Pediatric Emergency Care Applied Research Network

NIH/NICHD
Hypothermia for Pediatric Cardiac Arrest Planning Grant

"This study will collect pilot data which will be used to determine the feasibility of a future randomized clinical trial of hypothermia following pediatric cardiac arrest."

Principal Investigator:

Frank Moler, M.D., M.S. (PI)
University of Michigan, Ann Arbor, MI

The following PECARN (Pediatric Emergency Care Applied Research Network) Pediatric Critical Care Medicine and Pediatric Emergency Medicine clinical centers and investigators will participate:

University of Michigan, Ann Arbor, MI
Frank Moler, M.D., M.S. (PI)
Faye Silverstein, M.D.
David Treloar, M.D., M.S.
Ronald Maio, D.O., M.S. (Great Lakes PI)

Children's Hospital of Philadelphia,Philadelphia, PA
Vinay Nadkarni, M.D.
Elizabeth Alpern, M.D.

The Johns Hopkins Hospital, Baltimore, MD
Donald H. Shaffner, M.D.
Allen Walker, M.D.

Children's National Medical Center, Washington D.C.
Heidi Dalton, M.D.
James Chamberlain, M.D. (CARN PI)

Children's Hospital Medical Center, Cincinnati, Ohio
Richard Brilli, M.D.
Richard Ruddy, M.D.

Children's Hospital of Michigan, Detroit, MI
Kathleen Meert, M.D.
Prashant Mahajan, M.D., M.P.H.

University of California at Davis, Sacramento, CA
Robert Pretzlaff, M.D., M.S
Nathan Kuppermann, M.D., M.P.H. (ACORN PI)

University of Utah - Primary Children's Medical Center
Kimberly Statler, M.D.
Howard Corneli, M.D., M.S.
Michael Dean, M.D., M.B.A. (CDMCC PI)

Children's Hospital of Pittsburgh, Pittsburg, PA
Robert S. B. Clark, M.D.

Spectrum Health System, Grand Rapids, MI
Richard Hackbarth, M.D.
John Hoyle, M.D.

Children's Hospital of New York, Columbia University, New York, NY
Charles Schleien, M.D.
Steven Miller, M.D.
Nadine Levick, M.D., M.P.H. (PED NET PI)

Washington University St. Louis Children's Hospital St. Louis, MO
Fiona Levy, M.D.
David Jaffe, M.D.

University of Rochester, Strong Memorial Hospital Rochester, NY
Elise van der Jagt, M.D.
Julius Goepp, M.D.

Children's Hospital of Buffalo, Buffalo, NY
Bradlley Fuhrman, M.D.
Kathleen Lillis, M.D.

Children's Hospital of Wisconsin, Milwaukee, WI
Thomas Rice, M.D.
Marc Gorelick, M.D.

Version 9/19/2003

Abstract

Cardiopulmonary arrest with apnea and loss of palpable pulse (CA) in childhood is a tragic event that very often results in either death or poor quality long term neurologic survival. Recent randomized clinical trials (RCT) in adult populations have reported improved neurologic outcome and survival in groups that received short term mild hypothermia following out of hospital ventricular fibrillation (VF) arrest. The efficacy of hypothermia in children following cardiac arrest is not known. CA in children is commonly secondary to a respiratory etiology that results in hypoxia, which after a period of time results in cardiac arrest. Asystole or pulseless electrical activity is the most common presenting cardiac rhythms when resuscitation is initiated. In adults by contrast, a sudden cardiac event (without a preceding period of hypoxia) most often occurs with VF or ventricular tachcardia the common presenting rhythms. In this clinical trial planning grant application, 15 Pediatric Emergency Care Applied Research Network (PECARN) children's hospitals with intensive care units will obtain pilot data, from the medical records of patients who have sustained a CA with return of spontaneous circulation in either the outpatient or inpatient setting. Characterization of this population will include arrest specific events and etiology, patient characteristics, hospital course, interventions received, hospital survival, and neurologic outcome. Approximately 500-1000 patients will meet study criteria and their charts will be reviewed over the 12 month period of this pilot study. This information will be used to create inclusion and exclusion criteria, and to calculate sample size requirements for a future RCT of hypothermia following pediatric cardiac arrest. Duration of time to successfully enroll patients from this cohort of 15 children's hospitals for a future RCT will be estimated. This application will also result in creation of multiple documents needed to perform a RCT of hypothermia after cardiac arrest in childhood, including study related data forms, study protocols, manuals of operation, institutional review board and informed consent related documents, and other materials. The PECARN will support all phases of this application with its existing clinical trials research infrastructure that includes a steering committee, five clinical trials supporting subcommittees, and a central data management coordinating center (CDMCC). The CDMCC will make operational all data and analysis related tasks of this application, and assure all study sites are compliant with regulations concerning data security and confidentiality.

