Structure and Function of Emergency Care Research Networks: Strengths, Weaknesses, and Challenges

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Abstract

The ability of emergency care research (ECR) to produce meaningful improvements in the outcomes of acutely ill or injured patients depends on the optimal configuration, infrastructure, organization, and support of emergency care research networks (ECRNs). Through the experiences of existing ECRNs, we can learn how to best accomplish this. A meeting was organized in Washington, DC, on May 28, 2008, to discuss the present state and future directions of clinical research networks as they relate to emergency care. Prior to the conference, at the time of online registration, participants responded to a series of preconference questions addressing the relevant issues that would form the basis of the breakout session discussions. During the conference, representatives from a number of existing ECRNs participated in discussions with the attendees and provided a description of their respective networks, infrastructure, and challenges. Breakout sessions provided the opportunity to further discuss the strengths and weaknesses of these networks and patterns of success with respect to their formation, management, funding, best practices, and pitfalls. Discussions centered on identifying characteristics that promote or inhibit successful networks and their interactivity, productivity, and expansion. Here the authors describe the current state of ECRNs and identify the strengths, weaknesses, and potential pitfalls of research networks. The most commonly cited strengths of population- or disease-based research networks identified in the preconference survey were access to larger numbers of patients; involvement of physician experts in the field, contributing to high-level study content; and the collaboration among investigators. The most commonly cited weaknesses were studies with too narrow a focus and restrictive inclusion criteria, a vast organizational structure with a risk of either too much or too little central organization or control, and heterogeneity of institutional policies and procedures among sites. Through the survey and structured discussion process involving multiple stakeholders, the authors have identified strengths and weaknesses that are consistent across a number of existing ECRNs. By leveraging the strengths and addressing the weaknesses, strategies can be adopted to enhance the scientific value and productivity of these networks and give direction to future ECRNs.

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As biomedical discoveries lead to new therapies and diagnostics, a greater need for effective systematic evaluation through clinical studies arises. Clinical research networks can rapidly conduct large high-quality studies that concurrently address multiple research questions.

The Institute of Medicine (IOM) report on the future of emergency care in 2006[1] recognized the need to

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define optimal means of performing networked emergency care research (ECR). Since the outcome of acute disorders is often determined within minutes to hours after onset, intervention in the emergency department (ED), or even in the prehospital setting, may be necessary to provide meaningful benefit. Furthermore, because emergency care providers are usually the first to treat these patients, they are uniquely positioned to implement interventional clinical trials in the acute phase of the disease process.

The clinical research network model consists of a large, interdisciplinary, scalable, multicenter network of sites with a clearly defined multilevel governance structure, access to a diversity of patients in different geographical locations, and the allocation of resources to build a lasting infrastructure for use in multiple clinical trials. This structure allows the study of both low- and high-prevalence disorders in an effective and efficient manner without developing the infrastructure de novo each time. The benefits of such a model are evidenced by long-term, multicenter networks that have been successfully created and are productive, such as the National Institute for Neurological Disorders and Stroke (NINDS) Parkinson's Study Group, the Alzheimer's Disease Cooperative Study, and existing emergency care–based networks, such as the Emergency Infectious Disease Network (EMERGEncy ID NET),[2] the Emergency Medicine Network (EMNet),[3] the Pediatric Emergency Care Applied Research Network (PECARN),[4] the Resuscitation Outcomes Consortium (ROC),[5] and the Neurological Emergencies Treatment Trials network (NETT).[6] This article provides readers with a description of existing emergency care research networks (ECRNs); the strengths, weaknesses, and potential pitfalls of research networks focused on a particular disease or patient population; and how to best utilize research networks to facilitate ECR.

