COLLABORATIVE LEARNING PROJECT OF PERIOPERATIVE CARE OF INFANTS WITH CONGENITAL HEART DISEASE

VERSION DATE: June 04 2014

Funded by
the National Heart, Lung, and Blood Institute,
NIH/DHHS

1. GENERAL INFORMATION

1.1 Protocol Signature Page

I have read the foregoing protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study in accordance with the design and specific provisions outlined herein; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the conduct of the study.

I will use the informed consent form approved by the NHLBI and will fulfill all responsibilities for submitting pertinent information to the Institutional Review Board or Ethics Committee responsible for this study.

I also agree to report all information or data in accordance with the protocol.

I further agree that the NHLBI and/or its designee has access to any source documents from which case report form information may have been generated.

The below signed confirm herewith to have read and understood this study protocol and/or amendment and appendices; furthermore, to accomplish this study in accordance to the protocol and Good Clinical Practice guidelines, as well as local regulations and regulatory authorities.

PRINTED OR TYPED NAME(S)	SIGNATURE	DATE
Investigator		
Investigator		
Investigator		
Investigator		

1.2 Protocol Synopsis

Title	Collaborative Learning Project of Perioperative Care of Infants with Congenital Heart Disease
Grant Number	HL109777, HL109816, HL109818, HL109778, HL109743, HL109737, HL109673, HL109781, HL109741, HL068270
Study Objectives	1. To perform site visits among participating centers to catalyze collaborative learning 2. To determine whether a model that employs collaborative learning can effectively guide the development of, and subsequent adoption of, an early postoperative ventilation and extubation clinical practice guideline (CPG) for infants across congenital heart centers 3. To determine if the collaborative learning CPG results in an increased rate of early extubation
Significance	Practice variance is significant across pediatric congenital heart centers, and certain centers have demonstrated superior outcomes in specific aspects of perioperative care. Participation in a learning collaborative may allow all participating centers to improve care.
Study Design	1. Establishment of learning collaborative among 5 PHN core centers 2. Development of a CPG to allow early extubation following repair of coarctation of the aorta and tetralogy of Fallot in infants 3. Assessment of compliance with the CPG 4. Comparison of postoperative extubation practices before and after institution of CPG
Primary Aim	To determine whether a collaborative learning-derived CPG for early postoperative ventilation and extubation results in a higher proportion of subjects extubated early after infant heart surgery
Secondary Aims	1. To determine the impact of the collaborative learning-derived CPG on other patient clinical measures 2. To determine the impact of utilizing an early extubation CPG on systems and resources 3. To evaluate the association between implementation of a CPG for early extubation after infant cardiac surgery and hospital costs. 4. To determine whether a model that employs collaborative learning results in a high rate of compliance with a CPG for early postoperative extubation 5. To examine system factors that impact compliance with an early extubation CPG
Accrual Objective	Assess early extubation practices in infants with TOF or coarctation of the aorta at 5 collaborative learning and 5 control PHN sites over a 24-month period
Study Duration	Approximately 28 months

1.3 Table of Contents

1.4 List of Abbreviations

Common abbreviations are listed in tabular format below.

AE	Adverse Event
AUC	Area under the Curve
CEC	Clinical Events Committee
CHOP	Children's Hospital of Philadelphia
CI	Confidence Interval
CICU	Cardiac intensive care unit
CPG	Clinical Practice Guideline
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DCC	Data Coordinating Center
DMP	Data Management Plan
DMS	Data Management System
DSMB	Data and Safety Monitoring Board
EC	Executive Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HRQOL	Health-Related Quality of Life
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonization
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web-based Response System
LOS	Length of Stay
MedDRA	Medical Dictionary for Drug Regulatory Activities
MM	Medical Monitor
MOO	Manual of Operations
NHLBI	National Heart, Lung and Blood Institute
NNECVDSG	Northern New England Cardiovascular Disease Study Group
OHRP	Office for Human Research Protection
PHN	Pediatric Heart Network
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
QI	Quality Improvement
SAE	Serious Adverse Event
SC	Steering Committee

SMF	Site Master File
SMP	Site Monitoring Plan
SSL	Secure Socket Layer
TOF	Tetralogy of Fallot

2. STUDY AIMS AND HYPOTHESES

Assessment of a Quality Improvement Clinical Practice Guideline for Postoperative Extubation on Clinical Outcomes

2.1 Primary Aim

To determine whether a collaborative learning-derived clinical practice guideline (CPG) for early postoperative ventilation and extubation results in a higher proportion of subjects extubated early after infant heart surgery

Hypotheses:

- Adoption of a collaborative learning derived CPG will result in an increased proportion of subjects having successful early extubation following surgery for select infant heart operations
- Early extubation rates will increase to a greater degree in the 5 sites within the learning collaborative than in the 5 PHN sites not participating in the collaborative

Primary outcome:

- The proportion of subjects that are successfully extubated within 6 hours of return to the ICU from the operating room following complete repair of tetralogy of Fallot or complete repair of coarctation of the aorta in infancy

2.2 Secondary Aims

Secondary Aim 1: To determine the impact of the collaborative learning-derived CPG on other patient clinical measures

Hypothesis: Implementation of an early extubation CPG will be associated with less need for sedation and earlier initiation of oral feeding.

Outcomes:

- Total duration of mechanical ventilation
- Duration of sedation/analgesia
- Cumulative dose of sedation/analgesia
- Pain score for 12 hours following extubation
- Time to first introduction of oral feeds
- Significant hypertension following repair of coarctation of the aorta
- Postoperative ICU length of stay (LOS)
- Postoperative hospital LOS

Secondary Aim 2: To determine the impact of utilizing an early extubation CPG on systems and resources

Hypotheses:

- An early extubation CPG will not increase the time to complete documentation, order entry or initiation of medications by the ICU nursing staff
- Implementation of the CPG will not significantly alter the interval from the end of the operative case to the time of handoff in the ICU

Outcomes:

- Median time to complete specified nursing requirements for postoperative ICU admission

- Median interval from skin closure to completion of handoff in the ICU for select infant heart operations

Secondary Aim 3

- To evaluate the association between implementation of a CPG for early extubation after infant cardiac surgery and hospital costs.

Hypothesis:

- CPG implementation will be associated with lower hospital costs

Outcomes:

- Total hospital costs (the primary outcome variable) will be estimated during the time periods before and after CPG implementation at both the intervention and control hospitals using hospital charge data and cost-to-charge ratios

Assessment of Collaborative Learning on Clinical Practice Guideline Implementation

Secondary Aim 4: To determine whether a model that employs collaborative learning results in a high rate of compliance with a CPG for early postoperative extubation following select infant heart operations across congenital heart centers

Hypothesis:

- Use of a collaborative learning model will result in a high rate of compliance with the early extubation CPG

Primary outcome:

- Compliance with all elements of the CPG in eligible surgical cases for a 12 month period following implementation of the CPG

Secondary Aim 5: To examine system factors that impact compliance with an early extubation CPG

Hypotheses:

- Compliance rates with the CPG will vary among centers in the collaborative
- Operator and center-specific factors such as hemodynamic stability and adequate hemostasis at each participating site will influence the proportion of surgical cases that will meet pre-specified criteria for safe early extubation

Outcomes:

- Center-specific compliance with all elements of the CPG in eligible surgical cases for a 12 month period following implementation of the CPG
- The proportion of cases at each site meeting pre-specified criteria for safe early extubation

3. BACKGROUND INFORMATION

3.1 Background

Numerous studies have shown that surgical outcomes differ among congenital heart centers. Why do some centers achieve better outcomes? This is a complex question with many contributing elements. A large factor is the variability in patient characteristics and risk factors. With regard to non-patient factors, it is likely that outcomes are affected by a host of factors broadly related to experience, resources, and experimentation. For example, some centers may

commit greater resources to pediatric cardiac surgical cases. Other centers may encourage experimentation, resulting in adoption of changes in surgical and medical care that appear promising and divergence in management practices from those at other institutions.