Background/Introduction

Cardiopulmonary arrest with apnea and loss of palpable pulse (CA) in childhood is a tragic event that often results in either death or poor quality neurologic survival. This is especially true of CA that occurs in the out of hospital setting. A recent population based study from Houston reported an event rate of nearly 20 per 100,000 children at risk with only 11 percent of children having a return of spontaneous circulation (ROSC) (1). In this group of 33 children with return of ROSC after out-of-hospital CA, six (18%) patients survived to hospital discharge with five of six having poor neurologic outcome (1). For CA occurring in hospital settings, outcomes are also poor, but appear to be somewhat better in terms of survival and neurologic outcomes in more recent reports (16-18). Torres reported the outcomes of a series of 92 children with inhospital cardiac arrests in a large US children's hospital (17). None (0/44) of the children with a history of sepsis survived to one year. Additionally, no patients (0/24)

requiring CPR greater than 30 minutes survived one year. About one third were alive at 24 hours and only 10% (9 of 92) were alive at one year. Most of the survivors (8/9) had returned to their baseline pre arrest function at one year follow up, as measured by the Pediatric Cerebral Performance Category scale (17). Young and Seidel recently reviewed the literature of pediatric cardiopulmonary arrest and summarized 44 studies worldwide since 1970 (19). From these heterogeneous studies, a total of 3094 patients were analyzed. Mean survival from out-of-hospital arrests (8.4%) was lower than in-hospital occurring arrests (24%). Approximately half of the patients were less than one year of age. As a group, infants had lower survival overall (6%). Ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) were present in only 10% of pediatric CA; however, survival was observed to be much higher (30%) than observed in the more common pediatric bradyasystole arrests (5%). CPR for longer than 30 minutes and which required more than two doses of epinephrine was associated with very poor outcome. The authors stated the limitations of this literature review were that most studies consisted of small case series from single centers and that there existed a lack of uniformity in case definitions and outcomes. This was especially true of neurologic function outcomes in survivors.

***Hypothermia for out of hospital cardiac arrest*:** In experimental animal models there is strong evidence that post-ischemia hypothermia can protect the brain from injury (21-24). Until very recently, specific interventions to improve neurologic outcome and survival following CA had not been observed in randomized clinical trials conducted in humans. In early 2002, two international trials conducted in Europe and Australia, each reported higher survival and improved neurologic outcome in select adult patients who were treated with mild hypothermia (32-34º C) following out of hospital CA secondary to ventricular fibrillation (VF) (31,32).

Pediatric and adult CPR differences: Because limited effective interventions for neuroprotection following CA exist currently, extrapolation of the recent adult study findings to pediatric clinical practice has been recommended by some and will likely occur (31, 32,37). However, it is important to validate the adult hypothermia following CA findings of neuroprotection in infants and children. First, very different mechanisms of CA in pediatric versus adult populations exist. Asphyxia with a period of hypoxia followed by later ischemia is the usual sequence to CA in pediatric patients. This is in contrast to sudden cardiac arrhythmia events leading directly in ischemic CA in adults. Pediatric survival and neurologic outcomes following out of hospital arrests may also not be generalizable from adult studies because of differences in cardiac rhythms seen in adult and pediatric populations. In pediatric patients, CA occurs with asystole and/or pulseless electrical activity (PEA) being the most common presenting cardiac rhythms, while in adults a primary cardiac arrhythmia, usually VF or pulseless ventricular tachycardia, leads to CA. Survival from pediatric VF is reported to be much greater than survival from pediatric asystole (19). The goal of a post CA resuscitation intervention like hypothermia will be not only to increase the number of long term survivors, but most importantly, to increase the number of survivors with good neurologic outcomes. The use of mild hypothermia following pediatric CA could potentially result in increased numbers of survivors, but result in many more survivors with poor neurologic outcomes. On the other hand, should hypothermia be established to be efficacious in pediatric aged patients and result in both greater numbers of survivors and survivors with good neurologic outcome, this would represent a major advance in post resuscitation care of infants and children. However, since hypothermia use is potentially associated with adverse effects (e.g. cardiac arrhythmias, infection risk, neutropenia), it is important to validate pediatric efficacy in order to avoid this potentially harmful and somewhat resource intensive intervention in the event it is determined

to represent an ineffective therapy (38). If the efficacy of hypothermia for pediatric CA can be established with an appropriately powered and executed RCT, then major changes in emergency medicine and critical care therapeutic approach to such patients would be required at hospitals in the US and elsewhere.