A meeting was organized in Washington, DC, on May 28, 2008, to discuss the present state and future direction of clinical research networks as they relate to emergency care. At the time of preconference online registration, participants responded to a series of questions addressing the relevant issues that would form the basis for the breakout session discussions. During the conference, representatives from a number of existing ECRNs including EMERGEncy ID, EMNet, PECARN, ROC, and NETT participated in discussions with the attendees and provided a description of their respective networks, infrastructure, and challenges. Breakout sessions provided the opportunity to further discuss the strengths and weaknesses of these networks and patterns of success with respect to their formation, management, funding, best practices, and pitfalls. Discussions centered on identifying characteristics that promote or inhibit successful networks and their interactivity, productivity, and expansion. Other topics addressed during the breakout sessions included the specific features that make ECR unique;[7] how cross-disciplinary ECRN could be conducted in the existing Clinical Translational and Science Award (CTSA) program;[8] and how ECRN objectives can be measurable, explicitly defined, and customized for the multiple stakeholders involved.[9]

The answers to the preconference questionnaire were recorded and tabulated into a Microsoft Word (Microsoft Corp., Seattle, WA) document, and the discussion points from the second breakout session are described below.

PRECONFERENCE QUESTIONNAIRE AND BREAKOUT SESSION RESULTS

The most commonly cited strengths of population- or disease-based research networks identified in the preconference survey were access to larger numbers of patients; involvement of physician experts in the field, contributing to high level study content; and the promotion of collaboration and communication among investigators (Table 1). The most commonly cited weaknesses were conducting studies with too narrow a focus with very restrictive inclusion criteria, a vast organizational structure with a risk of either too much or too little central organization or control, and heterogeneity of institutional policies and procedures among sites (Table 2). Our breakout session provided valuable discussions on how to improve ECRNs; these points are summarized in Table 3.

CURRENT STATE OF ECRNS: STRUCTURE AND FUNCTION OF SOME EXISTING NETWORKS

Examples of existing ECRNs (presented chronologically by date established) include EMERGEncy ID, EMNet, PECARN, ROC, and NETT. A summary of each is provided in Table 4.

EMERGEncy ID NET

Background EMERGEncy ID NET[2] is an ED-based network established to conduct surveillance and research of emerging infections in the United States. EMERGEncy ID NET was established in 1995 in response to a Centers for Disease Control and Prevention (CDC) request for a proposal to create new sentinel systems. Experience for creating the network derived from previous ad hoc multicenter ED studies, such as of dog and cat bite infections, participation in industry-supported multicenter clinical trials conducted through the ED, and prior collaboration with CDC investigators.[10]

Structure and Function EMERGEncy ID NET currently consists of 12 geographically diverse, academically affiliated urban EDs with an annual census of approximately 1 million visits. EMERGEncy ID NET is funded through a cooperative agreement grant from the CDC and is now on its second 5-year renewal, having been in existence for 14 years. The network size and diversity is limited by funding, which varies between approximately $400,000 and $500,000 annually, with sufficient funding to provide support to maintain the quality of site data collection, which must be achieved in busy EDs with patient care priorities, and to effectively coordinate a maximal organizational size. In general, participating sites have a pre-established research infrastructure. Principal investigators (PIs) and a project director at Olive View–UCLA Medical Center

Table 1
Responses from Meeting Participants to the Preconference Survey Question ''What Are the Strengths of Research Networks That Focus on a Particular Disease or Patient Population?'' (n = 84)

Strengths	%
Large number of patients to study (good for low prevalence diseases).	22
Participation of physicians with significant expertise in a particular disease along with the involvement of leaders in the field that contribute to high level study content.	11
It promotes collaboration, communication, and synergy among researchers.	10
There is a diversity of patients to study.	8
Development of focused, well-defined research questions.	6
There is geographic diversity of sites and patients.	6
The participation of experienced sites with existing research infrastructure that have established protocols for recruitment and outcome assessment. With each study the infrastructure of the network improves and becomes more efficient.	5
There are greater funding opportunities.	5
There is improved external validity/ greater generalizability of results.	5
Timely and efficient research.	5
Experienced researchers conducting studies may be more effective.	4
The sharing of experiences among network researchers to resolve problems inherent to clinical research, e.g., ethical and institutional obstacles.	4
Data pooling with large amounts of available data to analyze.	3
Proven to work by other such networks, e.g., Alzheimer's and Parkinson's, and shown to improve translation into clinical practice.	2
Opportunity for promoting EM as a specialty as well as leaders in EM research.	2
Economies of scale (cost-effective research).	1
Political support and leverage.	1