Collaborative learning is a medical research technique based on a process called benchmarking. Benchmarking [1] is a method of comparing services or outcomes at an individual center to those at leading institutions. This practice was developed by the manufacturing industry to bring low-performing processes into line with the highest-performing, or benchmark, process. Through benchmarking, locations with superior outcomes are identified. Managers learn the practices of their more efficient rivals either surreptitiously or by openly observing the superior process. In the medical community, this is achieved by site visits, sharing protocols and ongoing communication. Collaborative learning involves several key steps including: 1) topic selection, 2) learning sessions, and 3) action periods in which teams test and implement changes in their local centers.

Investigators have applied collaborative learning to improve results for coronary artery bypass graft surgery by creating a regional group willing to compare outcomes, the Northern New England Cardiovascular Disease Study Group (NNECVDSG) [1]. This voluntary program, which involved reciprocal site visits, was undertaken with the goal of exchanging information concerning the treatment of cardiovascular disease so that each participating institution would benefit. The improvement in mortality among patients undergoing emergent or urgent coronary artery bypass graft surgery in the NNECVDSG experience was impressive (**Figure 1**). Not only did the centers with the worst outcomes improve, but the centers with the best outcomes also improved.

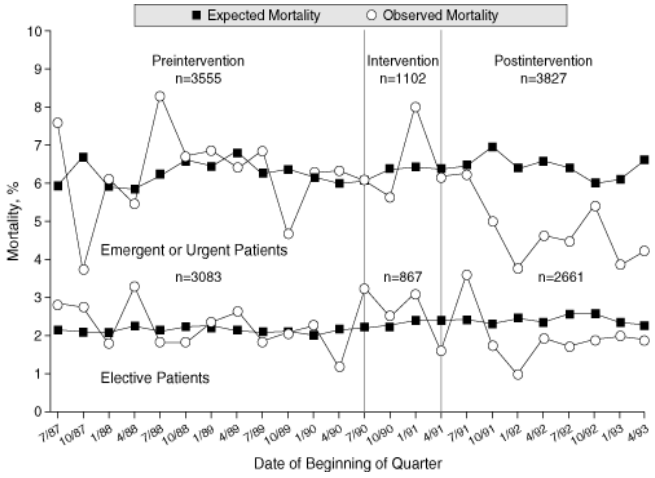

Figure 1 Flow Chart Demonstrating a Decrease in Mortality for Urgent/Emergent Patients after Intervention in NNECVDSG

The Michigan Society of Thoracic and Cardiovascular Surgeons has also employed a strategy of collaborative learning to improve focused aspects of adult cardiac surgical care. In Michigan in 2005, the rates for prolonged ventilation ranged from 14% to 36% following adult cardiac surgery. In 2007, following consensus-based multi-institutional intervention, the range dropped to 11.2% to 15.2% with the overall prolonged ventilation rate dropping from 19% to 14% (P<0.0004) [2]. There have been several successful quality improvement (QI) projects focused on critically ill children, performed predominantly in Pediatric ICUs. A number of these studies have sought to reduce blood stream infections. [3] [4]. In one study 29 centers participated in a collaborative QI project that was associated with a significant reduction in blood stream infections [5].

Site Visits to Understand Variation:
Whether collaborative learning can improve outcomes in pediatric cardiac surgery is not known. This field presents special challenges for pediatric subspecialties and rare diseases in general:

low volume, high complexity, and dispersed sites of care. In fields such as this, the randomized clinical trial to determine whether a new idea improves outcomes requires many years of data, even for a multi-institutional study, and is easily confounded by other changes in practice over the course of the trial. Randomized trials also usually test a major single change in management, and researchers are less likely to focus on small changes with small effects. Finally, translating the evidence-based improvement into widespread practice may take many more years or may not happen at all.

Collaboration and site visits as research tools overcome some of these obstacles. Collaboration can efficiently integrate and disseminate existing management strategies that are successful. Site visits are useful research tools in situations where numerous and intricate factors, often closely related, affect outcomes. These visits, in which data are collected largely from observations of practice, generate verbal and non-verbal communication, thereby increasing the likelihood that unmeasured but important factors receive attention. Site visits may be particularly valuable in quality improvement for congenital heart surgery given critical role of communication among various clinical teams (anesthesiologists, surgeons, cardiologists, nurses and others) involved in the care of an individual patient. The cumulative effect of several small changes may be impressive [1]. This aspect is especially important in congenital heart surgery, a complex and multi-faceted discipline whose volume cannot support the easy discovery of small effects. Collaboration has the added potential of stimulating new ideas for investigation or new management techniques, and increases our ability to conduct prospective research in a highly specialized clinical setting. Experimentation and discussion among colleagues can lead to the rapid adoption of innovations and avoid the replication of disadvantageous techniques. Collaboration and site visits have not yet been applied to pediatric cardiac surgery. Collaborative learning in pediatric cardiac surgery requires a multi-institutional approach due to relatively low volumes. A national structure for collaborative site visits has never been tried, to our knowledge, in any field.

Consensus Development:
In published experience with collaborative site visits, such as the NNECVDSG, involved centers have made practice changes based on their site visit learning. The researchers observed but made no attempt to standardize the changes. Allowing each site to choose which practices to apply was intuitively appealing because each could build on its strengths or avoid major structural changes if desired.

Another way to apply site visit learning is to accumulate the best management points of each site into a *standardized practice* or *clinical practice guideline (CPG)*. This is also appealing, since the spotty application of best practice can negate its overall effectiveness. The development and implementation of a CPG has been demonstrated to improve patient care [6][3]. These methods have been applied to a number of quality collaborative initiatives in pediatric medicine, including efforts to reduce central line infections and ventilator-associated pneumonia. Moreover, we anticipate that the collaboration and sharing of data and clinical protocols will provide opportunities for application of these methods to many future aspects of pediatric cardiac care, such as sedation, nutrition, and infection prevention, among others. We intend to use the techniques of clinical improvement to document and follow our outcomes.

3.2 Preliminary Studies
In preparation for this study a multidisciplinary team from Emory University and the Georgia Institute of Technology has already performed site visits to the 5 centers within the collaborative.

Our pilot team, comprising a pediatric cardiologist, a cardiac intensivist, a cardiac surgeon and a group of industrial system engineers, has focused on the observation of operative and postoperative care and has identified a number of important differences among these centers. These include significant inter- and intra-institution variability in ventilation management following infant heart surgery and in the use of anesthetic agents and opioids. Similarly, postoperative analgesia and sedation practice is highly variable. Institutions without an early extubation protocol tended to use higher doses of long-acting sedating agents than those centers with a formal approach intended to allow early extubation.

The "weaning goals" (in terms of expected duration of postoperative ventilation), and the role of personnel in the process of mechanical ventilation varied considerably among the 5 centers evaluated. Cardiac anesthesiologists play a large role at one center, whereas respiratory therapists lead the process at another, and intensive care fellows made most decisions at a third center. In addition, the approach to sedation and analgesia among centers differs in terms of medications, dosing and the extent to which established protocols guide decisions. The institutional signatures have been highlighted in numerous structured interviews performed by industrial engineers and the Emory site visiting team.