Objectives/Purpose of the Study

This investigation is a planning grant study that will collect pilot data to be used to determine feasibility of a future interventional study of hypothermia following pediatric cardiac arrest. This application is supported by the NIH/NICHD. It will plan, develop, and organize 15 sites within the Maternal Child Health Bureau (MCHB) funded Pediatric Emergency Care Applied Research Network (PECARN), in order to conduct future clinical trials related to childhood cardiopulmonary arrest. The initial future randomized clinical trial (RCT) of interest to the PECARN network will be an efficacy of mild hypothermia to improve neurologic outcome and survival of children following cardiac arrest. It is hypothesized that mild hypothermia therapy following pulseless pediatric cardiac arrest will result in improved survival and neurologic outcomes in children receiving this intervention. This application will collect pilot data at 15 PECARN clinical centers that will be used to estimate study sample size requirements and to determine general feasibility of these15 PECARN children's hospitals to conduct a future RCT interventional study of mild hypothermia following cardiac arrest in a pediatric population. Also, from this pilot data, development of inclusion and exclusion criteria for such a future RCT will be performed. Existing PECARN organizational resources including a steering committee, five subcommittees previously created to facilitate the conduct of clinical trials, and the PECARN Central Data Management and Coordinating Center (CDMCC) located at the University of Utah, will support and ensure the success of this RFA application. Other existing infrastructure resources of PECARN to be used to aid in the execution of this clinical trials planning grant are a secure, encrypted, digital workplace, eRoom^{TM}, maintained by the CDMCC and pre-existing funding for up to four yearly PECARN meetings; both of these resources will facilitate the creation of materials essential to conduct a future RCT of hypothermia following pediatric cardiac arrest. Materials such as IRB related consent documents for a RCT (including local, state, NIH, FDA, and other documents), data collection tools and training materials, study related protocols and manuals of operation, and other study specific documents will be created in this planning grant. This application has the following *six specific aims*:

Aim 1. To describe patient characteristics, information related to the cardiac arrest event, time intervals to death or live hospital discharge, patient outcomes, and other information from a cohort of pediatric patients who require cardiopulmonary resuscitation (CPR) for pulseless cardiac arrest at a subset of PECARN children's hospitals. Information from the hospital records of such patients hospitalized, as either inpatients or outpatients, will be abstracted.

Aim 2. To investigate factors associated with hospital discharge survival and neurologic outcomes in this population of pediatric patients who have sustained CPR for pulseless cardiac arrest.

Aim 3. To characterize a cohort of patients who would be eligible for randomization in a future clinical trial to study the efficacy of mild therapeutic hypothermia following pediatric pulseless cardiac arrest. Inclusion and exclusion criteria for such a study would be developed.

Aim 4. To estimate sample size required to conduct a RCT of therapeutic hypothermia to improve survival and neurologic outcomes following pediatric pulseless cardiac arrest.

Aim 5. To identify future study sites and investigators for a RCT of hypothermia for pediatric pulseless cardiac arrest.

Aim 6. To create documents necessary for planning and execution of a future randomized clinical trial of hypothermia for pediatric cardiac arrest. This includes data collection forms with training manuals; IRB forms and related documents required by local, state, federal agencies for study of vulnerable populations in a clinical trial; treatment protocols and manuals of operation for a RCT; planning for and methods of randomization in a future RCT; and other documents. Such materials will be needed for a future multicenter RCT application to study interventions, like hypothermia, aimed to improve pediatric outcomes following pulseless cardiac arrest.

As described above, this study will collect pilot data which will be used to determine the feasibility of a future randomized clinical trial of hypothermia following pediatric cardiac arrest. The end points to be examined will be hospital survival and neurologic outcome. At this time, a randomized clinical trial is not justified before obtaining pilot data that supports the feasibility of a trial within this network of pediatric children's hospitals.

Study Methodology/Design

This is an observational chart review study with the objective to collect information needed to determine the feasibility of a future randomized clinical trial. This study is not an interventional clinical trial. There are no randomization or control interventions as part of this study. The duration of data collection is one year. This is an observational study with no patient intervention and no direct patient follow up. We estimate that 500 to 1000 charts will be reviewed at the 15 PECARN children's hospitals with over 300 PICU beds. Trained research assistants will review the records of patients with a history of cardiac arrest. Data will be submitted to the CDMCC at the University of Utah over a secure, point to point connection. Patient identifiers will be removed at the originating clinical site and not submitted to the CDMCC.

The data abstractor's coding of patient records will be verified by the clinical center investigator at each site. A random sample of ten percent of charts will be reviewed by the clinical center investigator to ensure > 95% accuracy in the submitted records. In the event <95% accuracy is observed, the next three completed data forms will be reviewed to assure > 95% accuracy is attained. If <95% accuracy is again observed, the data abstractor will be retrained and or replaced at the discretion of the clinical center investigator. All other records will be screened by the center investigator for completeness of all data fields. In the event of the loss of a RA data abstractor at a clinical center during the 12 months of study data

collection, a similar training process will be conducted to train and certify the center' s new data collection personnel.

