomics data
2. Requirements for Writing Committees for genetic ancillary studies are as follows:
 - a. If the manuscript is primarily methodological, it is not required that all PHN Centers that contributed data/biological samples be invited to participate in the Writing Committee.
 - b. If the study utilizes phenotype data, all PHN Centers that contributed data/biological samples should be given the opportunity to participate in Writing Committee(s). The Center PIs will be invited to extend this opportunity to a qualified individual. Centers may opt out of participation. The Requirements for Authorship will be used to determine the Writing Committee.
 - c. If the opportunity for authorship is not extended to all centers, clear written justification must be submitted and reviewed by the ASC.
 - d. The PHN in general and the names of PHN centers that contributed data or biological samples must be included in the manuscript Methods and Acknowledgements sections, respectively. Individual investigator names from the centers are not required. If the origin of the data or biological

samples cannot be determined, then acknowledgement of only the PHN is required.

Please refer to [Chapter 9](#) for detailed Biorepository and biospecimen use policies.

7.10 PHN-PCGC Genomic and Clinical Data Sharing Policy

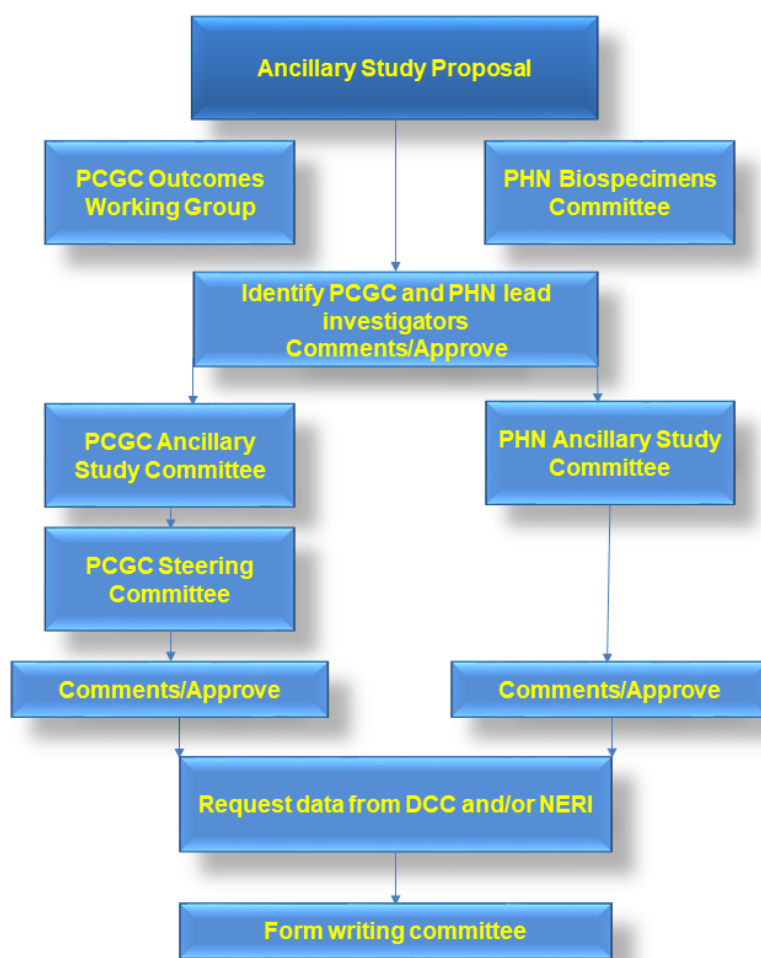
7.10.1 Scope of Work: PHN-PCGC Clinical Outcomes Collaborative Projects

The overall goal of this document is to establish the foundations for sharing genomic and clinical data between the PHN and PCGC as part of a collaborative endeavor to relate genomic variants to clinical outcomes in patients with congenital heart disease enrolled in the PHN or PCGC. The principal objectives of this Scope of Work are to provide guidelines for development and review of joint projects, to delineate the processes for sharing genomic and clinical data between the consortia and to ensure that all investigators have the opportunity to participate and be recognized in research projects relating genomic variants with clinical outcomes.

For the purpose of this document, clinical data that originates from subjects enrolled in the PHN are owned by the PHN and data (clinical or genomic) that originates from subjects enrolled in the PCGC are owned by the PCGC. Genomic data generated from PHN patients with PCGC funds are jointly owned by PCGC and PHN. Genomic data generated from PHN patients by the PHN (outside of the PCGC) are owned by the PHN.

An Ancillary Study that requires genomic and clinical data from the PHN and PCGC will first be reviewed by the PCGC Outcomes Working Group and the PHN Biospecimens Committee. The investigator submitting the proposal will be required to identify a co-lead investigator from the other consortium. The committees will vote to approve or recommend changes/clarifications that will be addressed by the submitting investigator. If independent projects are proposed with similar or overlapping aims, the Working Group and Biospecimens Committees will work collaboratively to merge or separate the two projects, as needed. Once approved, the proposal moves to the PCGC ASC and the PHN ASC for review. The ASCs will approve or recommend changes/clarification. For ancillary projects proposed by a PCGC investigator, the PCGC Outcomes Working Group has the authority to approve in lieu of review by the PCGC ASC, followed by approval by the PCGC Steering Committee. Following approval, the Co-leads will invite investigators from the two consortia to form a writing committee based on current consortium authorship guidelines.

FIGURE 7.3 STEPS FOR REVIEW OF ANCILLARY STUDY PROPOSAL INVOLVING BIOSPECIMENS



7.10.2 Mechanisms for Sharing Clinical and Genomic Data

1. PCGC Access to Published PHN Outcomes Data

While relevant outcomes data from published PHN clinical trials are available on the PHN Public Use Dataset webpage, a mechanism to relate outcomes to genomic variables is currently lacking. The PCGC Data Coordinating Center (DCC) and NERI are working together to create an additional column in the Public Use Datasets that includes the blinded ID

sample number that identified each PHN proband who underwent whole exome sequencing and analysis via the PCGC (GT040XXXXX). Investigators are required to register for an account to access Public Use Datasets.

2. PCGC Access to PHN Outcomes Data Not Yet Publicly Available

Access to PHN outcomes data that are not yet publicly available will follow the workflow pathway currently in use by the PHN ASC process. The designated PHN Co-lead investigator will request the specific data fields from NERI who will assign an analyst to download the requested data linked to PCGC blinded IDs (GT040XXXXX). Per PHN Ancillary Study guidelines, any additional costs related to data extraction and transfer from NERI are the responsibility of the PI/s of the Ancillary Study.