Ventilation/sedation management after uncomplicated infant heart surgery
In addition to direct observations, collaborative learning requires the sharing of both clinical practice models and unblinded outcomes data. Through direct observation and review of institutional data, it is clear that one of the centers participating in our pilot collaborative demonstrated a much shorter length of overall ventilation following two selected cardiac surgical procedures (**Table 1**). *Importantly, the need for reintubation within 48 hours among infants undergoing heart surgery at center B was less than 3 of the other 4 centers in the collaborative.*

Table 1: Median duration (hours) of ventilation following two infant cardiac surgical procedures in 2010-2011

	Center				
Procedure	**A**	**B (CHOP)**	**C**	**D**	**E**
Tetralogy of Fallot (complete repair)	28	0*	70	30	7
Coarctation of the aorta repair	30	0*	53	24	18

*Extubation within one hour of return to CICU counted as 0 hours

The rationale for a strategy of early extubation is based upon several principles of postoperative care. Extubation in the operating room is routinely employed following many pediatric surgical procedures such as abdominal surgery. The hemodynamics following most reparative cardiac procedures in children are quite robust and improved compared the preoperative state. Early extubation can allow for less need for postoperative analgesia and sedation [7],[8]. This, in turn, may potentially translate into earlier enteral feed advancement, a shorter hospital stay, and which in turn could lead to later benefits such as improved neurodevelopmental outcomes. While not clearly causal, it is worth noting that the center with the early extubation strategy reported the shortest total hospital length of stay (LOS) following reparative surgery for TOF and coarctation of the aorta.

This difference is particularly notable given that the 5 centers generally have median hospital lengths of stay less than national median benchmarks reported by the Society of Thoracic Surgeons.

3.3 Rationale for the Study

Multicenter randomized trials, such as those performed within the Pediatric Heart Network (PHN), have the potential to profoundly impact clinical practice and patient outcomes. However, improved outcomes achieved by some centers often result from a system-wide approach to clinical care. These system-wide approaches may not lend themselves to randomized trials and hence cannot be easily disseminated. Collaborative learning is an established, empirically-based approach that allows practices to be shared among institutions and changes in patient outcomes following such interventions to be measured and implemented elsewhere [9]. This innovative project seeks to use the principles of collaborative learning to address variation in the practice of postoperative mechanical ventilation in hopes of improving patient care. This process may in turn lead to more efficient use of resources and potential cost savings. While CPGs are common in modern healthcare systems, there are numerous barriers to the successful implementation of these guidelines. We expect that such barriers can be overcome with a collaborative learning model that leverages expertise from other partners in the PHN.

3.4 Rationale for the Study Outcomes

Shorter duration of postoperative ventilation is an attractive endpoint since this may translate directly into shorter length of stay, lower risk of ventilator associated pneumonia, shorter time to institution of enteral feeds, lower resource use and less sedation [10]. Duration of ventilation following heart surgery is an established measure of quality of care in adult cardiac surgery [2].

In addition, the study seeks to specifically address the possible benefit of collaborative learning on CPG implementation. The successful implementation of CPGs can be challenging, and compliance with CPGs is often disappointing [9]. Depending upon the complexity of the CPG, compliance rates can vary dramatically, but typical compliance rates are in the range of 30-90% [10], [11]. One potential method to improve CPG implementation and compliance is to leverage the expertise of peer institutions through collaborative learning. In the present study, we seek to demonstrate that collaborative learning can result in a high compliance rate (80%) with all elements of the CPG.

Other secondary outcome measures will address other aspects of patient care that may be impacted by the implementation of a CPG. It is possible that a CPG may favorably impact one aspect of patient care but adversely impact other aspects of patient care or provider functioning. As such, the present study will assess critical aspects of postoperative care, including work efficiency of nurses. In addition, the study will assess other system and patient level practice measures including the approach to pain management. These “balancing measures” are important to assess with the institution of any CPG.

Of particular interest is the possible impact on of an early extubation CPG on hospital costs. It is not known whether a collaborative learning model and implementation of a CPG across hospitals regarding early extubation will result in decreased hospital costs. There may be other practices and factors influencing cost of care for these patients across hospitals beyond the timing of extubation. While cost savings are the not only reason to consider a strategy of early extubation, the potential for reduced healthcare expenditure may make this practice attractive.

4. STUDY DESIGN

4.1 Overview

This is a non-randomized pilot study to determine whether collaborative learning can promote the successful implementation of a CPG focused on early extubation following infant heart surgery (**Figure 2**). Within the collaborative are 4 centers not routinely practicing early extubation and one that does. Through shared practices and collaboration, the 5 centers will implement changes in practice to achieve a higher rate of early extubation. A number of clinical variables will be assessed before and after CPG implementation. Data from 5 other PHN sites not participating in the learning collaborative will provide "control" secular data. These control institutions will be familiar with the goals and design of the learning collaborative, but will not be involved in site visits and will not be asked to adopt the CPG. The control institutions are free to alter their approach to anesthesia, sedation and postoperative ventilation during the study period.

The study has two distinct but complementary components.: 1) an *assessment of a postoperative extubation quality improvement CPG on clinical outcome and 2) an assessment of collaborative learning as a tool to enhance CPG development and implementation.*

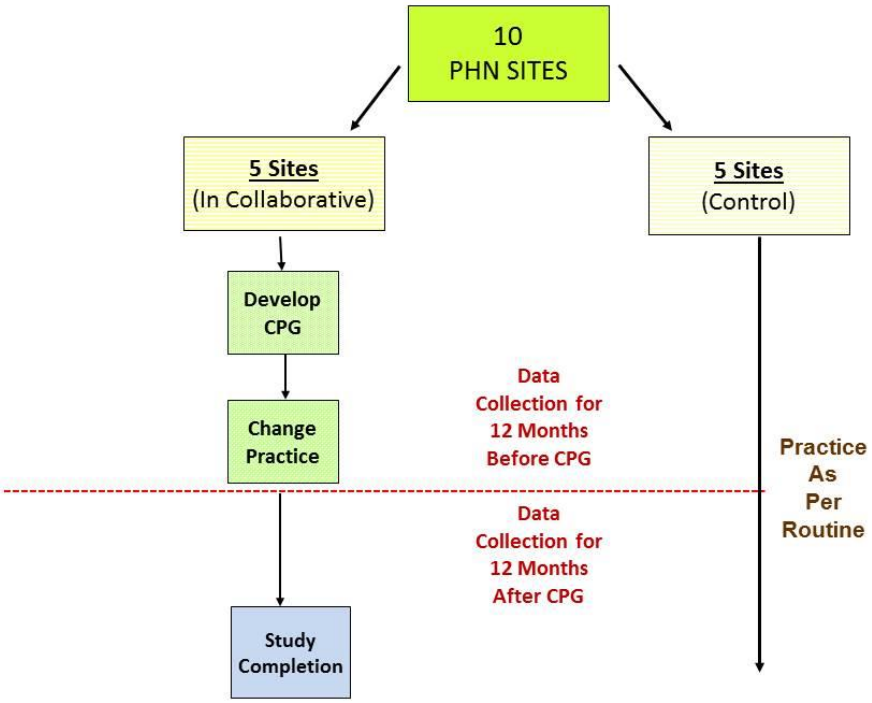

Figure 2 Study Design and CPG Implementation

This study has three main phases. The first is the observational phase, the second phase will focus upon CPG development, and the final phase will be the implementation phase. The first two phases represent the innovative aspects of the this study, which include the site visits and

face-to-face meeting. The third phase, implementation of a CPG, will be similar to a number of other QI projects routinely performed at participating centers. An estimated timeline for these phases is illustated in **Figure 3**. The resulting outcome metrics will be measured and contrasted. Each collaborating center will assemble a visiting team (**Table 2**). The visiting team will perform several key activities: 1) visit other centers, 2) help devise the guideline and 3) champion implementation of the guideline.