Patient identification for this study will be by way of review of emergency medicine department records, arrest team paging logs, and pediatric intensive care unit records daily. Additionally, 13 of 15 centers utilize the Pediatric Risk of Mortality Score (PRISM), which identifies patients with a history of cardiac arrest. Only patients with a history of pulseless cardiac arrest who achieved return of spontaneous circulation for a minimum of 20 minutes will be followed. For identified patients, records will be examined retrospectively to the concurrent hospitalization of children with a history of pulseless cardiac arrest. This will be done at least every week by the clinical center RA data abstractor.

Following satisfactory completed data form review or screen by the clinical center investigator (as described previously), a for-clinical-center-use only patient identification sheet will be removed and locked in a secure file cabinet at the originating clinical center. Personnel at the clinical center will then enter data from the paper form into an encrypted, secure, point to point connection site maintained by the CDMCC. To minimize data entry errors, data forms will be double-entered on-site. In this fashion, accurately entered data will be securely and electronically submitted to the CDMCC. We consider the streamlining of this data entry, transmission, and management process to be a key component of this development project. The paper data forms, minus the for-clinical-center-use only patient identification sheet, will be stored in a locked file cabinet at a different location separate from the locked file cabinet used to store the for-clinical-center-use only patient identification sheet.

The Project Data Coordinator for this clinical trial planning grant will be located in the CDMCC at the University of Utah and will perform a secondary review of all electronically received data. While the data entry module will be able to detect basic within-form errors (out of range values for variables, missing required fields), between-form inconsistencies, as well as site-specific global data quality issues such as unacceptably frequent missing values, will be detected during this review process. Clinical center investigators will be contacted for resolution of data inconsistencies, and also be regularly apprised of performance issues such as timeliness of data submission. Clinical centers will be instructed to keep locked and secure all patient study forms for a period of six years following the completion of the study. They then will be instructed to destroy all patient related forms related to this study. (Local laws or other rules may exist that supercede this plan of action). The data security, back up, and access are described in detail in the CDMCC information materials provided in the **appendix**.

All statistical analyses will be performed by the PECARN CDMCC core biostatistical staff using SAS 8.2 or later version (SAS Institute, Cary, NC) and S-Plus 6 (Insightful Co, Seattle WA). Handling of records with missing outcome data, such as may occur if the patient were transferred to another facility, will take place by way of a special data record completeness variable field at the end of the data collection form. This will occur uncommonly since participating centers are full service children's hospitals. Missing independent variable fields will be coded as such. In statistical packages like SAS, such missing cases are excluded from analysis when appropriate. The percent of cases with missing independent or dependent variables in each particular analysis report will be described and summarized.

The PECARN CDMCC under its cooperative agreement with the MCHB, will additionally provide the following support to all PECARN projects as is described in the MCHB Guidance

for Cooperative Agreements for CDMCC – March 2002, CDFA#93.127L document. To summarize, the CDMCC will provide support for all regulatory function and requirements associated with Institutional Review Board (IRB), Investigational New Drug (IND) applications, the Health Insurance Portability and Accountability Act (HIPAA), and the Investigational Devise Exemption (IDE) applications. Additionally, the CDMCC will monitor each study site, with direct site visits, to assess the adequacy of all site facilities to be used in future clinical trials. If needed, it will provide good clinical practices training to appropriate site personnel, and confirm that appropriate site personnel have completed human subjects training. There will be interim site visits to assess site compliance with the requirements for the PECARN clinical and observational study protocols being conducted. The CDMCC will standardize training for study site staff for the initiation of all PECARN protocols as well as the development of a Manual of Operations for all clinical and non-clinical protocols. It will delineate specific instructions and requirements for the appropriate implementation and monitoring of each clinical trial and/or observational study by site personnel, and if necessary to ensure appropriate training, provide group meetings for site personnel. The CDMCC will monitor and report monthly the progress of clinical trials and observational studies, and develop criteria and procedures for the evaluation of site performance, including correcting study site deficiencies and/or eliminating sites.

Participant Selection Criteria

Inclusion Criteria:
All pediatric patients will be eligible for study. The medical records of all pediatric patients from birth to 18 years of age (inclusive) with a history of cardiac arrest for greater than one minute and who survive a minimum of 20 minutes will be eligible for chart review in this observational study. There are no exclusions based on race, ethnicity, or gender.

Exclusion Criteria:
Records of patients cared for in neonatal ICUs and patients who experience cardiac arrest in the operating room as part of planned congenital heart disease surgical repair will be excluded.