3. PHN Access to Genomic PHN Data and Clinical and Genomic PCGC Data

Genomic data for PCGC and PHN subjects reside on the PCGC Data Hub administered by the DCC in the form of a genomic variant call file (gVCF). The gVCF contains genotype calls for each individual in the PCGC, PHN and autism control datasets compared to the reference genome in a format that is amenable to downstream analyses of variant prioritization, modes of inheritance, etc. Clinical data and processed genomic data for PCGC subjects reside on the HeartSmart database administered by the DCC. Following approval by the ASCs, PHN investigators will be given access to relevant gVCF and clinical data from the Heart Smart database as needed for approved analyses.

4. Data Use Agreement for Inter-consortium Sharing

A Data Use Agreement will be negotiated between NERI and the PCGC DCC to govern data sharing between the consortia, excluding data that are in the public domain.

5. Preparation of Manuscripts

Following the identification of Co-lead investigators from both consortia, the Co-leads will invite investigators to form a writing committee based on current consortium authorship guidelines and following the procedures described in the PHN and PCGC MOO (see Appendix 1 for PHN ASC guidelines). The PCGC Outcomes Working Group and the PHN Biospecimens Committee may also oversee access of additional participants, to ensure that all investigators have the opportunity to participate and be recognized in research projects relating genomic variants to clinical outcomes.

Chapter

8 PHN Scholar Program

To train junior investigators, National Institutes of Health Networks have historically used Research Skills Development Core funds provided to selected centers for their candidates who then receive intensive local training, education, and mentoring in focused areas. The Pediatric Heart Network Scholar program took a novel, more inclusive, team science approach and embedded a scholarship program into its successful multi-center research framework. The PHN Scholar Program will award study grants to support outstanding researchers in the field of translational, clinical, health services, or epidemiological pediatric cardiovascular disease or adult congenital heart disease.

Proposals related to existing or planned (full, pilot, or ancillary) PHN studies are encouraged, but not required. Collaborative proposals involving multiple PHN centers are also encouraged but not required. However, proposals should be related to an area of PHN interest or investigation. ***Applications in the basic science fields will not be considered.***

Candidates from underrepresented racial and ethnic groups or those with a disability are encouraged to apply.

8.1 PHN Scholar Program Goals

To protect the time of promising young investigators and create a framework for successful competition for the K award or alternative sources of extramural funding, the goals of this unique training program are to:

1. Provide an established network structure for the scholars/mentors to conduct their projects and execute their career development plan
2. Facilitate cross-germination of ideas and collaborative multidisciplinary mentoring across all PHN core centers
3. Encourage engagement in PHN activities
4. Leverage use of PHN resources
5. Teach regulatory documentation
6. Promote presentations and publications for academic advancement

8.2 Roles and Eligibility Criteria

8.2.1 Role of the Core Center

Although there are many promising investigators, this program is considered a benefit of successful competition as a PHN core center and eligibility is limited to the core centers. PHN core centers may submit no more than two separate, scientifically distinct applications. Each core center has a PHN Scholar champion who serves as a member of the PHN Scholar subcommittee. The center

champion/committee representative is responsible for promoting the program at their center, answering questions related to the program, creating and implementing their center's process of selecting their two candidates, assisting with their candidate's development and submission of their applications. During the process of eliciting and developing applications, they will submit any questions that arise to the Data Coordinating Center (DCC, at PHNMailbox@neriscience.com). To ensure all candidates/mentors/co-investigators have a level playing field, the DCC has compiled a list of [FAQs](#), which will be updated as new questions arise. The [FAQs](#) will be accessible to all candidates, primary mentors, and center PHN Scholar Committee members.

8.2.2 Eligibility Criteria for Candidates

A PHN Scholar candidate must be from one of the PHN core centers **and** intend to pursue formal research funding to support an academic career. The following individuals are eligible:

1. MD or PhD within 5 years of completion of their last fellowship at the time of funding
2. Categorical fellows at the time of funding
3. Post-categorical fellows accepted in advanced training subspecialty programs
4. Pre-doctoral/doctoral nurses already undertaking research

Any individual *who meets these criteria* and has the skills, knowledge, and resources necessary to carry out the proposed research as Principal Investigator(s) is invited to work with his/her PHN Core Center to develop an application.

8.2.3 Center Commitment to the Scholar's Travel Support

As part of the application, all Scholars will be required to attend two Steering Committee meetings. Each center must formally commit to support the candidate's travel for the following:

- Two PHN steering committee meetings
 - At the time of award notification to present the project
 - At the end of the funding period to present final results and strategies for future funding
- National scientific conferences and meetings for presentations of study results

8.2.4 Role of the Data Coordinating Center

In the PHN, the DCC (New England Research Institutes, Inc.) is responsible for the overall coordination of PHN operations, provides leadership in clinical and statistical science, and provides fiscal, administrative, and systems oversight. Within the Scholar Program, the DCC provides administrative support to the Scholarship Committee, provides contracting and disbursement of funds to awardees, and maintains the PHN Scholars Library on NERI Connect

8.3 Funding

The number of awards is contingent upon PHN appropriations and the submission of a sufficient number of meritorious applications. Awards are for a two-year period with a *maximum* of \$75,000 in total costs for the two year period. There are no funds for indirect costs. (Please see the Indirect Costs [form letter](#) for more details). Awards are distributed as subawards from NERI's grant funds.

Research support may be sought for some or all of the following:

- Salary (investigator and support personnel)
- Research consumables (laboratory materials, etc.)
- Laboratory costs
- Education (tuition, research training, educational materials)
- Statistical software

Funds for travel to scientific meetings and the two required PHN Steering Committee meetings are not allowed. Each center must commit to funding travel for the PHN Scholar for scientific meetings.

8.4 Scholar Award Philosophy

The purpose of the PHN Scholar award is to support junior investigators and assist their development into future independent clinician scientists. The PHN encourages candidates to develop innovative research applications for translational, clinical, health services, or epidemiological pediatric cardiovascular research or adult congenital heart disease. These may be new pilot studies or ancillary studies related to existing or planned PHN studies. This funding opportunity will provide a stepping stone for junior faculty development.

Candidates from underrepresented racial and ethnic groups or those with a disability are encouraged to apply.

To maintain a level playing field, it is crucial for the candidates to carefully review and adhere to the guidelines and instructions in Chapter 8 as well as the PHN Program Announcement and Application Instructions specific to their grant cycle. The applications of candidates who fail to adhere to deadlines or stated requirements will **not** be reviewed.

8.4.1 The Scholars' Committee

The corresponding PI from each PHN Core Center will nominate a committee member from their center. Although this is at the discretion of the center PI, they are encouraged to select mid-level Faculty who have experience in mentorship and grant submission/development. In addition, a biostatistician from the DCC and a NHLBI representative will be nominated to serve as full members of the committee.

