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Review Article

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The Pediatric Emergency Care Applied Research Network: a history of multicenter collaboration in the United States

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In this article, we review the history and progress of a large multicenter research network pertaining to emergency medical services for children. We describe the history, organization, infrastructure, and research agenda of the Pediatric Emergency Care Applied Research Network (PECARN), and highlight some of the important accomplishments since its inception. We also describe the network's strategy to grow its research portfolio, train new investigators, and study how to translate new evidence into practice. This strategy ensures not only the sustainability of the network in the future, but the growth of research in emergency medical services for children in general.

Keywords Pediatric Emergency Care Applied Research Network; Research infrastructure; Multicenter collaboration

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Capsule Summary

What is already known

The Pediatric Emergency Care Applied Research Network (PECARN) has a long-standing record of successful multicenter research in emergency medical services for children in the United States. Since its inception in 2001, numerous research studies regarding the care of acutely ill and injured children have been performed and published.

What is new in the current study

We summarize the activities and accomplishments of the network since the last summary of its activities was published in 2006. During this time, PECARN has continued this record of productivity and innovation with increased emphasis on randomized controlled trials, use of the electronic health record, and translation of research into practice. PECARN also has increased its focus on sustainability through development and mentoring of young investigators, and broadened the applicability of its work through additional international collaboration.

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INTRODUCTION

The Pediatric Emergency Care Applied Research Network (PECARN) is a research collaboration of pediatric emergency departments (EDs) across the United States focusing on the care of acutely ill and injured children. Recognizing the need to generate definitive evidence to inform the treatment of acutely ill and injured children, PECARN was established in 2001.[1] Led by experienced investigators with expertise in pediatric emergency care, and with the support and oversight of the Emergency Medical Services for Children (EMSC) program of the Health Resources and Services Administration (HRSA), PECARN is the first research network of pediatric EDs funded by the Federal Government of the USA. The network is committed to conducting high-quality research in all phases of emergency care in children, including prevention, prehospital and ED treatment, and rehabilitation. PECARN leverages a combined population of more than one million children treated annually in 18 EDs throughout the USA to overcome many of the barriers inherent to pediatric emergency care research.

BACKGROUND

Previously, the ability to generate scientific evidence regarding the optimal care of acutely ill and injured children in EDs was limited by several barriers.[1,2] The rarity of adverse outcomes in many pediatric conditions makes it difficult, if not impossible, to enroll a sufficiently large patient population at a single center to achieve the necessary statistical power to answer pressing clinical questions definitively. Additionally, it can be difficult to obtain high quality data when enrolling patients into research studies in busy EDs, as ED clinicians have multiple competing demands on their time. Obtaining informed consent from the patient's family may be difficult under the stressful conditions of the ED, or even impossible if the patient's guardian is absent or also injured. The results of research findings performed in tertiary care (research) centers may be difficult to generalize to community hospitals, where most acutely ill and injured children are cared for. Finally, translating research results into the daily practice of clinicians working in acute care settings can be challenging. The infrastructure of PECARN supports collaboration on large multicenter studies and the sharing of experiences and best practices with com-