Recruitment:
Patients will not be recruited. The medical records of patients with a history of cardiac arrest will be examined.

Informed Consent
We are requesting a waiver of the requirement of informed consent for this observational study. This has been granted at the principal investigators institution (University of Michigan) and by the NIH study section.

Each site will be responsible for HIPAA compliance when requesting waiver of informed consent and authorization.

Description of Agent(s) involved:

Not applicable

Study Procedures

This research project titled *"Hypothermia for Pediatric Cardiac Arrest Planning Grant"* will have no direct involvement with human subjects and will utilize only existing information contained in the medical records of children with a history of cardiac arrest. For this observational chart review planning grant study, research assistants at each clinical center site will review cardiac arrest documentation sheets and Pediatric Risk of Mortality Score (PRISM) for all patients less than 19 years of age with a history of cardiac arrest at their clinical center. It is standard patient care practice in the U.S. to document patient cardiac arrest events on defined institutional forms that are part of the patient medical record. Additionally, the majority of the children's hospitals participating in this planning grant study, also utilize the PRISM mortality score as a quality assurance tool which also identifies patients with a history of cardiac arrest prior to ICU admission.

The research assistants will retrospectively review the medical records of all children with a history of cardiac arrest and complete the study data forms on all records that meet the study entry criteria. Patient identification for this study will be by way of review of emergency medicine department records, arrest team paging logs, and pediatric intensive care unit records daily. There will be no contact with the patient or patient's family during this chart review study. After completion of the study data form by the research assistant, the clinical center investigator will review the record for completeness. In 10% of data forms, the clinical center investigator will do a limited secondary chart review to verify data accuracy. After completion of this task, a single patient identifier sheet [one page (sheet) that will have a study number and patient registration number] will be removed from the original data form and stored in a lock file cabinet in a locked room. After data entry to the CDMCC as described in Study Methodology/Design, the original data form will be stored in a separate locked file cabinet in a locked room. The duration of the data collection will be for the twelve month period from Jan 1, 2004 to December 31, 2004.

Statistical Methods, Data Analysis and Interpretation

Aim 1 of this application will characterize a cohort of children hospitalized at PECARN children's hospitals with a history of cardiac arrest and spontaneous return of circulation. Trained data collection personnel will abstract information from medical records of patients, hospitalized with a history of CA that occurred in either inpatient or outpatient setting. Information abstracted will include the following: patient specific characteristics (age including age strata (67), gender, ethnicity/race, special needs and chronic conditions characteristics; zip code as a measure of socioeconomic status); event characteristics including witnessed arrest status, bystander CPR status, in or out of hospital arrest location, initial cardiac rhythm, duration of CPR, medications administered (including number of epinephrine doses administered), airway support measures, and time to arrival at first emergency medicine department; and time to arrival at a PECARN facility emergency department or pediatric intensive care unit will be abstracted. The presumed etiology of cardiac arrest will be categorized into major classifications such as drowning, sudden infant death-like event, respiratory failure, sepsis, cardiac arrhythmia, cardiac surgery or congenital heart disease,

cancer or related conditions, trauma, end stage terminal condition, and other miscellaneous conditions. Patient temperature during the first 24 hours of admission will be abstracted. The requirement for inotropic and vasopressor agents and vital signs during the initial 24 hours will also be examined. For patients who die after admission to the PICU, reasons for death or withdrawal of life support will be categorized. Hospital survival outcomes (including ROSC for greater than 20 minutes, 24 hours, seven days, 30 days, and survival to hospital discharge), and assessment of neurologic injury outcome information will also be collected. Additionally, easily measured surrogate measures of neurologic injury status at hospital discharge will be recorded, such as, need for tracheostomy, need of a mechanical ventilation devise (ventilator, bipap, cpap), gastrostomy or other artificial feeding devise, and hospital discharge location. Patients discharged to home without the previously mentioned technologies or devices will be considered survivors with good neurologic outcomes, while cases with new placement of these devices or discharged to a chronic care facility will be considered to have poor neurologic outcomes**.** The frequency and duration of therapeutic hypothermia in actual clinical practice at PECARN hospitals will also be recorded. Documentation of the time until the patient's parents or caregiver are available at the clinical center will be noted in order to anticipate and plan related to informed consent issues in the future RCT of hypothermia. The timing for the initial rehabilitation consultation and types of services received will be ascertained and utilized for planning of the future RCT. Center counts of cases of pediatric CA will be described.