8.5 Submission Process for PHN Scholar Applications

8.5.1 Core Center Selection Process

The initial study proposals will be reviewed locally at the PHN core center. Each core center will be responsible for their local process to select their candidates. Their top candidates (maximum of two per PHN core center) will submit proposals for review by the members of the PHN Scholars Review Committee. Each Center is responsible for devising their own internal review process to ensure that no more than two applications are submitted to the PHN Scholar Review Committee.

All proposals will be considered confidential. Written consent will be obtained from successful Scholars who agree to have their applications available on [NERI Connect](#) as examples for future candidates.

8.5.2. PHN Scholar Program Announcement

Approximately three months before the Letter of Intent and six months before the application deadline, the PHN Scholar Award Committee will finalize the formal Program Announcement and the Application Instructions and the DCC will send these documents to each core center's Scholar Award committee member and the PHN Corresponding Primary Investigators. The Program Announcement will provide the following information:

- PHN Scholar Program overview
- Key dates for the steps in the submission process
- Funding opportunity description
- Award information
- Eligibility criteria
- Letter of intent requirements
- Application and submission information
- Application review criteria
- Award administration information
- Award details
- Publications and presentations
- Links to the Scholar Portal and FAQs

8.5.3 Letter of Intent

To allow the PHN Scholarship Committee members to ascertain review needs in terms of workload and reviewer expertise, all final candidates from each core center are required to submit a Letter of Intent to the [DCC](#) by the deadline provided in the PHN Scholar Announcement.

1. All PHN candidates planning to submit a full application must submit a Letter of Intent.
2. No late Letters of Intent will be accepted.

The Letter of Intent should include the following:

- Descriptive title of the proposed research
- A structured short abstract (250 words or less) describing the project (background, research design and methods, specific aims)

- Special review expertise, if applicable
- Name, email address of the Candidate Principal Investigator (PI)
- Name of Mentoring PI
- Names of other key personnel
- Anticipated participating centers

8.5.4 Application

It is critical that candidates follow the instructions for the PHN Scholar Application. Applications that are out of compliance with these instructions will **NOT** be accepted for review.

Application formatting: Margins must be ½ inch. Font must be 11 points or larger. Smaller text can be only be used in figures, graphs, diagrams, and charts and it must be legible when the page is viewed at 100%.

The complete application must include the following documents *in this order*:

1. Informational Table/Disclosures provided in the PHN Award Announcement (see below)
2. Proposal with the required contents and specifications for submission
3. References
4. Biosketch of the Candidate in the current NIH format
5. Biosketch of the Mentoring PI in the current NIH format. Do **not** include additional Biosketches. Applications with additional Biosketches or those not adhering to the NIH format will not be reviewed
6. Letter of Support from the person designated as the PHN Center Corresponding PI. If the Mentoring PI is the PHN Center Corresponding PI, the Letter of Support should be from the Division Chief. Do **not** include additional Letters of Support. Applications with additional Letters of Support will not be reviewed.

8.5.5 Instructions for the Proposal

Completion of the Informational Table and Disclosures is required and forms are available on [NERI Connect](#). This form must be placed at the beginning of the application. It does not count in the page limit.

Title of Proposed Study:
Principal Investigator:
Mentoring PI:
Co-investigators/mentors:
Applicant is of an underrepresented racial or ethnic group*: <input type="checkbox"/>

Applicant has a disability*: <input type="checkbox"/>
*Please make sure your mentor's letter of support documents and details this in order to receive special consideration
Institution:
Address:
Telephone:
Fax:
E-mail:
DISCLOSURES for all investigators*:

*Include Disclosure of any significant financial interest(s) exceeding \$5000.00 that might be related to the proposed area of research.

The proposal must **not** exceed 10 single-spaced pages (11 pt Arial—Arial narrow is **not** permitted) as described below.

- The Specific Aims section must **not** exceed one page
- The rest of the application must be no more than nine pages
- The page limits next to the content descriptions below are suggestions (except the Specific Aims page), the authors may format the application as they see fit within the page limits
- References do not count toward page limits
- **No** appendices are allowed
- Incomplete applications and applications that fail to comply with these instructions will **not** be reviewed

8.5.6 Required Content for the Proposal

1. *Specific Aims (restricted to 1 page)*: State a brief background, the goals of the proposed research, specific objectives (and hypotheses, if applicable), and summarize the expected outcome(s), including the impact of the results of the proposed research on the research field(s) involved.
2. *Candidate's Background (~1/2 to 1 page)*: Describe your research background, indicating how the award fits into past and future research career development.
3. *Career Goals and Objectives (~1/4 to 1/2 page)*: Describe your short-term and long-term career goals. Describe how the career development award will enable you to develop and/or expand your research career. Describe local opportunities that will be leveraged to advance your research career. You are encouraged to include a timeline, including plans to apply for subsequent grant support.

4. Mentors (~1/4 to 1/2 page): Describe the expertise, role and how each member of the mentoring team will interact with the candidate – include specific details. Demonstrate the Mentoring PI's previous experience in fostering the development of independent investigators and current research productivity.
5. Project fit with the PHN mission and unique PHN environment (~1/4 page): Describe the contributions the mentors have made (or plan to make) to the success of the PHN. Describe how the project fits with the mission of the PHN and how the unique aspects of the PHN will be leveraged to accomplish the proposed research and/or the research career development of the candidate.
6. Research Plan (~5-7 pages):
 - a. **Significance:**
 - i. Explain the importance of the problem that the proposed project addresses.
 - ii. Describe the scientific premise and rationale for the proposed project.
 - iii. Preliminary studies are not required, but if they exist, they should be described here.
 - b. **Approach:** This section must address all of the following:
 - i. *Study/Trial Design*: Include a brief overview of the study design, consider including a study schematic diagram. Describe procedures to minimize bias if relevant. List outcome measures. If applicable, provide a schedule of measurements and visits.
 - ii. *Selection of subjects*: Describe inclusion and exclusion criteria, data regarding subject availability, and an estimate of the accrual period. List participating institutions for pilot studies and collaborating institutions, if relevant.
 - iii. *Treatments*: If applicable, describe the treatments to be administered. Treatments can include drugs, biologics, surgery, devices or diagnostic procedures. Describe the regulatory (e.g. FDA; Health Canada) status of the proposed treatment, if applicable.
 - iv. *Protection of Human Subjects, Safety Considerations and Assessments*. Provide an attestation of training in the Responsible Conduct of Research (RCR) for human subjects' research for all investigators.
 - v. *Statistics*: Include a sample size calculation as well as a preliminary analysis plan. For Phase III trials and other studies where power calculations are appropriate, calculate sample sizes based on a minimum of 85% power. Assumptions used for the calculation of target sample size should be provided, including but not limited to the Type I and II error rates and the detectable effect size.
 - vi. *Limitations/Potential problems, Alternative Strategies, and Benchmarks for Success*

7. *Budget (~1/4 page or less)*: Include a general description of budget items and an estimate of the costs. Application budgets should reflect actual needs of the proposed project. Travel costs are not permissible.
8. *References (not included in the total 10 page limit)*
9. *PHN Checklist*
10. Questions should be directed to the PHN Scholarship Committee Representative from the candidate's center or one of the chairs ([Will Border](#), [LuAnn Minich](#), or [Lara Shekerdeman](#))
11. Completed applications must be submitted electronically to the [PHN Mailbox](#) by midnight EST on the published deadline. No late applications will be accepted.