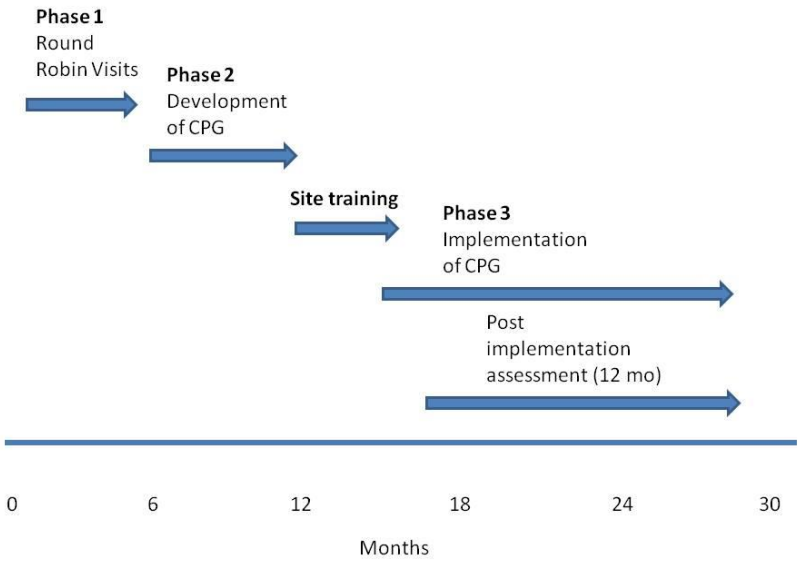

Figure 3

4.2 Phase 1 – Site Visits, Data Sharing and Practice Variation Analysis

Phase 1 will build on preliminary work of the Emory team in conjunction with industrial engineers and will consist of round-robin visits by the guiding team from each collaborating center to one of the other 5 participating PHN centers.

Table 2. Visiting Team

- Cardiac intensivist
- Cardiac anesthesiologist
- Cardiac surgeon
- CICU nurse
- Respiratory therapist
- Quality officer/specialist

Round-robin visits. These two-day visits are designed to allow each team to observe and understand some of the practice variation across centers and to foster future projects within the collaborative learning framework. Each institution participating in the collaborative will participate in one site visit to another center and will host a visit by one center. For any given center, the center hosted and the center visited will be different so as to allow the maximal exposure to other practices. The composition of the guiding team will be multidisciplinary to include physicians, nurses and other ancillary personnel. While the visiting teams will pay particular attention to the factors that impact postoperative ventilation (e.g., anesthesia, sedation, and ICU hand-offs), the visits are meant to review all facets of perioperative care. All 5 of the sites within the learning collaborative have well-established quality improvement programs. This study seeks to leverage this expertise by including quality specialists in the design and implementation of the CPG.

The visiting team will be accompanied by industrial system engineers to assist in measurement and documentation. In preparation for the site visit, the visiting team will set specific goals for the visit and review their counterpart host's practice protocols. Additionally, the host team will circulate relevant clinical protocols and CPGs to be reviewed by the visiting team prior to the visit. A visit agenda will be developed jointly by host and visit site leaders as well as the study PI. The visit will start with a meeting of the host and visiting teams to review the cases for observation, answer questions, and establish ground rules. Each visit will include structured scheduled interviews with key clinical personnel. The host site will also present clinical outcome data. This will include surgical outcomes, length of stay, ventilation data, infection rates and readmission data.

In addition, the visits will focus on observation of direct clinical care. Each visiting guiding team member will then accompany his or her counterpart at the host site through a normal day's activities and take note of similarities and differences with a known process of care.

Visitors will complete the individual checklist as well as the professional group checklist (included in the Manual of Operations). Visitors will record observations via paper, voice recording or electronic media. The site visits will be scheduled so as to ensure that the host institution will be performing a number of infant cardiac operations over the two-day visit. However, it is not expected that the host institution will schedule specific procedures or alter patient care to showcase particular expertise.

Minimum documentation at each site includes:
a) preoperative management: process map of transfer from preoperative care unit to operating room (OR).
b) operative management: process map of surgeon, perfusion, and anesthesia.
c) postoperative management: process map of OR to ICU transfer. Documentation of monitor use, lab frequency, charting frequency, parent presence.

General questions for each team member to address during the visit are listed in **Table 3**. At the end of both days' cases, the host and visiting teams will again meet to go over any other questions that arose and those that should be addressed by other team members.

Table 3: Questions for On-Site Observation

Responsibility:
Who is responsible for a particular process?
Who does the work?
Is there confusion about who the decision-maker is?
How are protocols, guidelines, and other decision aids used?
What are the assigned roles for patient hand-offs?
Is there obvious variability in personnel assuming responsibility for clinical decisions?
Communication:
Are communication paths clear and effective?
What is content and method of communicating information with patient hand-offs?
Are there mechanisms for feedback?
Is there potential for confusion?
Is there obvious variability?
Does individual style introduce variability?
Measurements:
What data are collected to support decision-making?
How are data collected?
How are checklists used?
Is there obvious variability between caregivers?
Environment:
How does the team deal with training levels, staff fatigue, equipment and facility design, lighting, and supply storage?

Post-Visit: Immediately after the site visit, the visiting team will meet with the research team to capture key observations from the visit. Each team member will write a report of his or her observations, to be submitted within 7 days of the visit, which will be shared with the host team. Working with the industrial engineers, the study PI will collate the findings and provide a summary to be shared within the collaborative.

Outcomes from Site Visits:

1) Identification and description of alternative practices
2) Written report of observations by each team member to be shared with the host
3) Dissemination of the findings from the robin round visit with physicians, nurse, allied health providers and administrators at the home institution

Data collection, interview techniques and report summaries will follow standards devised by healthcare industrial engineers.

4.3 Phase 2: Protocol Development Phase

Central meeting of all participating sites. The goal of this phase will be the development of a multidisciplinary CPG aimed at successful early extubation (within 6 hours of return from the operating room) after selected infant cardiac surgical procedures.

Once the “round-robin” site visits are complete and reports have been collated, the five guiding teams will meet at a central location for a two-day meeting to develop the CPG for early extubation. The study PI, along with the team of healthcare industrial engineers and the Data Coordinating Center (DCC), will prepare the materials and agenda for the meeting.

It is expected that the CPG will be influenced in large part by the protocol for early extubation developed by the Children’s Hospital of Philadelphia (CHOP). CHOP currently leads the practice of early extubation and has the highest proportion of infants extubated soon after arrival in the CICU. Collaborators from CHOP will share their experience and current protocols with other participating centers. Prior to the in-person meeting, the PI and industrial engineers will visit with the CHOP team to perform in-depth interviews and obtain video recordings of various aspects of the early extubation practice. This will supplement data obtained from a site visit performed in 2012.

The in-person meeting of the collaborative learning participants will include the sharing of CHOP’s institutional protocols and video presentation of key elements of the process, including the anesthesia-to-CICU handoff and the delegation of responsibilities. During this meeting, other participating centers will share the standard practices at their institutions. This presentation and discussion will provide the foundation for the CPG development. It should be recognized that the exchange of ideas among collaborative participants will also influence the practice at CHOP.

Using data gathered from site visits and reports from the each center’s guiding team, center-specific barriers to implementation will be explored. It is not expected that all aspects of perioperative care be standardized across participating centers. Rather a “bundle” of key elements that can be implemented throughout the collaborative will be identified. These will form the basis of the CPG. Exemplary key elements likely to guide the CPG are shown in **Table 4**. The development of the CPG will be in keeping with the Institute of Medicine’s Standards for Developing Trustworthy Clinical Practice Guidelines [13].

This in-person meeting will be followed by a series of additional in-person or teleconference meetings involving all 5 centers, following which we will generate, revise and finalize the CPG.

Table 4. Key Elements to Guide Development of Early Extubation CPG

Preoperative Phase
Planned surgical repair (likely to permit stable hemodynamics in the immediate postoperative period)
Identification of respiratory or neurologic contraindications to early extubation
Operative Phase
Anesthetic strategy that would permit early tracheal extubation
Checklist of hemodynamic stability
Evaluation of residual lesions or depressed myocardial function
Postoperative Phase
Staffing support to allow early extubation
Sedation plan
Hemodynamic reassessment (bleeding, arrhythmias, etc.)
Evaluation of respiratory status following extubation

Finally, the research team, led by the study PI, will meet on-site with the patient management team of each center to discuss implementation of the CPG, overcoming barriers to implementation, and potential incompatibilities.