Aim 2 will investigate factors associated with survival and neurologic outcome in this population of pediatric patients who have sustained CA. Variables described above under *Aim 1* above will be examined for differences between outcome groups (survivors versus non-survivors and good versus poor neurologic status). All data collection related activities and statistical analyses will be supervised by the PECARN CDMCC and reviewed by the *Data Analysis and Management Subcommittee* of PECARN. We outline below basic approaches we plan to employ, and point out that we have both the expertise and computing/software resources to carry out more advanced or demanding analyses as appropriate. Descriptive statistics of the pilot data resulting from this RFA will be utilized to depict the cardiac population studied. Means with standard deviations or medians with ranges will be used to characterize continuous variables, while categorical variables will be described by counts and percents. For continuous variables, an independent sample t-test (normal distributed variables) or a Wilcoxon rank sum test (non-normal distributed variables) will be used to compare groups such as survivors and non-survivors. Categorical variable comparisons between groups will be performed by a Pearson's chi-square or Fisher's exact test. Multivariate logistic regression will be used to examine whether differences observed between groups are due to confounding by dissimilarities in baseline characteristics (of these groups), and more generally which factors are most strongly and independently predictive of good/adverse outcome. A p-value < 0.05 will be considered to represent a statistically significant difference, although many analyses performed will be highly exploratory in nature.

In addition to modeling quantitative effects of factors on outcome, we will plan to use the Classification and Regression Trees (CART) technique to model both binary and continuous outcome (108). This approach, which recursively splits the data into subgroups that are as different from each other as possible, is useful for exploratory identification of interactions that are difficult to assess via traditional quantitative modeling, and has been successfully applied in the neurology arena (109). This tree-based approach may also be of substantial utility in the identification of patient subgroups, which are at particularly high risk of mortality, and thus appropriate candidates for an RCT (see *Aim 3* below).

Aim 3 is to characterize a cohort of patients who would be candidates eligible for a RCT of therapeutic hypothermia following pediatric CA. Along with the study investigators, the PECARN CDMCC, the *Data Analysis and Management Subcommittee (DAMS)* of PECARN, and the *Safety and Regulatory Affairs Subcommittee* (SRAS), will have an integral role of defining the suitable entry and exclusion criteria for a future RCT of hypothermia following pediatric CA. Patients identified as having high risk of mortality and/or severe neurologic injury will represent the candidate population to be identified by these pilot data. The CART approach outlined above may be helpful in finding combinations of factors associated with high, but not uniform mortality. It is conceivable that a simple criterion, such as the requirement of two or more doses of epinephrine for ROSC, would identify a high mortality and severe neurologic injury population for the future RCT of interest. Patients characterized with severe hemodynamic instability and determined to have a very low likelihood of survival to 24 hours needed for a course of therapeutic hypothermia may be a future exclusion. Also, patients transferred to a PECARN clinical center several hours (e.g. > 360 minutes) after a CA event may be excluded since an interval of time in which hypothermia could be effective may be exceeded. If patient groups can be characterized as having very low mortality and/or neurologic injury risk after CA, such as may occur with very brief durations of CPR (e.g. <1 minute), then these groups might be excluded to avoid the ethical issue (risk versus benefit ratio) of exposure to a potentially detrimental experimental therapy (hypothermia). Patients with cold-water drowning and body temperature measurement less than 32º C will be excluded. The *Safety and Regulatory Affairs Subcommittee* of PECARN will review the final entry and exclusion criteria to ensure these criteria for appropriateness in terms of ethical principles and regulatory laws (institutional, local, state, and federal government of each center). If needed, an expert external ethics advisory panel will be convened to give their recommendations related to inclusion and exclusion criteria (see **d.7** under ***Special ethical issues planning***).

Aim 4 is to estimate the sample size required for a future hypothermia following pediatric cardiac arrest RCT. A key component of this application is the acquisition of pilot data for planning of a future RCT. Currently, sample size estimates for a RCT of hypothermia following CA in pediatrics can only be crudely approximated using published data from centers that would not be reliably generalizable to a future multicenter RCT study population. A crude sample size estimate based on a 15% hospital survival after pediatric CA can be performed based on a report from Schindler (2). Assuming a 15% (approximated average absolute risk difference observed in adult RCTs) increase in survival with hypothermia, power (1-beta) of 0.8 and alpha=0.05 (two-sided), then 133 patients would be required in each group (266 total) for a RCT to investigate survival outcome. Such a sample size strongly indicates multicenter participation in a RCT will be required. Much more reliable sample size estimates, using current information obtained from PECARN centers where a future RCT would be conducted, will be possible after pilot data are collected and analyzed. After the appropriate study entry and exclusion rules are developed by PECARN subcommittees and investigators, estimates of a future control group's actual outcome risks for survival and neurologic outcome will be available. This control group may exhibit a lower risk of death than previous literature reports would suggest, because a proportion of cases, who would not survive the 24 hours needed for a course of therapeutic hypothermia, will very likely be excluded. Because neurologic outcomes of pediatric survivors of CA are so poorly described in the literature at this time (19), sample size estimates for a RCT are highly problematic for these outcomes and require PECARN pilot data. When actual PECARN cohort pilot data for feasibility is available, then this value will be substituted for the control hospital discharge proportion, and the mean absolute risk difference