8.5.7 Letter of Support

The application must include a Letter of Support from the PHN Center Corresponding PI. If the Mentoring PI is the PHN Center Corresponding PI, the Letter of Support should be from the Division Chief. This Letter of Support should address the candidate's research potential and guarantee adequate protected research time. The Letter of Support must also assure the Division or Department will cover travel costs (including the person responsible for approving these costs) to a minimum of two PHN Steering Committee meetings as well as appropriate scientific conferences and meetings.

8.5.8 Scholar Award Application Checklist

- ☐ Informational Table with disclosures
- ☐ Proposal
- ☐ References
- ☐ Biosketch of the Candidate in current NIH format
- ☐ Biosketch of the Mentoring PI in current NIH format
- ☐ Letter of Support

8.6 Review Process for PHN Scholar Award Applications

All applications submitted to the PHN are evaluated for scientific merit. The review process focuses on the research plan, candidate, mentor(s), and environment. The review criteria are adapted from the NHLBI K23 Award program.

8.6.1 Review Criteria

Research Plan

- Does the project address an important problem in pediatric cardiovascular disease or adult congenital heart disease research?
- Is the project aligned with the mission of the Pediatric Heart Network?
- How will scientific knowledge, technical capability, and/or clinical practice be improved?

- Are the proposed research questions, design, methodology, and statistical analyses well-reasoned and appropriate to accomplish the Specific Aims of the project?
- Are the proposed aims and procedures relevant to the study design and hypothesis?
- Does the research identify a clinically relevant and feasible primary study endpoint which is achievable within the proposed timeline for the study?
- Is there a strong scientific premise for the project?
- Has the candidate presented strategies to a well-reasoned, robust, unbiased and appropriate approach for the work proposed?
- Is the research plan appropriate to the candidate's stage of research development and as a vehicle for developing the research skills described in the career development plan?
- Have the investigators demonstrated that the patient populations are of sufficient size and will be available?
- Have the investigators demonstrated that funds are adequate and available for proper conduct of the study?

Candidate and Career Development Plans

- Does the candidate have the potential to develop as an independent and productive researcher?
- Has the candidate provided adequate evidence that they intend to pursue formal research funding (i.e., next steps, specific funding sources, timelines, etc.)
- Are the candidate's prior training and research experience appropriate for this award?
- Is the candidate's academic and research record of high quality?
- What is the likelihood that the plan will contribute substantially to the scientific development of the candidate?
- Is the candidate engaging in local learning opportunities which are critical aspects to a research career?
- Does the Letter of Support address the above review criteria
- Does the Letter of Support provide evidence that the candidate has a high potential for becoming an independent investigator?
- Does the Letter of Support guarantee travel to two steering committee meetings and scientific meetings for presentation of study results?

Mentor(s) and Collaborators

- Is the mentoring team appropriate to ensure all facets of the study will be strong? For example, sometimes a solid mentoring team includes a statistician, methodologist or ancillary domain, in addition to the person who is the topical expert.
- Is there adequate description of the roles of the mentoring team, and how they will interact with the candidate? Is the Mentoring PI identified?

- Is there evidence of each member's commitment to both the candidate and the project?
- Is there evidence of the mentor's, consultant's, and/or collaborator's previous experience in fostering the development of independent investigators?
- Is there evidence of the mentors' current research productivity and peer-reviewed support?
- Have the mentors demonstrated contributions to the success of the PHN or is there a detailed plan for future contributions to the success of the PHN?

Institutional and PHN Environment

- Will the environment in which the work will be done contribute to the probability of success?
- Will the project benefit from the unique features of the PHN—build on prior PHN studies, utilize the demonstrated expertise of the PHN investigators, fall within the focused areas of interest for the PHN?
- Is there evidence that the institution will provide sufficient protected time for the project to be carried out?
- Is the institutional commitment to the career development of the candidate strong as demonstrated in the Letter of Support?

8.6.2 Review Participants

Reviewers for the applications submitted in response to the PHN Scholar Award program announcement will be the members from the PHN Scholarship Committee. Each core center will select representatives for the PHN Scholar Award Committee to act as champions of the award at their center. Requirements for the position include: 1) clear interest in serving, 2) guaranteed time commitment to fulfill the duties of the committee, 3) agreement to serve as the point person for communication of all requirements and aspects of the award at their center, and 4) review all applications where the representative has no conflict of interest. To promote consistency, the committee members will participate in an in-person mock review of a previously submitted PHN application at the PHN steering committee immediately before the deadline for that cycle's applications. Reviewers will identify conflicts of interest they may have with certain applications and will be recused from all review activities for these applications.

Ad hoc reviewers will be added as dictated by the Letters of Intent.

The *Chair* of the review process will be recruited who is independent of the PHN and the core centers and has extensive experience in the review of mentored awards. The chair will introduce the application and facilitate the discussion to clarify important strengths and weaknesses but will not score the application.

The *Scientific Review Officer* (SRO) who is familiar with the policies, goals and conduct of the Pediatric Heart Network will be recruited from outside the PHN core centers to summarize the feedback for all candidates. The strengths and weaknesses of the proposal, candidate, and mentoring environment/team will be included in a detailed summary. The summary will include the written reviews by the primary and secondary reviewers and a detailed summary of the review committee's discussion. Summaries will be sent to each candidate regardless of whether their application was funded or not.