4.4 Phase 3: Intervention Phase (Application of the Quality Improvement CPG to Clinical Care)

Numerous analyses have been undertaken to identify strategies that are associated with effective implementation of a CPG. These key components are displayed in **Table 5**. The processes necessary to implement a CPG will be reviewed with all collaborative learning team members.

Table 5. Implementation Strategies for CPG

Audit & Feedback	Summaries of clinical performance (e.g. based on review of charting or one-to-one observation of clinical practice) used to increase the target group's awareness of their and/or others' practice
Educational materials	Distribution of non-interactive educational printed, audiovisual, or computer-produced information
Educational outreach visits	One-to-one visits by study investigators to individual target staff to explain the desired change
Interactive educational meetings	Learner involvement through discussion and active participation (e.g. work group tasks, problem-based learning, etc.)
Local consensus processes	Inclusion of participating practitioners in discussions to ensure they agree that the chosen clinical problem is important and the suggested approach is appropriate
Local opinion leaders	Respected academic and clinician peers who can influence others to change behavior
Marketing	The management process responsible for identifying, anticipating and satisfying customer requirements profitably. This includes all functions of development, research, planning, design, promotion, and public relations.

The early extubation protocol will have a 'go live*'* implementation date. The 'lag phase' between completion of CPG development and the 'go live' date will be used for site training and for education of the institutional care teams. The key to success will be readiness to apply the protocol seamlessly which requires buy-in from the surgical, anesthesia and postoperative ICU teams. Providing adequate staffing resources will also be essential. All 5 collaborative learning sites will implement CPG within a window of several weeks of each other.

During the 12 months of post-implementation data collection research coordinators will complete case report forms for all subjects undergoing the surgical procedures of interest (complete repair of TOF and repair of isolated coarctation of the aorta) to assess compliance with CPG. In each case, the coordinator will review preoperative planning, operative and anesthetic management and immediate postoperative care. The measures of compliance will include: 1) documentation by clinical providers, 2) clinical practice such as sedation/anesthetic strategy and 3) system factors such as staffing in the ICU.

Research coordinators will assess the compliance with components of the CPG by review of medical records and by direct observation of patient care. A training manual will be developed to enable coordinators to assess specific performance criteria for each guideline recommendation. Before beginning data collection, an in-person meeting will be held to train all abstractors. Once data collection commences, monthly conference calls will be held to clarify and resolve issues encountered at each site.

Coordinators will also be responsible for recording a number of secondary outcome measures, including time to complete standard admission documentation and time to complete medication order entry. Coordinators will also record data on postoperative sedation, pain scores, feeding, and LOS.

4.5 Study Measures

4.5.1 Measures of Primary Outcome

- Proportion of subjects that are extubated within 6 hours of return to the ICU from the operating room following surgery for complete repair of tetralogy of Fallot or complete repair of coarctation of the aorta in infancy. Time of ICU admission is defined as time the subject arrives in designated bed space.

4.5.2 Measures of Secondary Outcomes

Clinical measures:

- Duration (in hours) of mechanical ventilation, defined as time from arrival in ICU to removal of the endotracheal tube. Extubation in the operating room is defined as time = 0 hours.
- Reintubation event within 48 hours of initial extubation (yes/no)
- Duration of sedation: Time (hours) from arrival in ICU to final continuous dose of opioid, benzodiazepine or dexmedetomidine
- Pain scores (median and range) using the FLACC pain scale from time of extubation to 12 hours following extubation. FLACC is a pain scale with five categories: (F) Face; (L) Legs; (A) Activity; (C) Cry; and (C) Consolability. Each category is scored from 0-2, which results in a total score between 0 and 10. FLACC is currently used as a standard clinical tool at all 5 collaborative centers.
- Significant hypertension following repair of coarctation of the aorta, defined as systolic blood pressure >99th percentile for 1 hour or more or hypertension requiring the use of more than one intravenous antihypertensive agent in the first 48 hours after surgery
- Cumulative dose of sedation/analgesia: Cumulative opioid dose, cumulative benzodiazepine dose, cumulative dose of dexmedetomidine from arrival in ICU up to 48 hours after arrival in ICU. Opioid and benzodiazepine equivalency conversion charts will be employed.
- Time from arrival to ICU following surgery to first introduction of enteral feeds
- Postoperative ICU LOS
- Postoperative hospital LOS

Hospiital cost measures:

- Cumulative hospitalization cost
- Component categories of cost including: room and board, pharmacy, imaging, lab, clinical, supplies, other

System measures:

- Knowledge of CPG
  - Questionnaire focused on components of CPG administered to care providers of various disciplines involved in perioperative care
- Staffing resources
  - Nursing- cumulative support (bedside nurses + resource nurse) required in first 6 hours following admission to the ICU
- Postoperative patient care and handoff time
  - Time (minutes) from skin closure to completion of handoff of the patient in the intensive care unit
- Nurse documentation time
  - Time (minutes) required to complete defined direct patient-care and documentation as part of postoperative admission to the intensive care unit

It is expected that additional outcome measures will be identified during Phase 1 (round robin visits) and Phase 2 (development of a CPG).

Compliance measures:
The primary outcome measure is the proportion of cases in which there was compliance to all elements of the CPG. Typically there are 5-15 key elements or "bundle" that make up a CPG. The primary outcome of compliance will be a dichotomous measure: compliant or not compliant. Compliance is defined as a patient's perioperative care complying with all elements of the CPG.

4.5.3 Covariate Measures

The population of infants with TOF and coarctation of the aorta undergoing reparative surgery before and after institution of extubation CPG may differ in some key characteristics. To account for such differences, it will be necessary to collect and analyze covariates likely to impact measures of patient outcomes and system outcomes. These covariates include:

- Age at surgery
- Gestational age
- Weight at surgery
- Prior cardiac surgical history
- Cardiac surgical approach at time of implementation of the CPG:
  - TOF: Transannular vs. non-transannular repair, pulmonary artery plasty
  - Coarctation: Surgical technique

4.5.4 Schedule of Measurements

A schedule of measurements is included in **Table 6**. Pre-CPG data will be collected retrospectively for the 12-month period immediately prior to the 'go live' date of the CPG. Collection of post-CPG data will start on the implementation date of the CPG and continue for 12 months.

Table 6. Schedule of Measurements

MEASURE	Pre-CPG	Post-CPG
Individual level data:		
CPG compliance		X
Sedation use	X	X
Pain scores	X	X
Ventilation data†	X	X
Length of stay†	X	X
Time to enteral feeding	X	X
Cost assessment		
Cumulative cost	X	X
Category component costs	X	X
System level assessment:		
Responsibility for extubation planning*	X	
Decision process*	X	
Communication & documentation*	X	
Care coordination*	X	
Timeline of processes/events*	X	
Nurse documentation time	X	X
Intra-facility practice variance*	X	X
Inter-facility practice variance*	X	X
Staffing for operative and early postoperative care	X	X

†Control centers included

*Assessed by industrial engineers with site visits

4.6 Study Visits

Data collection will be limited to the single hospitalization for reparative surgery.

5. SELECTION OF CLINICAL CASES

For purposes of inclusion in this study, infants with planned surgical repair of specified heart conditions will be potentially eligible. The development of the CPG in Phase 2 will further determine which cases may be considered for early extubation following index surgical procedure and therefore eligible for inclusion in the study. Eligibility criteria are described below.

5.1 Criteria for Eligible Cases

1. Patient age < 12 months
2. Diagnosis of:
   a. TOF or
   b. Coarctation of the aorta (isolated)
3. Planned complete surgical repair

5.2 Criteria for Ineligible Cases

These criteria will be based on the CPG to be developed in Phase 2 and are likely to follow some of the principles currently employed at CHOP (listed below).