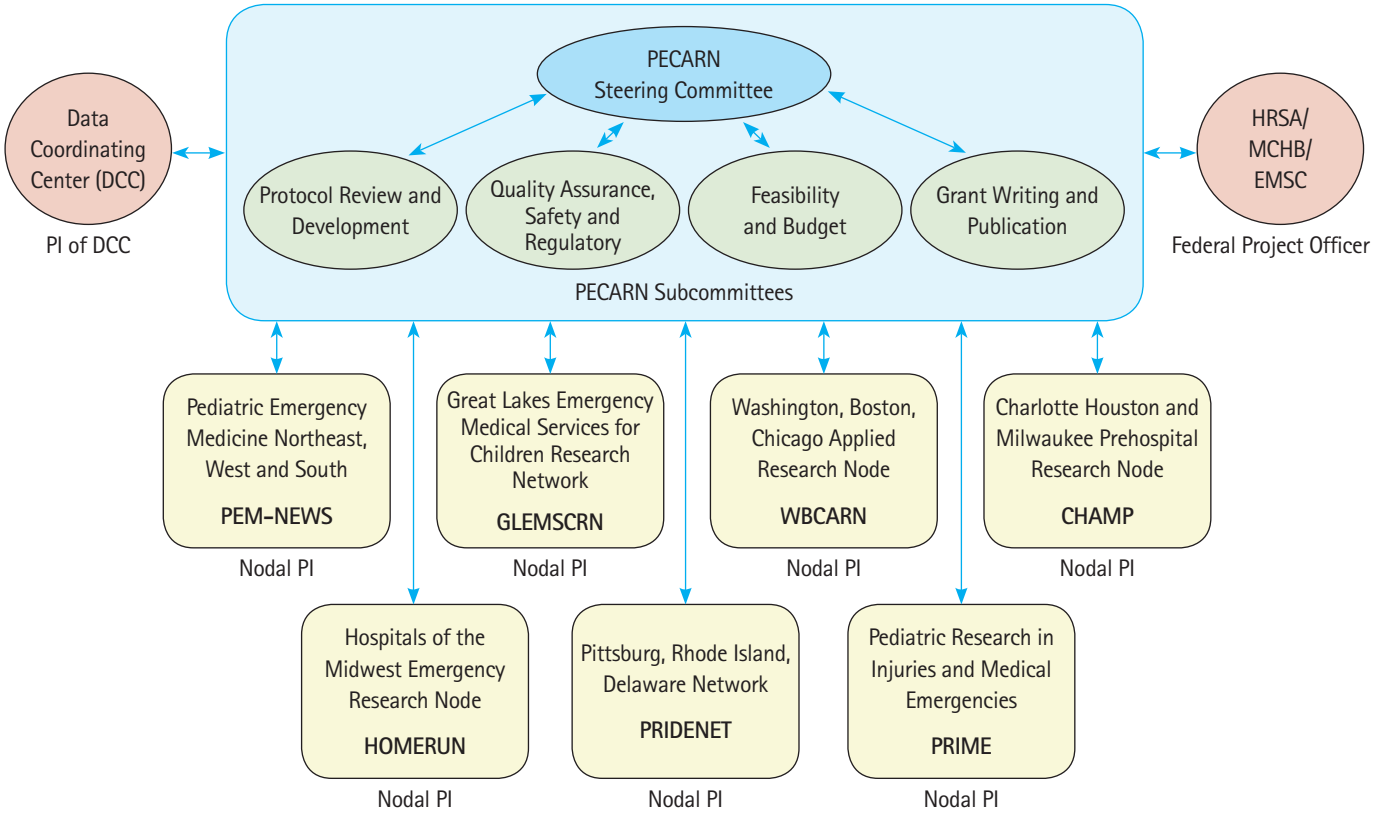

Fig. 1. Pediatric Emergency Care Applied Research Network (PECARN) network structure. PI, principal investigator; HRSA, Health Resources and Services Administration; MCHB, Maternal Child Health Bureau; EMSC, Emergency Medical Services for Children.

Fig. 2. Locations of current Pediatric Emergency Care Applied Research Network (PECARN) sites.

munities of physicians, thus overcoming many of the barriers to performing pediatric emergency care research and then translating it into practice.

ORGANIZATION AND INFRASTRUCTURE

PECARN is composed of seven research node centers (RNCs), located throughout the United States. Fig. 1 depicts the PECARN structure, and Fig. 2 illustrates the locations of current PECARN sites. Funding from the United States Federal Government is directed to each RNC through the EMSC program, established under HRSA, Maternal Child Health Bureau (MCHB). An independent data coordinating center (DCC) is also funded by EMSC and works collaboratively with the RNCs. The principal investigators of the RNCs (the nodal principal investigator [PI]), the PI of the DCC, and a representative from the federal funding agency form PECARN's executive committee.

Six of the RNCs each coordinate and provide oversight of three academic children's EDs, known as Hospital Emergency Department Affiliates (HEDAs), for a total of 18 ED sites within the network. The seventh RNC was recently established and coordinates three emergency medical services agencies, instead of EDs, in order to focus on pre-hospital research. Each HEDA agrees formally to participate in any PECARN research study appropriate for its facility.