8.6.3 Review Process

All PHN Scholarship Committee members are expected to participate in the training, mock review, and scoring of all applications where they have no conflict. The review process will consist of the following steps:

1. Applications are collated by the DCC and posted for review by the Scholarship Committee chairs
2. Committee chairs identify and recruit additional experts (if needed, as determined by the Letters of Intent).
3. Committee chairs identify conflicts of interest (COI) and recuse reviewers from those applications. Representatives from centers with mentors/investigators listed on the Informational Table or those with self-identified conflicts are considered to have a COI. The DCC will distribute an allocation spreadsheet to the committee chairs and SRO summarizing applications and reviewers to assist in the identification of COIs.
4. For applications where a reviewer has a COI:
 - a. Reviewers will have no access to that application
 - b. Reviewers will not be present during discussion of the application
 - c. Reviewers will not score the application
5. The Committee chairs will assign Primary and Secondary Reviewers to each application.
6. DCC distributes allocations to Primary and Secondary reviewers and DCC stats representative, keeping details of other reviewers confidential at all times.
7. Within 24 hours of receipt of their assignments, Reviewers must contact the DCC and indicate that they do or do not have an unexpected COI with the application. If unexpected COIs arise, the committee chairs will reallocate.
8. The Primary and Secondary Reviewers will critique the application and fill out the Critique Template. Preliminary scores should be assigned at this time and submitted to the DCC for collation within the time period specified by committee chairs and DCC.
9. Preliminary scores will be averaged by the NHLBI representative. None of the Scholar chairs or the committee members will have access to the preliminary scores.
10. By looking only at the spread of scores, an upper limit will be determined for cutoff by the NHLBI representative, statistician, and SRO. Applications above that score (poorer applications) will be triaged and not discussed with committee unless rescued by a reviewer who has no COI.

11. DCC will schedule a call for the entire Scholarship Committee and any additional reviewers to discuss all applications below the triage cut-off as well as any triaged applications rescued by a committee member. At this time, the DCC will open a link on NERI Connect for committee members to access applications.
12. All committee members should review all applications (if no COI) for sufficient familiarity with them to allow active participation in the discussion. During this review, they should note discussion points and score the application, but do not submit scores to DCC; committee member scores serve as reference points during the main discussion.
13. The designated statistician from NERI will critique all applications and send his/her comments to the SRO to be included in the summary.
14. During the call, the Primary Reviewer will provide his/her preliminary score, briefly summarize the application, and succinctly present the strengths and weaknesses. The identified strengths and weaknesses should clearly justify the score.
15. The Secondary Reviewer will provide a preliminary score and add any strengths and weaknesses that have not been identified by the Primary Reviewer. If the Secondary Reviewer disagrees with previous comments, these points should be clarified and discussed at this time.
16. All remaining committee members should participate in the discussion to ensure clarity and obtain as much consensus as possible regarding the strengths and weakness of the application.
17. The SRO will summarize the strengths and weaknesses and solicit any additional comments.
18. The Chair will ask the Primary and Secondary Reviewers to provide a final score based on the Discussion.
19. All eligible reviewers (no COI) will score the application.
20. At the end of the review, all score sheets will be sent to the [DCC](#). Scores will be averaged and a priority score assigned by the NHLBI PHN designee.
21. The priority scores will be sent to the PHN leadership for final funding decisions.
22. The Primary and Secondary Reviewers will make edits (if needed) to justify their final scores and submit their reviews to the [DCC](#). These reviews will be provided to the SRO.
23. The SRO will summarize the strengths and weaknesses of the application (including those identified by the Primary and Secondary Reviewer as well as during the discussion). This summary will be returned to the applicant as feedback regardless of the funding decision.
24. Applicants will be notified of decision by the NHLBI PHN designee.
25. Funded scholars will be contacted by the DCC with additional information, including contracting steering committee meeting details, etc.

8.6.4 Review Critique Form

Candidate:

Mentoring PI:

Overall Impact

Reviewers will provide an Overall Impact Score to reflect their assessment of the scientific merit of the project and of the potential for the candidate to exert a sustained, powerful influence on the research field(s) involved. The following 5 scored review criteria, and additional review criteria should be considered. The overall impact score is NOT intended to be a mean of the 5 categories but rather reflects the overall quality of the application. An application does not need to be strong in all categories for the applicant to be judged as likely to succeed as an academic pediatric cardiovascular specialist.

Applicants should be rated on a 9-point scale (score 1-9). A score of 1 is an exceptionally strong application with essentially no weaknesses; whereas, a score of 9 indicates serious and substantive weaknesses with very few strengths. A score of 5 is considered average.

Overall Impact Score ____. Write a paragraph summarizing the factors that informed your Overall Impact Score. Include strengths and weaknesses. These strengths and weaknesses should justify your Overall Impact Score.

Reviewers will consider each of the 6 review criteria below in the determination of scientific and technical merit, and give a separate score for each on a 9-point scale (score 1-9).

1. Significance

Significance score ____. Does the project address an important problem in congenital or pediatric acquired heart disease research and the mission of the Pediatric Heart Network? Is there a strong scientific premise for the project? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Strengths

-

Weaknesses

-

2. Mentors

- **Mentors score ____.** Are the mentors/collaborators well suited to the project? Is the mentoring team appropriate to ensure all facets of the study will be strong? Do they have appropriate experience and training and well-defined roles for the protocol and for mentoring? Is there evidence of the mentors' current research productivity and peer-reviewed support? Have the mentors demonstrated contributions to the success of the PHN? Is there evidence for prior success of the Mentoring PI in fostering the development of independent investigators?

Strengths

-

Weaknesses

-

3. Approach

Approach score ____. Are the overall strategy, methodology, and analyses well-reasoned, robust, unbiased and appropriate to accomplish the Specific Aims of the project? Have the investigators demonstrated that the patient populations are of sufficient size and will be available? Are the requested funds adequate for proper conduct of the study? Does the research identify a clinically relevant and feasible primary study endpoint which is achievable within the proposed timeline for the study? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?

Strengths

-

Weaknesses

-

4. Environment

Environment score ____. Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Is there evidence that the institution will provide sufficient protected time for the project to be carried out? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements? Is it clear how the structure of the PHN will be used to accomplish the Aims of the project? Does the Letter of Support assure the Division or Department will cover travel costs (including the person responsible for approving these costs) to a minimum of two PHN Steering Committee meetings as well as appropriate scientific conferences and meetings.

Strengths

-

Weaknesses

-

5. Candidate and Career Development

- **Candidate and Career Development score ____.** Is the candidate advancing in the clinical skills required to pursue a successful career in their chosen subspecialty? Is the research plan appropriate to the candidate's stage of research development and as a vehicle for developing the research skills described in the career development plan? Is the candidate engaging in local learning opportunities which are critical aspects to an academic career? Has the candidate shown a commitment to an academic career as reflected by the personal statement of career goals? Does the Letter of Support address the above review criteria, and does it provide evidence that the candidate has a high potential for becoming an independent investigator? What is the likelihood that the plan will contribute substantially to the scientific development of the candidate?