The criteria which may preclude early extubation include:

1. Known primary lung disease
2. Known airway anomalies
3. Corrected gestational age at time of surgery of <36 weeks
4. Patient receiving mechanical ventilation immediately prior to surgery (relative contraindication)
5. Known congenital or acquired neurological injury
6. Patients with a known chromosomal abnormality or syndrome likely to impact airway or lung function
7. Use of deep hypothermic circulatory arrest or regional cerebral perfusion during cardiac repair
8. Receipt of inhaled nitric oxide
9. Neonatal pulmonary hypertension
10. Significant active bleeding
11. Clinical reason which precludes early extubation, at the discretion of medical team (e.g.: hemodynamic instability, postoperative bleeding)
12. Lack of sufficient personnel for patient observation
13. Need for additional significant surgery that was not anticipated
14. Enrollment in the Phase I Study of Dexmedetomidine Bolus and Infusion in Corrective Infant Cardiac Surgery: Safety and Pharmacokinetics

5.3 Subject Withdrawal Criteria

N/A

5.4 Subject Availability

There will be 5 collaborataive centers participating in the project and five control sites. The number of potentially eligible subjects at the 5 collaborative sites is displayed in **Table 7**.

Table 7. Annual # of cases based on 7/07 to 6/11 Society of Thoracic Surgeons Database

	Center				
Procedure	**A**	**B**	**C**	**D**	**E**
Tetralogy of Fallot (complete repair)	21	16	13	15	20
Coarctation of the aorta repair (<12 mo. of age)	28	22	23	12	29

It is expected that over the same 24-month period that the control sites will have a similar number of eligible subjects.

5.5 Data Collection

There will be several phases of data collection. At collaborative learning centers, data from the 12 months prior to the institution of the CPG will be collected for subjects meeting the clinical inclusion criteria noted above. Following implementation of the CPG at collaborative learning sites, data will be collected prospectively. Data will be collected up to the time of hospital discharge.

6. TREATMENTS TO BE ADMINISTERED

6.1 Description of the Study Intervention

The primary aim of this study is to to determine whether collaborative learning can promote the successful implementation of a CPG focused on early extubation following infant heart surgery. Implementation of the CPG involves a strategy of early extubation that represents a system-wide effort to plan for sedation, analgesia, ventilation and staffing. The specifics of management will not be known until the CPG is finalized. However, the CPG will be based in large part upon the strategy currently practiced at CHOP. The key features of that approach are as follows:

1. Preoperative assessment for candidacy of early extubation
2. Anesthetic management
    a. Fentanyl 5 -10 mcg/kg
    b. Volatile anesthetic (isoflurane)
    c. Dexmedetomidine 1 mcg/kg administered upon sternal closure if age >28 days
3. Hand-off in CICU
    a. Sufficient staffing to observe and manage patient
    b. Extubation by staff anesthesiologist
    c. Confirmation of satisfactory respiratory status
        i. Blood gas and chest x-ray are satisfactory

The model at CHOP favors extubation in the ICU rather than the operating room. This is a reflection of institutional resources. It is possible that the CPG will permit extubation either in the operating room or in the ICU.

7. SAFETY ASSESSMENTS AND MONITORING

7.1 Data and Safety Monitoring Plan

The Data and Safety Monitoring Plan for this study will follow standard PHN monitoring principles. Oversight of data and safety is provided by the PHN DSMB, appointed by NHLBI. The DSMB, which meets at least semi-annually, is composed of experts in pediatric cardiology, congenital heart surgery, biostatistics and study design, and ethics, as well as a lay member. For this study, the DSMB will review study accrual, data quality, and protocol violations on a regular basis and make recommendations about study conduct to the Director, NHLBI.

8. STATISTICS

8.1 Statistical Analysis Plan

8.1.1 Analysis of the Primary Outcome / Endpoint

The primary outcome for this study is the proportion (or change in proportion) of patients successfully extubated within six hours of return to the ICU following surgery for select infant

heart conditions. Early extubation rates will be calculated individually by center as well as aggregated across all participating centers and all control centers.

The primary analytic approach will utilize confidence intervals for the proportion of patients extubated within six hours of return to the ICU. These interval estimates will be constructed for and compared between the 12-month period preceding CPG implementation and the 12-month period following CPG implementation within participating centers.

As improvements in clinical outcomes may be greater when an institution has more experience with the CPG we will also examine whether extubation rates change with time after implementation of the CPG using an interrupted time-series approach. Briefly, the outcome will be modeled as a function of time and center using generalized linear mixed models with specific components estimating the correlation within centers over time and allowing for possible break-points in the slope of the time-outcome relationship. As the study enrollment is limited by time we may be underpowered to sensitively detect effects with this approach.

8.1.2 Analysis of Secondary Outcomes

Secondary outcomes for this study will be treated in a manner parallel to the primary outcome. Outcomes will be calculated individually by center as well as aggregated across all participating centers and all control centers. To determine whether outcomes change with time after implementation of the CPG, outcomes will be compared between the 12-month period preceding CPG implementation to the 12-month period following CPG implementation within participating centers as well as among participating centers and between participating and control centers. Analytic approach will be informed by the type of outcome with parametric (e.g. paired-t-test) and non-parametric (e.g. Wilcoxon signed-rank test) applied as appropriate.

As with the primary outcome we will also undertake secondary analyses using interrupted time-series methods. Outcomes will be modeled as a function of time and center using generalized linear mixed models with specific components estimating the correlation within centers over time and allowing for possible break-points in the slope of the time-outcome relationship, applying varying link functions depending on the form of the outcome (e.g. log-link for binary outcomes, poisson link for count data, identity for normally-distributed outcomes) and outcomes will be examined and transformed as necessary to comply with assumptions of the analyses.

<u>Cost Data</u>
Data from both Collaborative Learning Study participant and control hospitals will be utilized for this study. Study data will be linked to resource utilization information from the Children's Hospital Association datasets. This administrative database collects standardized information from the hospital bill from nearly all US children's hospitals. The table below shows the overlap between PHN hospitals and hospitals who submit data to Children's Hospital Association. There is a 1:1 overlap with the exception of one control site (Toronto) who as expected does not submit billing data to any US administrative dataset.

<u>Data linkage:</u>
Data from the PHN collaborative learning study and information collected in the Children's Hospital Association dataset will be linked on the patient level using the method of indirect identifiers, as previously described and validated (5-8, 10). Briefly, this method has been used previously to link information from clinical and administrative datasets in the pediatric cardiac

population, and involves matching patients between datasets on the values of center where hospitalized, date of birth, date of admission, date of discharge, and sex. This linkage will results in a merged dataset containing information collected both with in the PHN collaborative learning study and within the Children's Hospital Association dataset on each patient.

Data collected from the Children's Hospital Association dataset will include total hospital charges, hospital and department specific cost to charge ratios, and standard categories of charges including: room and board, pharmacy, imaging, lab, clinical, supplies, other. For the purposes of this study we will also evaluate ventilator-associated charges and charges related to ICU vs. non-ICU care.

Analysis:
In order to test our hypothesis that CPG implementation will be associated with lower hospital costs, the following analysis will be performed:
Total hospital costs (the primary outcome variable) will be estimated during the time periods before and after CPG implementation at both the intervention and control hospitals using hospital charge data and cost-to-charge ratios as previously described (8,10). The CMS price wage index will be used to account for regional differences and values will be indexed to 2015 dollars (when data collection for the CPG ends) in order to account for inflation. In order to evaluate the impact of the CPG on total hospital costs, a "difference in difference" type analysis will be performed (9). This analytic strategy, which employs econometric techniques, isolates changes in outcomes associated with an event of interest above and beyond any secular changes observed prior to the event, or changes in a control group not exposed to the event or change. This methodology will allow us to best evaluate the impact of the CPG, taking into account any trends in hospital costs before the implementation of the CPG at the intervention sites, as well as cost trends during the study period at the control sites. We will model cost as a continuous variable and will account for the skewed distribution of cost. Models will also account for non-independence (clustering) of patients within hospitals, and we will also adjust for important differences across hospitals in patient characteristics or case mix. Separate models will be constructed for the TOF and coarctation patients.