observed in the adult CA hypothermia studies will be substituted. Using similar methods, sample size for neurologic outcome will be estimated. Sample size estimates will also permit calculation of the duration of patient enrollment for a hypothermia RCT using PECARN sites. If the duration of patient enrollment is expected to exceed three years, then additional clinical sites outside of PECARN will be considered, based on recommendations from the CDMCC, *Data Analysis and Management Subcommittee, the PECARN Steering Committee* and future funding agencies. It should be noted that the addition of a fifth and sixth node to PECARN is anticipated in the future.

Data Management

Data management activities and statistical analytical support will be coordinated through Central Data Management and Coordinating Center (CDMCC) at the University of Utah in Salt Lake City, Utah. The CDMCC will also prepare summary reports of the data so that progress of the study can be monitored.

The CDMCC has substantial experience with research data transmission, security and encryption. Data will be entered onto a paper case report form (CRF) and then entered into an electronic data system. Electronically-entered data will be entered by trained site personnel and transmitted to the CDMCC via an encrypted secure point-to-point connection provided by VPN (Virtual Private Network), SSL (Secured Socket Layer) or equivalent technology. If secure network technology is unable to be created with clinical sites, data will be entered electronically at the site into a local database, and that database will then be encrypted prior to transmission to the CDMCC via a secure delivery service with full package tracking and signature delivery. In addition to electronic data entry at the clinical site, copies of the CRF will be transmitted to the CDMCC via a secure delivery service with full package tracking and signature delivery, and the CDMCC will enter those data into the electronic system. Secure locked storage of paper forms will be implemented with either approach, and careful attention will be paid to minimizing (and, if possible, eliminating) transmission of protected health information from the HEDA.

Site research assistants will perform double entry on all case report forms to insure accuracy. The online data entry screens will contain range and logic checks to minimize data entry errors. Site research assistants will also send a random 10% of identifier-stripped case report forms to the CDMCC as described in the previous paragraph, via a secure overnight delivery service with full package tracking and signature delivery, where data entry will be repeated to further insure data accuracy. The Data Manager will monitor data accuracy, contact sites with repeated data entry errors, and identify ways to resolve these errors.

The data security, back up, and access are stored on servers at the CDMCC that are located behind a firewall. All network traffic is monitored for intrusion attempts. Security scans are periodically run against the servers. Datasets are stored in SQL Server and security is provided via user authentication and password protection. Full data backups are performed weekly, and incremental backups nightly, with at least one recent full backup stored off site. (see "Resource" page for further information about the CDMCC).

Study Monitoring

The CDMCC will monitor all clinical sites of this study. There is no need for a DSMB or medical monitoring for this observational planning grant study. The CDMCC will provide good clinical practices training to appropriate site personnel, and confirm that appropriate site personnel have completed human subjects training. There will be interim site visits to assess site compliance with the requirements for the PECARN clinical and observational study protocols being conducted. The CDMCC will standardize training for study site staff for the initiation of all PECARN protocols as well as the development of a Manual of Operations for each clinical and non-clinical protocol. It will delineate specific instructions and requirements for the appropriate implementation and monitoring of each clinical trial and/or observational study by site personnel, and if necessary to ensure appropriate training, provide group meetings for site personnel. The CDMCC will monitor and report monthly, the progress of clinical trials and observational studies, and develop criteria and procedures for the evaluation of site performance, including correcting study site deficiencies and/or eliminating sites.

Confidentiality

All data collected during the study will be treated as confidential medical information by all involved staff at the clinical center, the regional node center, and the CDMCC. All research staff and personnel must maintain patient confidentiality, and all staff at the CDMCC signs specific confidentiality agreements as a condition of employment at the University of Utah.

The CDMCC has substantial experience with research data transmission, security and encryption. The CDMCC at the University of Utah will provide data security of all electronically submitted and stored information for this study.

. At each clinical center, the clinical center investigator will store in a secure locked file cabinet the data forms in which patient identifiers have been removed. In another separate locked file cabinet, patient identifier information with the study number of the data form will be stored.

At the CDMCC data forms will be protected in the same manner as medical records. Such data forms will be maintained in locked file cabinets in locked offices, and will only be accessible by authorized staff.

Records will be maintained for six years in compliance with HIPAA regulations at each center.