Strengths

-

Weaknesses

-

ADDITIONAL REVIEW CONSIDERATIONS:**Protections for Human Subjects**

Have the investigators provided strategies to protect human subjects from research risk relating to their participation according to the following five review criteria: (1) risk to subjects, (2) adequacy of protection against risks, (3) potential benefits to the subjects and others, (4) importance of the knowledge to be gained, and (5) data and safety monitoring for clinical trials

_____ Acceptable _____ Unacceptable

Training in the Responsible Conduct of Research

Have the investigators provided an attestation that all investigators have completed training in the Responsible Conduct of Research (RCR).

_____ Acceptable _____ Unacceptable

8.7 Biannual Update and Annual Report

Award recipients will be required to participate in a biannual conference call with their mentors and the PHN Scholar Committee Chairs. The members of the PHN Scholar committee as well as the PIs from the Scholar's centers will be invited (but not required) to participate. The goal of the call will be to monitor the Scholar's progress and offer help, suggestions, and encouragement, as appropriate. Each Scholar will prepare 1 slide outlining the progress of the project and any barriers impeding progress and have approximately 5 minutes for discussion. The DCC will schedule the call at 6 month intervals after receiving input regarding the availability of each required participant via a Doodle poll.

Award recipients will also submit an annual progress report to the [PHN Scholar Committee](#), including a complete summary of progress and research product. The standard template for this form is available at this [link](#). In addition, the committee will collect scholarly product whether it is related to the application or not: abstracts accepted for presentation at a scientific meeting, grant applications; including amount of the award and the outcome of review; and publications.

The award recipient will be required to adhere to the PHN's Publication and Presentations Committee regulations regarding dissemination of research information. This information can be found in the PHN Manual of Operations ([Chapter 6](#)).

8.8 Special Considerations

1. Since this is a mentored award, care must be taken by the candidate to describe in detail the role of the Mentoring PI in their project and career development. Co-mentors from other PHN Core Centers can be utilized,

but mentorship plans and communication strategies must be very clearly laid out in these situations. Members of the PHN Scholar Award Committee who are co-mentoring an application will have a COI and be recused from the review process for that application.

2. Sample applications are posted on [NERI Connect](#), under “Resources for Applicants and Awardees.”
3. The applicant must also address protections for human subjects, if applicable, and training in clinical research as described below.

Protections for Human Subjects

For research that involves human subjects but does not involve one of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate the justification for involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria: (1) risk to subjects, (2) adequacy of protection against risks, (3) potential benefits to the subjects and others, (4) importance of the knowledge to be gained, and (5) data and safety monitoring for clinical trials.

For research that involves human subjects and meets the criteria for one or more of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate: (1) the justification for the exemption, (2) human subjects’ involvement and characteristics, and (3) sources of materials. For additional information on review of the Human Subjects section, please refer to the [Guidelines for the Review of Human Subjects](#).

Plans for human subject protections will be rated as *ACCEPTABLE* or *UNACCEPTABLE*, and the summary statement will provide the consensus of the review committee.

Training in the Responsible Conduct of Research

All applications must include an attestation that all investigators have completed training in the Responsible Conduct of Research (RCR) prior to any human subjects’ research.

Evidence provided for training in the responsible conduct of research will be rated as *ACCEPTABLE* or *UNACCEPTABLE*, and the summary statement will provide the consensus of the review committee.

BIOREPOSITORY AND BIOSPECIMEN USE GUIDELINES FOR PHN STUDIES (PHN BIOSPECIMENS COMMITTEE)

The PHN Biospecimens Committee is responsible for assisting with the development of projects and for reviewing proposals involving biospecimens use. All biospecimens collected for future research or leftover from a primary genetic study are deemed a central PHN resource. Biological data is defined as sequencing, genotyping, gene expression, proteomics, metabolomics or other biological data generated from biospecimens collected in the PHN.

9.1 Development of PHN study proposals involving biospecimens

PHN proposals involving biospecimens collection will be sent to the Biospecimens committee chair/s for input during the development stage before protocol finalization. This will help ensure that standard biorepository language is used in the proposal consistent with best practices and appropriate budget has been included. For studies involving biobanking of samples for future research, investigators are encouraged to refer to the PHN biorepository consent template available through [NERIConnect](#). The consent can be offered as a stand-alone consent or the required elements can be incorporated into the main study consent at the discretion of the parent study committee.

9.2 Primary genetic study or genetic aim of a parent study (including studies involving biomarkers)

For a primary genetic study / aim that is clearly developed and integrated into the parent study and funded by the PHN, the biospecimens will be used as described in the parent protocol and the established procedures for developing a writing committee at the conclusion of the parent study will be pursued.

9.3 Request for use of stored biospecimens or biological datasets

The guidelines below refer to studies proposing use of stored biospecimens that were not fully integrated within the parent study. The PI(s) for the parent study will work with the Biospecimens Committee to develop strategies for testing and analysis of the secured biospecimens. In some cases, optimal testing strategies will require coordination across multiple studies to achieve adequate power.

9.3.1 *Who can propose a study?*

Any PHN member or an external PI in collaboration with a PHN member can propose studies using the stored biospecimens or associated biological datasets. Prior consultation with the parent Study Chair and the Biospecimens Committee Chairs is encouraged. The proposal must be

submitted in writing to the PHN Biospecimens Committee using the [Ancillary Study Application Form](#) and the supplemental [Biospecimens / Biological Data Request Form](#). Both forms can be accessed in the Policies and Templates section of the PHN Administrative website [NERIConnect](#).

9.3.2 *Administrative review for feasibility*

NERI will perform an administrative review to ascertain if requested samples are available, and if there are any restrictions on sample use based on individual consent. This information will be released to the Biospecimens Committee Chairs along with the study application. Expected turnaround time for administrative review from receipt of request = 2 weeks.

9.3.3 *Biospecimens Committee Review*

If the biospecimens related study is relevant to a primary or secondary aim of one/more parent PHN studies, the chairs of the parent studies will be consulted to ensure alignment and responsible use of study data and determine the timeline for release of clinical data if the data are unpublished. The application will then be circulated to the Biospecimens Committee which will determine if a request for samples or biological data is appropriate, if funding is available, if the study is scientifically meritorious and feasible, and ensure there is no overlap with ongoing studies in the PHN. Expected turnaround time for Committee Review from receipt of application = 2 weeks.

9.3.4 *Ancillary Study Committee Review*

For a new biospecimens related study that is independent of the primary or secondary aims of a parent study, or if the genetic study involves the collection of additional biospecimens or generation of additional data from existing biospecimens that were not part of the parent study, it will be considered an ancillary study and will require approval by both the PHN Biospecimens and the Ancillary Study committees (and by the PCGC Clinical outcomes working group if involving the PCGC). The results of the Biospecimens Committee review will be submitted to the Ancillary Study Chairs. If the proposed study is limited to the use of biospecimens or biological data only, the Ancillary Study Chair and Co-chair may administratively approve the proposal. If the proposed study involves use of PHN study data in addition to the biospecimens or biological data, the proposal may be reviewed by the full Ancillary Studies Committee. The Ancillary Study Chairs will determine the level of review needed based on these criteria. Please refer to [Chapter 7.10](#) for detailed PHN-PCGC clinical and genomic data sharing policy.