Members of the PECARN steering committee loosely include investigators and research coordinators from each HEDA, as well as DCC staff and research administrators from the RNCs. Only one representative from each HEDA and one representative from the DCC, however, comprise the PECARN steering committee *voting membership*, which acts as the primary governing body and arbitrator of the network. All nodal PIs are voting members of the steering committee, as is the PI of the DCC. One nodal PI also serves as the chair of the PECARN steering committee, a position that rotates every three years in order to share opportunities for leadership and to ensure equity among the RNCs. Early in the development of the network, the PECARN steering committee established bylaws, which describe its structure and membership, its policies and procedures, and its code of ethics and conduct.

PECARN's subcommittees were also established early in the network's development to advise the steering committee and perform specific tasks for the network. These subcommittees have evolved over time, to serve the ever-changing needs of the network. Currently, the four subcommittees are the:

- Protocol Review and Development Subcommittee, which reviews specific research concepts and protocols and makes recommendations to the investigators, with the goal of improving the science of each proposal.
- Feasibility and Budget Subcommittee, which reviews research concepts and protocols specifically to ensure that the studies can practicably be performed in PECARN, that budgets are sufficient to conduct the research and that funding is allocated appropriately.
- Grant Writing and Publications Subcommittee, which collaborates with investigators to help create study authorship plans, and reviews and critiques documents (grants, abstracts, presentations, manuscripts) prior to submission or presentation.
- Quality Assurance and Safety Subcommittee, which reviews research concepts and protocols to ensure compliance with standards for protection of human subjects, and monitors ongoing research to ensure rigorous adherence to patient safety and study protocols.

The funding provided by HRSA/MCHB/EMSC supports PECARN's infrastructure as described above and also supports two in-person meetings of the steering committee and one in-person meeting of the PECARN executive committee per year. The steering committee conducts approximately three additional meetings per year via teleconference. Other ad hoc meetings and teleconferences are held throughout the year, typically to address short turnaround requests for grant proposals from federal funding agencies. Investigators and research coordinators also participate in research study-specific meetings and teleconferences on a routine or as-needed basis.

Because funding for PECARN supports only its infrastructure costs, investigators who lead research studies that are approved/endorsed by the steering committee must compete for and be awarded extramural research grant funding in order to perform multicenter studies through the network. The typical funding sour-

ces for PECARN research include the National Institutes of Health, the Centers for Disease Control and Prevention, and the Agency for Healthcare Research and Quality, although the changing funding environment encourages the network to look creatively for diverse funding sources.

Extramural research grant funding augments the research infrastructure at participating PECARN sites and also funds study-related activities at the PECARN DCC. The PECARN DCC employs project managers and data managers, as well as both doctorate and masters-level statisticians in order to provide support and leadership of study design, coordination and statistical analysis for PECARN projects. The PECARN DCC acts as a central repository of network data and maintains highly sophisticated systems for secure transfer of electronic data. The DCC also performs a variety of quality assurance and training activities on behalf of the network and its research studies.

RESEARCH AGENDA

PECARN's research priorities are guided by the network's published research agenda, which the steering committee developed in 2002 using the Nominal Group Process and Hanlon Process of Prioritization.[3] Using this well-established and validated qualitative process, steering committee members participated in facilitated discussions during which they identified high-priority research topics in pediatric emergency care and ranked the topics in order of perceived importance. The committee then refined the list of research priorities by taking into account each condition's prevalence, its seriousness (i.e., morbidity and/or mortality of the condition or the disruption it causes to society), and the practicality and feasibility of studying the condition in PECARN (including the potential for external funding). The resulting research priorities list (Table 1) serves to maintain our focus on topics of great importance to emergency medical services for children. However, PECARN will diverge from the published agenda at times, for specific reasons. For example, we will study new pressing health issues as they arise. Our success as a network is largely dependent on the desire and drive of individual investigators to have a research concept approved by the PECARN steering committee and ultimately his/her ability to secure funding to conduct the project, whether or not the topic of study is on the research priority list.