Description of Potential Risks and (or) Adverse Effects

This is not an interventional study. There are no risks for patients in this observational planning grant study. Only the medical records of patients with a history of cardiac arrest will be reviewed and abstracted for information which may be helpful in determining the feasibility of a future clinical trial.

Description of Potential Benefits

There are no direct benefits for study participants. This clinical trials planning grant will determine the feasibility of a future interventional trial of hypothermia for cardiac arrest in a pediatric population. The clinical trials would answer the question of whether hypothermia should be given to pediatric patients after cardiac arrest.

Costs to Subjects

None

Study Finances

1). Funding Source

NIH/NICHD

2). Conflict of interest

None

Contractual Agreements

Fifteen (15) clinical centers with identified investigators will provide data from the medical records of pediatric patients with a history of cardiac arrest. Start up funds ($2500) and $75 per record completed will be paid by the University of Michigan per approved NIH funding grant.

The protocol originated at the University of Michigan.

References

1. Sirbaugh PE, Pepe PE, Shook JE, Kimball KT, Godman MJ, Ward MA, Mann DM. A prospective, population-based study of the demographics, epidemiology, management, and outcome of out-of-hospital pediatric cardiopulmonary arrest. Ann Emerg Med 33:174-184, 1999

2. Schindler MB, Bohn DB, Cox PN, McCrindle BW, Jarvis A, Edmonds J, Barker G. Outcome of out-of-hospital cardiac or respiratory arrest in children. N Engl J Med 335:1473-1479, 1996

16. Gillis J, Dickson D, Rieder M, Steward D, Edmonds J. Results of inpatient pediatric resuscitation. Crit Care Med 14:469-471, 1986

17. Torres A, Pichert CB, Firestone J, Walker WM, Fiser DH. Long-term functional outcome of inpatient pediatric cardiopulmonary resuscitation. Pediatr Emerg Care 13:369-373, 1997

18. Reis AG, Nadkarni V, Perondi MB, Grisi S, Berg RA. A prospective investigation into the epidemiology of in-hospital pediatric cardiopulmonary resuscitation using the internation Utstein reporting style. Pediatrics 109:200-209, 2002

19. Young KD, Seidel JS. Pediatric cardiopulmonary resuscitation: a collective review. Ann Emer Med 33:195-205, 1999

21. Thoresen M. Cooling the newborn after asphyxia - physiological and experimental background and its clinical use. Semin Neonatol 5:61-73, 2000

22. Colbourne F, Corbett D, Zhao Z, Yang J, Buchan AM. Prolonged but delayed postischemic hypothermia: a long-term outcome study in the rat middle cerebral artery occlusion model. J Cereb Blood Flow and Metab 20:1702-1708, 2000

23. Hicks SD, DeFranco DB, Callaway CW. Hypothermia during reperfusion after asphyxial cardiac arrest improves functional recovery and selectively alters stress-induced protein expression. J Cereb Blood Flow and Metab 20:520-530, 2000

24. Gunn AJ, Gunn TR, de Haan HH, Williams CE, Gluckman PD. Dramatic neuronal rescue with prolonged selective head cooling after ischemia in fetal lambs. J Clin Invest 99: 248-256, 1997

31. The Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 346:549-556, 2002

32. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 346: 557-563, 2002

37. Safar PJ, Kochanek PM. Therapeutic hypothermia after cardiac arrest. Editorial. N Engl J Med 346: 612-613, 2002

38. Bohn DJ, Biggar WD, Smith CR, Conn AW, Barker GA. Influence of hypothermia, barbiturate therapy, and intracranial pressure monitoring on morbidity and mortality after near-drowning. Crit Care Med 14:529-534, 1986

67. Zaritsky A, Nadkarni V, Hazinski MF, Foltin G, Quan L, Wright J, Fiser D, Zideman D, O'Malley P, Chameides L. Recommended guidelines for uniform reporting of pediatric advanced life support: the pediatric Utstein style. American Academy of Pediatrics, American Heart Association and the European Resuscitation Council. Ann Emerg Med 26:487-503, 1995

108. Breiman L, Friedman JH, Olshen RA, and Stone CJ. "*Classification and Regression Trees*". Belmont, CA: Wadsworth International Group, 1984

109. Temkin NR, Holubkov R, Machamer JE, Winn HR, Dikmen SS. Classification and regression trees (CART) for prediction of function at 1 year following head trauma. J Neurosurg 82:764-771, 1995

16. Appendices

1). Provide copies of all questionnaires or survey instruments to be used in the study.

None

2). Provide copies of all Case Report Forms used in the study.

Data collection tool

3). Provide copies of lab values, flow charts, etc.

None

4). Miscellaneous materials

Principal Investigator's University of Michigan Institutional Review Board – approval documentation (completed form and approval documentation