9.3.5 *PHN-PCGC collaborative studies*

For studies proposed jointly by the PHN and PCGC, and/or where sequencing or genotyping costs of PHN samples are covered by the PCGC, the proposal will need approval by both the PHN Biospecimens committee and the PCGC Clinical Outcomes working group before review by the Ancillary Study Committee.

9.3.6 *Biospecimens and Data release*

Biospecimens and/or data release for approved projects will be done after NERI confirms that appropriate IRB approval and Material Transfer Agreements are in place as needed.

9.3.7 *Public use datasets*

In cases where either the clinical data or the biological data are already in public databases, the Biospecimens Committee will review any request for linking clinical and biological datasets. If approved, NERI will link the datasets in a de-identified manner that protects subject identity.

9.4 Funding

For biospecimen studies not budgeted within the parent PHN study, funding for biological characterization and analysis is the responsibility of the study proposer although the Biospecimens committee may assist in securing funding through the PHN, PCGC or from external funding sources if appropriate.

9.5 Biological Data Storage

The biological datasets generated with funding from the PHN or PCGC will be stored in a PHN or PCGC central repository with regulated access limited to investigators with approved studies within the scope of the original consent. For studies funded by external sources, it is expected that the investigator will return the biological datasets to the PHN after study completion for broader use as appropriate.

9.6 Requirements for Writing Committees

The Biospecimens committee will assist in the formation of writing committees.

1. If the manuscript is primarily methodological, it is not required that all PHN Centers be invited to participate in the Writing Committee.
2. For all other studies, all PHN Centers that contributed data and biological samples will be given the opportunity to participate in Writing Committee(s). The Center PIs will be invited to extend this opportunity to a qualified individual. Centers may opt out of participation. The Requirements for Authorship will be used to determine the membership of the Writing Committee.
3. If the opportunity for authorship is not extended to all centers, clear written justification must be submitted and reviewed by the Biospecimens and

Ancillary Study Committee Chairs who may administratively approve or refer for review by the entire committee membership.

4. For studies involving the PCGC, the PCGC will also be invited to nominate members.
5. The PHN in general and the names of PHN centers that contributed data or biological samples must be included in the manuscript Methods and Acknowledgement sections, respectively. Individual investigator names from the centers are not required. If the origin of the data or biological samples cannot be determined, then acknowledgement of only the PHN is required.

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Conflict of Interest Policies and Procedures

A1.1 Financial Conflicts of Interest

The PHN and the NHLBI are committed to avoiding any real or perceived conflicts of interest, such as circumstances that would bias study design, conduct, data analysis or interpretation of the research. All PHN key personnel have an obligation to disclose potential ethical, legal, financial or other conflicts of interest that reasonable peers or an informed public could construe to conflict or appear to conflict with the investigator's unbiased contributions to the research.

Federal regulations ([42 CFR Part 50, Subpart F](#)) establish financial conflict of interest standards, and provide that a conflict of interest exists when the designated official at the grantee institution "reasonably determines that a significant financial interest could directly and significantly affect the design, conduct, or reporting of the...funded research." A significant financial interest is defined as anything of monetary value including but not limited to salaries or other payments, equity interest, and intellectual property rights. This does not include salaries or other payments from the investigator's institution, or income from public or nonprofit entities for selected services. The threshold for triggering reporting for a publicly-traded entity is the aggregated value of any remuneration and value of equity interest in the previous 12 months that exceeds \$5,000. The threshold for triggering reporting for a non-publicly traded entity is remuneration that exceeds \$5,000 in the previous 12 months and any equity holding regardless of value or remuneration. These limits apply to investigators and their immediate households.

Clinical Center PIs, the DCC PIs, and the Protocol and Network Chairs will be asked to provide information about significant financial interest annually, and at the beginning of new study development. The annual reporting will be study-specific. The DCC will coordinate the conflict of interest assessment process, and NHLBI staff will review and identified conflicts and develop a plan for addressing them.

A1.2 Conflict Resolution

During the conduct of a study, or at any time during the conduct of PHN business, issues may arise that are sensitive or difficult to resolve. These could be issues such as perceived scientific misconduct, potential financial conflict, or concerns about fairness in application of PHN policies.

1. If such an issue arises, it should be brought to the attention of the NHLBI PHN Project Scientist, who will attempt to resolve it.
2. If it cannot be resolved to the satisfaction of everyone in this fashion, a 3-member panel will be formed of the NHLBI Project Scientist, the DCC PIs, and an independent party at NHLBI's request to consider the concern in detail and

determine the best course of action. The results of this deliberation will be communicated to the concerned party or parties, and appropriate action taken.

3. If the concern raised is about the NHLBI Project Scientist, it should be brought initially to the attention of the DCC PIs. If the concern is about one of the DCC PIs, then it should be brought to the attention of the NHLBI Project Scientist. If a 3-member panel is convened, a Clinical Center PI will be placed on the panel instead of the NHLBI Project Scientist or the DCC PI of Operations.
4. In the unlikely event that the issue cannot be resolved within this framework, the next step would be to have the matter brought before the voting members of the Executive Committee. Additional information about conflict resolution in the context of a cooperative agreement can be found in the Notice of Grant Award.
5. In a case where fraud is suspected related to NHLBI grant monies, the individual who suspects this should call the DHHS Office of the Inspector General at 800-447-8477, or the NIH Office of Management Assessment, at 301-496-5586. Federal investigators are then called in to investigate the situation and take appropriate action.

2 Policies for Ancillary Studies Involving Biospecimens or Biologic Datasets

A2.1 Review Process

If the proposed Ancillary Study involves use of existing biospecimens or existing biological datasets generated from biospecimens, the proposal will first be reviewed by the PHN Biospecimens Committee for appropriate use of the specimens/data. The proposal must be submitted in writing to the PHN Biospecimens Committee using the Ancillary Study Application Form and the supplemental Biospecimen/Biological Data Request Form. Both forms can be accessed in the Policies and Templates section of the PHN Administrative website NERISConnect. The results of the Biospecimens Committee review will be submitted to the ASC Chair. If the proposed study is limited to use of biospecimens or biological data only, the ASC Chair may administratively approve the proposal. If the proposed study involves use of PHN study data in addition to the biospecimens or biological data, the proposal will be reviewed by the full Committee. Biological data is defined as sequencing, genotyping, gene expression, and proteomics or metabolomics data.