Table 1. Pediatric Emergency Care Applied Research Network research priorities

1. Respiratory illness/asthma
2. Prediction rules for high stakes/low likelihood diseases
3. Medication error reduction
4. Injury prevention
5. Urgency and acuity scaling
6. Race, ethnic, class disparities in health
7. Mental health
8. Treatment of infectious diseases
9. Best practices in patient care
10. Pain & anxiety management
11. Education/training outcomes
12. Development of treatment algorithms
13. Improvement in health outcomes for cardiac arrest
14. Practice protocols
15. Seizure management
16. Cervical spine immobilization
Special mention: prehospital research

SCIENTIFIC REVIEW PROCESS FOR CONCEPTS/PROTOCOLS

One of the strengths of PECARN is the quality and scope of the research studies conducted. This strength may be credited in part to a robust and coordinated scientific review process where subcommittees work on behalf of investigators and the steering committee to refine and improve research studies during their development.

This process begins with a brief preliminary research concept, which is developed in conjunction with one of the PECARN nodes. This concept may come from a member of PECARN or from an investigator outside of PECARN; both are given equal consideration and priority. The sponsoring node conducts an initial and comprehensive concept review and discussion with member investigators and may also invite specific content experts to participate as appropriate. Typically, modifications to the research concept occur during this step of the process. If the research concept is approved by the node and subsequently approved by representatives of EMSC, the investigator then presents the concept to the entire steering committee at either an in-person meeting or teleconference. After the presentation, the investigator fields questions from the steering committee. The steering committee will hold a closed discussion (without the investigator present), followed by a confidential vote to endorse or reject the research concept. If the concept is endorsed by the steering committee, the investigator will use the steering committee's formal feedback to improve and refine the research question and expand it into a full research protocol. This expanded protocol is the precursor to the grant application that the investigator will eventually submit for external funding.

The investigator typically develops the concept into a protocol in collaboration with the PECARN DCC, often in-person during a pre-arranged working session. The PECARN DCC will engage its

PI, biostatisticians and data managers to provide input into protocol development to the study PI, with consideration given to feasibility and statistical issues. After the initial protocol is developed, the PECARN subcommittees review the protocol and provide additional feedback to the investigator. After subcommittee feedback is incorporated by the study PI, the steering committee votes on the final protocol version. By reviewing and approving every research study conducted within the network, the PECARN steering committee ensures that each study meets established network research priorities and contains high-quality science, and is ultimately feasible for conduct in the network. This process also ensures that PECARN members are invested in a research study's successful completion. Ultimately, this rigorous review process increases an investigator's likelihood of obtaining external funding and of performing successful studies in the network. The substantial track record of high-quality research in the network is in large part a testament to the comprehensive, collaborative and diligent process of network study development, as well as to the drive and determination of individual investigators.

EVOLUTION OF PECARN RESEARCH AND DESCRIPTION OF RESEARCH STUDIES

As PECARN evolves, the research studies we perform as a network also grow and evolve. PECARN's initial research studies were funded by core infrastructure funding only and descriptive in nature. Subsequently, we received external funding for and performed several large observational cohort studies. As the network continues to mature, randomized clinical trials and studies of knowledge translation are becoming more common.

One of the earliest unfunded, but nevertheless important and ongoing research studies is the PECARN Core Data Project (PCDP). In this observational, epidemiological study, specific data elements from all ED visits across all participating PECARN sites are uploaded electronically to a central repository annually.[4] This PCDP database was used for some early research studies, including two studies comparing the availability and accuracy of administrative versus clinical data elements for pediatric emergency visits.[5,6] PCDP data were also used to demonstrate differences in ancillary testing (chest radiography and laboratory studies) associated with patient, provider, and hospital characteristics among children with asthma.[7] Additionally, PCDP data were used to develop a consensus-based and clinically sensible diagnosis grouping system. The diagnosis grouping system includes 21 groups and 77 subgroups, which account for the vast majority of diagnoses among pediatric ED visits.[8] Study investigators also developed a diagnosis-based severity classification system associated with actual measures of ED resource use.[9] As PECARN research studies are now more frequently interventional trials, PCDP data continue to be essential in providing background data, generating hypotheses, and determining feasibility of conducting prospective studies, including the likelihood of obtaining adequate sample sizes in children with specific medical and traumatic conditions.