8.2 Number of Subjects to be Enrolled

In this pilot study, subject enrollment will be limited by the number of eligible cases presenting at both the collaborative and control centers involved in the project. Based on historical data from the five collaborative sites, the mean annual number of eligible cases from these 5 centers is 199. Thus, in a 24-month period we estimate approximately 400 cases will be observed and that over the same time period the control sites will have a similar number of cases. Data will be collected for 12 months prior to the 'go live' date of the CPG and 12 months after the implementation of the CPG. As such, we present below the precision with which we will be able to estimate the primary outcome under various enrollment and extubation scenarios (Table 8).

Table 8. Hypothetical precision of estimates of the change in extubation rates within participating centers under various enrollment and extubation-rate scenarios. Note that confidence bounds may be asymmetric about the hypothetical change in observed proportions of early extubation.

Total Cases Among Participating Centers	Hypothetical Increase Within Centers in Observed Early Extubation Rate	Estimated 95% Confidence Interval (LCL, UCL)
199		
	0.1	(0.06, 0.15)
	0.2	(0.14, 0.26)
	0.3	(0.24, 0.37)
	0.4	(0.33, 0.47)
100		
	0.1	(0.05, 0.18)
	0.2	(0.13, 0.29)
	0.3	(0.22, 0.40)
	0.4	(0.30, 0.50)
50		
	0.1	(0.04, 0.23)
	0.2	(0.11, 0.34)
	0.3	(0.19, 0.44)
	0.4	(0.27, 0.55)

Secondary outcomes are addressed similarly. Table 9 presents the hypothetical precision with which we will be able to estimate overall CPG compliance among participating centers with scenarios where we would conclude that compliance was below 80% in bold, while Table 10 presents the hypothetical precision with which we will be able to estimate differences in compliance among centers, and cases where it would be concluded that there are significant center-specific variations in compliance rate are in bold.

Table 9. Hypothetical precision of CPG compliance estimates under various enrollment and CPG compliance scenarios. Note that confidence bounds may be asymmetric about the hypothetical observed proportion.

Total Cases Among Participating Centers	Hypothetical Observed Proportion of Cases Compliant with CPG	Estimated 95% Confidence Interval (LCL, UCL)
199		
	0.90	(0.85, 0.94)
	0.80	(0.74, 0.85)
	0.75	(0.68, 0.81)
	0.70	**(0.63, 0.76)**
100		
	0.90	(0.82, 0.95)
	0.80	(0.71, 0.87)
	0.75	(0.65, 0.83)
	0.70	**(0.60, 0.79)**
75		
	0.90	(0.80, 0.95)
	0.80	(0.70, 0.87)
	0.75	(0.63, 0.84)
	0.70	**(0.57, 0.79)**

Table 10. Hypothetical precision of estimates of differences in compliance rates between/among participating centers under various enrollment and CPG compliance scenarios. Center A is more compliant than Center B if the confidence interval for the odds-ratio does not include 1.

Cases In Each Center Being Compared	Hypothetical Observed Proportion of Cases Compliant with CPG (Center A; Center B)	Estimated Odds-Ratio (95% Confidence Interval for Odds-Ratio). Center A more compliant than Center B if confidence interval does not include 1.
25	0.9; 0.7	5.2 (0.9, 56.7)
25	0.8; 0.7	1.85 (0.4, 8.7)
25	0.8; 0.6	2.6 (0.6, 12.0)
25	0.8; 0.5	**4.2 (1.1, 19.0)**
20	0.8; 0.7	1.3 (0.3, 9.9)
20	0.8; 0.6	2.6 (0.5, 14.8)
20	0.8; 0.5	3.9 (0.8, 20.7)
20	0.8; 0.4	**5.7 (1.2, 32.7)**
15	0.8; 0.6	2.6 (0.4, 20.4)
15	0.8; 0.5	3.4 (0.6, 26.3)
15	0.8; 0.4	5.6 (0.9, 44.9)
15	0.8; 0.3	**7.4 (1.2, 61.0)**

8.3 Level of Significance
The type I error probability for the trial will be 0.05. No adjustment will be made to account for comparing the treatment groups with respect to more than one outcome variable. However, the report will note the number of comparisons made and the possibility that, when many outcomes are analyzed, it is not unexpected that one or more might have a statistically significant finding just by chance.

8.4 Spurious Data Procedures
Consistency checks and range checks will be built into the data management system. This will allow many errors to be identified and corrected at the time of data entry. Queries regarding any problems with data will be sent to site coordinators regularly throughout the course of the study. Sites will also be monitored during the study. Therefore, spurious data are expected to be rare. Any data which are judged by the medical monitors to be definitely incorrect, and which cannot be resolved, will be set to missing.

The study report will indicate the number of subjects who have missing data on each study endpoint. For covariate-adjusted analyses, the number of subjects who have missing data on the covariates will be reported.

8.5 Deviation Reporting Procedures
Any modifications or deviations from the statistical plan described in this protocol will be documented in a "Revised Statistical Plan" document.

8.6 Subjects to be Included in Analyses
All clinical cases meeting eligibility criteria during the two 12-month intervals will be included in the analysis.

9. DATA MANAGEMENT
An Electronic Data Capture (EDC) system will be used for the study that is designed to support reliable and secure data entry for clinical research purposes. The system also provides seamless integration of eCRFs and paper-based CRFs within a single protocol if desired; implementation of protocol amendments; and SAS and XML study data exports.

9.1 Data Entry
Data can be entered directly from multiple study sites via a fully validated and 21 CFR Part 11 compliant, secure Web application and stored centrally. A configurable sample-based double data entry system is available. Data are entered by subject study identification number; names will not be linked with subject data in the database. Study sites will maintain records in secure areas, linking the subject name with the identification number assigned for the study. Study sites will have full access to their own data and be able to view these data remotely. Study staff will not be able to view subject data associated with other sites.

9.2 Data Validation and Monitoring
Integrated into the data entry system are real time validations, including both inter- and intra-instrument data checks. Inconsistent or questionable values are flagged during entry, and an edit report is automatically generated to the data entry client. These edit reports provide the information necessary to investigate any data entry errors or resolved questions regarding out-of-range or questionable values. Second level query tracking allows monitors and data

managers real time access to unresolved queries as well as the date and time of query generation and resolution.

9.3 Data Security and Integrity

All data changes are written to an audit trail. The audit trail identifies the data item by table, column and key field. The entry includes the user, date and time, as well as the old value and new value. Both patient related data as well as trial configuration data are written to the audit trail. Data are saved at regular intervals during data entry to prevent loss of information in the event of a disruption of the Internet connection. In the unlikely event of a major disruption, a backup connection allows full access to the DMS.

Several levels of security are employed to ensure privacy and integrity of the study data, including the following: Study access requires use of assigned user names and passwords. Individual roles and access levels are assigned by the study data manager. Passwords are changed regularly. Web-based entry uses secure socket layer data encryption. Data will not be stored on laptop computers.

The cost data merger and analysis will be performed at the University of Michigan within the Michigan Congenital Heart Outcomes Research and Discovery (M-CHORD) Program. The M-CHORD Program, housed within the Michigan Congenital Heart Center, is Co-directed by Dr. Pasquali. M-CHORD has a full time dedicated research staff with experience in conducing these types of data mergers, and multicenter clinical investigations in pediatric cardiovascular medicine. Due to Children's Hospital Association data use policies, their dataset cannot be shared outside of member institutions so it is not possible for this data merger and analysis to be performed at NERI. It has instead been feasible in the past to share PHN study data from NERI to allow projects such as these to take place – for example, this approach is currently being used for the PHN Scholar project mentioned above. Therefore, we believe this approach will be feasible for the proposed study. The study team will work in close collaboration with NERI personnel to ensure the integrity and appropriate analysis of PHN variables, and will follow PHN guidelines regarding all presentations and publications.