A2.2 Requirements for Writing Committees

If the Ancillary Study utilizes PHN primary study or core laboratory data or banked biospecimens for main outcome(s), all PHN Centers that contributed the data must be invited to participate in writing committees for all papers resulting from the study. At the earliest possible opportunity, the Ancillary Study PI should draft a list of intended writing committee members and submit it to NERI for circulation to PHN participating center/ core PIs for approval. The approved list of nominees will then go to the PPC and the PPC chair will finalize the writing committee. The Ancillary Study PI and the PHN center PIs should exercise discretion in making these nominations:

- a) At a minimum, nominees must have contributed to the acquisition of the data and must read and revise the manuscript critically for important intellectual content.
- b) Each participating PHN center and core laboratory will be invited but not obliged to participate in the writing committee.
- c) In general, each center will have no more than one representative on the writing committee.
- d) Under exceptional circumstances, the requirement for PHN co-authors may be waived by advance agreement with the ASC and PPC Chairs, in consultation with the respective main study Chair(s).

3 Biospecimens Policy and Procedures

A3.1 Policy

Consistent with the NIH mission to improve public health through research, the PHN believes that the full value of biospecimens can be realized only if made available to a wide range of scientific investigators. The PHN encourages investigators in the field to use these materials and to foster collaborative research where appropriate. This Policy and Procedures applies to the use of biospecimens in ancillary studies. These ancillary studies can be proposed either by PHN Investigators or by other investigators who agree to collaborate with a PHN Investigator.

The Pediatric Heart Network (PHN) currently has biospecimens in core labs or biorepositories, including [BioLINCC](#), the NHLBI-funded Biological Specimen Registry in Rockville MD. This policy applies to all stored biospecimens from PHN studies.

- The Centers of the PHN will share biospecimens collected in PHN studies for use in ancillary studies.
- Biospecimen sharing will be consistent with NIH's [Best Practices for the Licensing of Genomic Inventions](#) and its [Research Tools Policy](#).
- Investigators requesting access to PHN biospecimens will abide by the PHN Ancillary Studies Policy and Procedures and the Publication and Presentation Policy and Procedures.

A3.2 Procedures for Biospecimen Access and Utilization

A Biospecimens Committee will be responsible for the oversight of the biospecimens collected and stored during PHN studies. Committee membership will include PHN Investigators with expertise in relevant assays and cardiovascular genetics in addition to study expertise, a DCC Investigator, a representative of the NHLBI Program Office, and a member of the Ancillary Studies Committee who will serve as the liaison to facilitate ASC review. Outside expertise can be enlisted if required for a proposal and not available among Committee members.

The Committee may propose specific uses of the biospecimens or may request and/or receive proposals from outside parties.

Access to the PHN biospecimens and associated clinical annotation and genomics data will be prioritized as follows:

1. PHN investigators.
2. PCGC investigators

3. Non-PHN or non-PCGC investigators of approved ancillary studies, should there be an interest.

The following terms and conditions for access to PHN biospecimens apply:

1. Collaboration Requirement: Collaboration with a PHN investigator is required for all ancillary studies.
2. Scientific Merit: The project is deemed scientifically meritorious and provides good justification for proposed sample use.
3. Patient Consent: Only de-identified samples and data will be released and any restrictions to the consent will be taken into consideration before sharing biospecimens.
4. IRB Approval: Investigators will be required to provide evidence of Institutional Review Board (IRB) approval of their proposed research prior to receipt of biospecimens or data.
5. Funding: Investigators will be required to provide evidence of funding of the ancillary study prior to release of biospecimens.
6. Conditional Approval: The Committee may provide “conditional” letters in support of grant applications with the understanding that release of biospecimens will be contingent upon proof of receipt of funding.
7. Material Transfer Agreement or Limited Data Use Agreement: Investigators granted access to PHN biospecimens or data for use in an ancillary study must execute and adhere to the requirements of a Material Transfer Agreement. It is agreed that the specimens will be used only for the purposes described in the approved protocol. Materials released from the biorepository will not be distributed to third parties.
8. Reporting of Findings and Sharing of Data: Investigators agree to provide a progress report of their findings annually and a final report within six months of study completion. Investigators agree that all biologic data including raw genetic, genomics (sequencing and genotyping), gene expression and proteomics data will be submitted to the PHN, or to a federally funded data repository (e.g. dbGaP for genome-wide data) where appropriate, to benefit future research, after a pre-specified embargo period.
9. Sample Related Costs: The investigator will be responsible for the costs related to sample preparation, aliquotting and shipping, and other related costs deemed appropriate on an individual case basis. Any unused specimens are to be appropriately discarded by the investigator in accordance with standard guidelines and appropriate documentation must be submitted to the PHN.
10. Adherence to PHN PPC Policy: The investigator must adhere to the [PHN Publications and Presentations Policy](#) for all publications and presentations related to the study.
11. Acknowledgment: Use of the materials from the PHN represents the establishment of collaboration and investigators are required to acknowledge the PHN when

reporting their work. Descriptors of approved projects may be made publicly available on the PHN website and other postings.

Proposal Process for Accessing Biospecimens

It is expected that biospecimens will be used in the context of an ancillary study (Ancillary Study Policy and Procedures).

Investigators interested in accessing biospecimens should submit their [Ancillary Study Application Form](#) and [Biospecimen/Biologic Data Request Form](#) to the PHN DCC. The PHN Biorepository Committee must review and approve the proposed use and requested amount of biospecimens prior to submission of the Application to the Ancillary Studies Committee. Approval of both Committees is required for any ancillary study proposing the use of biospecimens.

Review Process for Ancillary Studies

Applications will be administratively reviewed for completeness by the DCC and then distributed to Committee members for review. Information about number and amounts of available samples will be provided to Committee members along with the application materials.

Committee members will return completed Project Evaluation Forms within two weeks. The Committee will consider the following in its review:

- Scientific merit, including clinical/scientific relevance;
- Compatibility with the active PHN portfolio including other approved ancillary studies using biospecimens, with absence of overlap with ongoing studies;
- Justification for the type and amounts of requested biospecimens;
- Technical feasibility and availability of the requested biospecimens;
- Justification for the use of PHN biospecimens, as opposed to specimens from other sources;
- Efficient use of the biospecimens; and
- Experience of the requesting laboratory.

The DCC will summarize the comments and forward to the Committee Chair. The Chair can defer final evaluation until after a formal discussion at the Committee conference call for applications that require additional discussion amongst the members.

The Chair will send the outcome of the Committee review to the Ancillary Studies Committee for its use in consideration of the proposal.

The DCC will maintain a list of submitted and approved projects. An annual report will be provided by the Committee to the PHN Steering Committee.