PECARN investigators also have performed large, observational cohort studies to develop clinical prediction rules for pediatric patients who have experienced blunt trauma. Using both prospective cohort and retrospective case-control methodology, investigators attempted to identify pediatric patients who were at low risk for severe intracranial, intra-abdominal, and cervical spine injuries after blunt trauma and in whom evaluation may be safely limited, and radiation from radiography avoided.[10-12]

The largest of these studies was a prospective cohort study of 42,412 children with minor blunt head trauma. Based on data from these patients, two clinical prediction rules were derived and validated, one for patients <2 years and another for those 2 years until their 18th birthday. The rules reliably identify patients at very low risk of clinically important traumatic brain injuries.[10] Sub-analyses of data from this study demonstrated the likelihood of clinically important traumatic brain injury associated with presence of several isolated individual risk factors.[13-16] All of these studies and sub-studies provide the evidence to help clinicians limit computed tomography (CT) use to only those children at non-negligible risk of clinically-important traumatic brain injuries after trauma.

A similarly designed, cohort study of 12,044 children with blunt torso trauma resulted in a prediction rule using patient history and physical examination findings to identify those at very low risk for intra-abdominal injuries requiring acute intervention.[11] Additionally, PECARN performed a large retrospective case-control study of 540 children with cervical spine injuries from blunt trauma, comparing these patients to 2,774 controls. The investigators identified eight factors associated with cervical spine injuries.[12] PECARN investigators are planning to pursue further study of cervical spine injuries in a prospective fashion with the goal of limiting the use of cervical immobilization and radiation in children with blunt trauma.

Another focus area of PECARN research is improving the *safety* of care delivered to children in the ED. In this area, PECARN investigators performed a research study describing ED characteristics related to and staff perceptions of safety,[17] as well as a study describing the frequency and characteristics of medication errors in pediatric EDs.[18] Additionally, PECARN investigators developed an infrastructure for reporting and analyzing safety events occurring in EDs throughout the network.[19]

Toward the goals of developing standards and methods for measuring the *quality* of care delivered in pediatric EDs, one group of investigators identified and categorized performance measures relevant to pediatric emergency care.[20] Another group is completing analysis in a study to assess the consistency, reliability, and validity of a specific assessment tool to evaluate the quality of care provided at pediatric ED visits (data analysis ongoing). That study is also attempting to identify hospital, ED, physician, and patient level factors that influence the quality of care delivered to ill and injured children in the ED. Yet another ongoing study pertaining to the quality of care delivered in the pediatric ED uses the electronic health record, as well as Natural Language Processing, to compare severity-adjusted quality measures of care across different institutions. In that study, investigators are using data from a registry of electronic medical records at six hospitals within the network.[21] This novel "PECARN Registry" is using state-of-the-art information technology with the goal of providing feedback to clinicians regarding their practice patterns and whether they are achieving accepted quality metrics in the care of acutely ill and injured children.

As PECARN has matured, it has also demonstrated the ability to perform large, randomized clinical trials which seek to provide definitive evidence regarding treatment of acutely ill and injured children. PECARN's first randomized controlled trial was a double-blind comparison of oral dexamethasone versus placebo in infants with moderate-to-severe bronchiolitis. This study was conducted at 20 PECARN sites and demonstrated no difference between the groups in admission rates or respiratory status after four hours of observation.[22] This high-profile study has been widely referenced and hopefully has decreased the inappropriate use of corticosteroids in this population.

In another large, double-blind, randomized PECARN trial, investigators demonstrated no improvement in the safety or efficacy of intravenous lorazepam over diazepam in the treatment of pediatric status epilepticus.[23] This study was particularly significant because it represented the first pediatric study in the USA that was granted Federal Exception from Informed Consent (EFIC) for emergency research. Performing a trial under EFIC required extensive planning and preparation as each participating hospital engaged in a mandatory period of "community consultation" where the surrounding public was informed that children presenting to the hospital in status epilepticus may be enrolled and randomized before the guardians consented for their children to participate in the study. Clinical trials performed under EFIC are likely to become more frequent in PECARN's future, as the network tries to address more complicated clinical issues under emergent situations.