10. QUALITY CONTROL AND QUALITY ASSURANCE

The DCC has primary responsibility for QC/QA activities of the phenotypic data. The DCC also requires that the sites complete certain QC activities, most of which are monitored by the DCC. The key QC/QA activities are:

- Development of a Study Manual;
- Clearly formatted and carefully constructed Case Report Forms (CRFs) with clear, up-to-date manuals of instruction;
- Sign-Off Procedures for selected CRFs;
- Central protocol training and certification of all site data collection staff with the use of standardized checklists;
- Data management training and certification of site personnel completing data entry and/or data management;
- Verification of clinical case eligibility;
- On-going monitoring of all protocols/data collection activities; and
- Monitoring visits to sites as required with pre-specified goals and/or remote monitoring activities.

11. ETHICS AND HUMAN SUBJECTS CONSIDERATIONS

11.1 Consent

The protocol will seek a waiver of consent. A waiver is justified because the research involves no more than minimal risk to the subjects and that the research could not practicably be carried out without the waiver or alteration.

The protocol's primary objective is to examine how collaborative learning enhances the development and implementation of a CPG. The programmatic effort to minimize the duration of postoperative ventilation is a quality initiative based on guiding principles of perioperative care enumerated in section 3.4. In addition, since the implementation of a CPG in the ICU requires system-wide changes and uniform practice it is not practical to apply the CPG to only some patients based upon consent. It is anticipated that the early extubation CPG will become the institutional standard of care for these index operations.

11.2 Potential Risks

The present study examines the impact of a collaborative learning strategy on the development and implementation of a CPG. As such, the only risk related to the study for the subject is the potential for breach of confidentiality.

Application of the CPG may place stress on the healthcare system as a whole. An early extubation strategy may require the presence of the cardiac anesthesiologist at the bedside in the intensive care unit following the hand-off process. If the anesthesiology staffing is limited, this may impact patient flow or care elswhere in the system. The study will include balancing measures such as the cumulative dose of analgesia and sedation. These are assessments of other aspects of patient care that may be impacted by application of the CPG.

11.3 Confidentiality, Protection against Risks

Investigators will take all reasonable measures to protect the confidentiality of subjects and their families, including the following:

<u>Use of Subject ID numbers</u>

Each subject is assigned a subject identification number (SID). All clinical research data are stripped of identifiers and labeled with the study number. The enrollment log with participant identifiers will be maintained at each site in a secured, locked location available only to the study staff. The subject's name and any other identifying information will not appear in any presentation or publication resulting from this study.

11.4 Potential Benefits

Development and implementation of CPG may enhance care of children with congenital heart disease through comprehensive assessment of anesthesia, sedation and ventilation practices at each participating institution. In addition, implementation of CPG often results in a reduction of unwanted practice variation. If found to be successful, this strategy of collaborative learning could also be applied to numerous other aspects of cardiac care in children.

11.5 Risk/Benefit Ratio and Importance of Information to Be Obtained

The risk/benefit ratio is favorable for this study, and adverse events are not anticipated. The baseline risk is minimal because there are no therapeutic interventions. In addition, although an individual subject may not benefit from participation, the results of this study will make important

contributions to the improvement of knowledge postoperative care of congenital heart disease and ultimately in the improvement of treatment and prognosis.

12. STUDY LIMITATIONS

The study will not be able to demonstrate that a collaborative learning model of developing and implementing a CPG is superior to other quality improvement methods to impact patient care. Although the inclusion of "control" PHN centers is part of the design, such a strategy is meant to primarily adjust for temporal trends in postoperative care.

Also, the sustained benefit of collaborative learning and incorporation of a CPG into postoperative care remains a concern. In principle, incorporation of a CPG allows a center to incorporate a new care paradigm into routine care. However, adherence to CPGs can wane over time. It is possible that the benefit from collaborative learning may result predominantly from close observation of an observed practice and that, once protocol data collection is completed, extubation practices may revert to pre-intervention levels.

Lastly, this pilot study is primarily designed to assess the utility of a collaborative learning model and not to assess the benefit of early extubation per se. While it is assumed that this project will provide valuable data on the relationship of early extubation on numerous variables, an alternative study design would be needed to assess more fully the other variables potentially related to early extubation.

13. REFERENCES

1. **O'Connor, G.T., et al., A regional intervention to improve the hospital mortality associated with coronary artery bypass graft surgery. The Northern New England Cardiovascular Disease Study Group. Jama, 1996. 275(11): p. 841-6.**

2. **Prager, R.L., et al., Cardiac surgeons and the quality movement: the Michigan experience. Semin Thorac Cardiovasc Surg, 2009. 21(1): p. 20-7.**

3. **Wheeler, D.S., et al., A hospital-wide quality-improvement collaborative to reduce catheter-associated bloodstream infections. Pediatrics, 2011. 128(4): p. e995-e1007.**

4. **McKee, C., et al, Reduction of catheter-associated bloodstream infections in pediatric patients: Experimentation and reality. Pediatr Crit Care Med, 2008. 9(1): p. 40-46**

5. **Miller, M.R., et al, Decreasing PICU Catheter-Associated Bloodstream Infections: NACHRI's Quality Transformation Efforts. Pediatrics, 2010. 125(2): p. 206–213**

6. **Hayes, L.W., et al., A multicenter collaborative approach to reducing pediatric codes outside the ICU. Pediatrics, 2012. 129(3): p. e785-91.**

7. **Joffe, D., et al., Early extubation after cardiac operations in neonates and young infants. J Thorac Cardiovasc Surg, 1998. 116(3): p. 536.**

8. Heard, G.G., et al., Early extubation after surgical repair of congenital heart disease. Crit Care Med, 1985. 13(10): p. 830-2.

9. Kwon, S., et al., Creating a learning healthcare system in surgery: Washington State's Surgical Care and Outcomes Assessment Program (SCOAP) at 5 years. Surgery, 2012. 151(2): p. 146-52.

10. Honess, C., P. Gallant, and K. Keane, The Clinical Scholar Model: Evidence-based practice at the bedside. Nurs Clin North Am, 2009. 44(1): p. 117-30, xii.

11. Leone, M., et al., Variable compliance with clinical practice guidelines identified in a 1-day audit at 66 French adult intensive care units. Crit Care Med, 2012. 40(12): p. 3189-95.

12. Brown, K.L., et al., Risk factors for long intensive care unit stay after cardiopulmonary bypass in children. Crit Care Med, 2003. 31(1): p. 28-33.

13. Institute of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines [Internet], 2011.

14. Robbins JM, Bird TM, Tilford JM, et al. Hospital stays, hospital charges, and in-hospital deaths among infants with selected birth defects-United States 2003. MMWR, 2007. 56:25-29.

15. Keren R, Luan X, Localio R, Hall M, McLeod L, Dai D, Srivastava R. Prioritization of comparative effectiveness research topics in hospital pediatrics. Arch Pediatr Adolesc Med, 2012.166(12):1155-1164.

16. Pasquali SK, He X, Jacobs ML, Shah SS, Peterson ED, Hall M, Gaynor JW, Hill KD, Welke KF, Mayer JE, Jacobs JP, Li JS. Variation in congenital heart surgery costs across hospitals. Pediatrics, 2014. 133(3):e553-60.

17. Dimick JB, Nicholas LH, Ryan AM, Thumma JR, Birkmeyer JD. Bariatric surgery complications before vs after implementation of a national policy restricting coverage to centers of excellence. JAMA, 2013. 309(8):792-799.

18. Pasquali SK, Jacobs JP, Shook GJ, O'Brien SM, Hall M, Jacobs ML, Welke KF, Gaynor JW, Peterson ED, Shah SS, Li JS. Linking clinical registry data with administrative data using indirect identifiers: Implementation and validation in the congenital heart surgery population. Am Heart J 2010;160:1099-1104.