With its experience and large patient populations, PECARN is poised to perform trials to definitively answer even more complicated and challenging medical and traumatic controversies. Several such trials are ongoing currently. A trial of therapeutic hypothermia after pediatric cardiac arrest seeks to determine if this practice, previously studied in adults, should be applied to children after cardiopulmonary arrest.[24] This study includes children who have experienced cardiac arrest, either out-of-hospital or in the in-hospital setting. The in-hospital arrest arm of this trial is nearing completion; the out-of-hospital arrest arm has already completed enrollment. Another ongoing large, complex study of acutely ill children is a randomized trial of four different intravenous fluid regimens (using a factorial study design) in children with diabetic ketoacidosis. Different rates of administration and sodium content of intravenous fluid are being compared to determine any differences in the development of cerebral injury between treatment groups.[25]

PECARN trials also seek to study new therapeutic options for emergent conditions in children. A placebo-controlled trial of probiotics to hasten recovery from acute gastroenteritis began patient enrollment in 2014. With the large burden of diarrheal disease worldwide, this study has the potential for global impact, including in developing nations. Additionally, a randomized, placebo-controlled study of intravenous magnesium for the treatment of acute pain crisis in children with sickle cell disease concluded patient enrollment very recently.[26]

Knowledge translation is a logical next step for many PECARN studies, as the network has generated much evidence in the past decade, and now strives to improve the delivery of evidence-based care in EDs throughout the USA and around the world. One recent study investigated whether embedding the PECARN traumatic brain injury prediction rule[10] into the electronic health record would decrease the frequency of unnecessary CT imaging in patients at very low risk for clinically important traumatic brain injuries.[27] Enrollment in this study is complete and data analysis is under way. The results of this project are one step in helping PECARN achieve its goal of developing robust systems of studying the translation of evidence into practice. This is a particularly important goal as the network nears completion of several definitive trials for the care of acutely ill and injured children.

PECARN is also working on research studies evaluating cutting-edge technologies. One PECARN study is assessing new diagnostic techniques to evaluate febrile infants younger than 60 days of age. This study analyzes ribonucleic acid (RNA) expression of blood leukocytes (transcriptional "biosignatures") in these young infants' host-responses to bacterial infections. Initial analyses suggest that these new microarray techniques will allow discrimination between febrile infants with and without culture proven

bacterial infections with excellent accuracy.[28,29] With refinement, these techniques may eventually challenge the reference standard of bacterial culture for diagnosing serious bacterial infections in young febrile infants.

Current and future PECARN studies harness the screening potential of the ED in the study of pediatric and adolescent health issues. An ongoing study seeks to determine if a brief, two-question screen can accurately detect alcohol use and alcohol-related problems in adolescents. Additionally, an upcoming study of adolescents in the ED will attempt to prospectively determine an optimal suicide risk screening strategy and an algorithm to triage these adolescents for immediate care or follow-up based on their risk stratification.

In recent years, PECARN has also engaged in new international collaborations, contributing as a member of Pediatric Emergency Research Networks (PERN)[30,31] PERN's initial research study was published in 2013 and identified clinical and patient history factors for severe outcomes in children with H1N1 influenza infections.[32] Ongoing studies with PERN include a prospective, multicenter study to determine the epidemiology and management differences of acute poisonings in children in eight different regions of the world[33] and a study of the association of pharmacotherapy and outcomes in infants presenting to the ED with acute bronchiolitis.

CHALLENGES AND BENEFITS OF PECARN RESEARCH

Although PECARN has overcome many of the barriers to performing ED network research and performed many successful research studies, some challenges to the network and its investigators persist. The substantial size of multicenter studies can make them unwieldy and difficult to fund and perform. In order to ensure uniform implementation of protocols and collection of high quality data, study investigators must invest in extensive initial and continuing training of study personnel. Additionally, investigators must develop an explicit protocol and manual of operations describing standardized study procedures for all sites, and must monitor regularly for correct implementation. Initiating a study at multiple sites is time consuming and requires an initial face-to-face meeting of many investigators, as well as ongoing meetings either electronically or in person. Secure and timely transmission of data from study sites to the lead site and/or the data-coordinating center must be established. In PECARN, all studies must be reviewed and approved by the local Institutional Review Board (IRB) or ethics committee at each study site. IRBs have varying standards, which often result in multiple modifications to a study protocol before its approval across all participating sites. For this and other reasons, development and implementation of a centralized IRB is a long-term goal of PECARN.[34] Once a study is underway, ongoing monitoring of study data, protocol implementation processes, and regulatory documentation are performed either remotely or by trained personnel who travel to individual sites. We are currently evaluating a process of virtual monitoring of study sites remotely via access to the electronic health record in order to enhance efficiencies, and decrease costs.

A notable challenge which PECARN faces is obtaining adequate funding for studies. Because network multicenter studies are frequently expensive compared to single institution studies, the amount of funding required to perform them frequently exceeds the standard limit of many funding agencies. In an era when only a small percentage of federal grant applications for clinical research in the USA are successfully funded, the necessity of exceeding established funding caps can further challenge the ability of investigators to obtain funding. Moving forward, large networks like PECARN must be creative and diverse in seeking funding for research.

Even with these challenges, multicenter research within PECARN has many benefits for investigators. The network provides a clinical laboratory in which large-scale studies can be performed. Often, small, pilot research studies suggest a benefit of a new practice or medication, and PECARN then provides the opportunity to test the study results by conducting large-scale, definitive, and potentially practice-changing research. Performing a study within a network with an established reputation for performing and publishing high-quality studies may increase an investigator's chance of successfully obtaining grant funding, offsetting some of the funding challenges of research conducted outside of such a network. PECARN investigators also play a role in shaping the future of pediatric emergency medicine (PEM) by providing crucial leadership and mentorship to the next generation of PEM investigators.

Young investigators involved in PECARN studies directly benefit from senior mentorship and exposure to the network's research process. Serving as a co-investigator or as a site PI for a PECARN study provides an introduction to the research process as well as insight into the challenges and benefits of multicenter research. Involvement as a site PI on a multicenter study also offers authorship opportunities, including opportunities to be a supporting author on the study's main manuscript or the primary author on a planned secondary analysis.

In recent years, PECARN has made concentrated efforts to focus on mentorship and development of future investigators. These efforts include inviting junior investigators to observe the process at network steering committee meetings. This allows them to view and participate in study proposal development and provides them

access to the mentorship and guidance of experienced investigators. Specific training sessions are held annually during which junior investigators present their research concepts for constructive review by senior PECARN investigators, many of whom are content experts as well as seasoned researchers who have conducted one or more large multicenter studies. If a junior investigator's research concept is accepted for review by the PECARN steering committee, he or she also benefits from the feedback of experienced statisticians and epidemiologists at our independent data coordinating center.

Participation in a research network also provides benefits at an institutional level. Participation in PECARN fosters development and growth of a solid research program at local institutions by helping to instill a culture of research (particularly in multicenter/collaborative research) and by providing specific infrastructure in the form of support for research and study coordinators. Each study-specific grant provides additional funding for each participating institution.

FUTURE DIRECTIONS

PECARN has evolved substantially since its inception in 2001, with progression from retrospective epidemiologic studies to prospective observational studies and then to interventional trials and implementation research. As it moves into the future, PECARN will continue to pursue its mission of performing high-quality and definitive research in the prevention and treatment of acute illnesses and injuries in children. It is critical that evidence generated by PECARN research be disseminated, implemented, and incorporated into the care of children in various acute care settings. In partnership with EMSC, PECARN strives to be a leader in PEM in each step of this continuum. Through leadership, mentorship, and development of new and junior investigators, PECARN hopes to ensure the continuation of high-quality PEM research over time. Finally, through increased and broadening collaboration both nationally and internationally, PECARN will continue to generate and widely disseminate new evidence in the care of acutely ill and injured children.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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