Table 2
Responses From Meeting Participants to the Preconference Survey Question ''What Are the Weaknesses and Potential Pitfalls of Research Networks That Focus on a Particular Disease or Patient Population?'' (n = 84)

Weaknesses/pitfalls	%
Studies have a very narrow focus, so trials are limited to a particular disease and others are left out. Also, there may be very restrictive inclusion criteria that reduce generalizability of results.	17
Vast organizational structure; risk of either too much or too little central organization and control.	14
Variation in infrastructure at each site; heterogeneity of institutional policies, and ethics/ IRBs.	10
Selection of study questions and projects may be subject to personal agendas, narrow focus, or funding availability.	8
Variation in practice patterns at different sites may lead to lack of standard treatment procedures and protocol violations. Erratic enrollment patterns make data difficult to interpret.	8
Young or less experienced investigators may be left out, and existence of networks may reduce or limit the funding available to these individuals.	7
Disease-specific vs. complaint-specific: it is more difficult to enroll patients from the ED as they may not have a diagnosis.	7
Sites selected are typically academic tertiary care centers, so findings may not be applicable to community settings (sampling bias).	6
May limit opportunities for investigators at both participating and nonparticipating sites (protocols, resources, and funding priority given to the network).	6
Lack of personal ownership and commitment from researchers at each site. May have issues with ownership of results and authorship.	5
Potential for disagreement among researchers from different sites—it may be too difficult to monitor the biases of the experts involved.	4
Studies may collect very specific data and lose the opportunity to record other data that could be used for analysis (e.g., comorbidities).	3
Sustainability is questionable because funding is finite.	3
There is a lack of awareness of existing networks, even among participants of networks, resulting in duplication of studies and missed opportunities for collaboration.	2

IRB = institutional review board.

direct EMERGEncy ID NET. EMERGEncy ID NET and CDC investigators meet semiannually at the spring and fall emergency medicine (EM) professional society meetings.

Ideas for new investigations are identified from EMERGEncy ID NET and CDC investigators and are approved after consensus is reached based on potential public health importance and study practicability in the ED. Study targets are typically clinical syndromes with clear disease case definitions with an expected frequency that can be detected among ED patients. Syndromic surveillance allows understanding of disease prevalence in a

Table 3
Suggestions From the Breakout Session Discussions on How to Improve ECRNs

Global issues
There is a need for translational research linking bench to clinical practice; increased participation in Phase II and III clinical trials should be encouraged.
In addition to translation of novel therapies, there should be greater support of translation of existing/known therapies into clinical practice.
Investigators and networks should be more proactive in approaching industry with ideas about ''investigator-initiated'' studies.
Promote and improve the visibility of EM specialty as a discipline with the ability to conduct research in acute therapeutic time frames.
The network does not have to be disease-based or population-based, but should focus on critically ill, life-threatening conditions that enroll patients prior to diagnosis. For instance, inclusion into the study should not require a diagnosis.
Increase the scope of the patients beyond those who present to the ED. Include primary care and appropriate specialty clinics. Involve subspecialists and primary care physicians who are involved with the care of the study population in the studies as well.
Partner with other researchers and other networks.
Encourage the participation of young investigators in the networks and support their research interests.
Network issues
There is a need for committed and motivated researchers. Networks should encourage physician champions at each of their sites.
When reviewing/designing/analyzing protocols, integrate independent researchers from outside the network who have no vested interest in the topic.
Facilitate the IRB procedure across sites and account for variations in state laws.
Establish central monitoring of data and Web-based communications.
Establish a well-managed and flexible infrastructure that is scalable, so the network can be tailored to size and needs of specific studies.
Sustain the network through different funding sources, and have a plan for sustainability.
Select realistic outcome measures that can be adequately captured and measured uniformly across sites.
Ensure that there is a standard of care for the condition being studied across sites to minimize practice bias.
Ensure that the network hierarchy is democratic and has a number of voting members.
Establish committees at the involved sites to monitor study process and budget.
Define processes for diagnostic studies versus therapeutic studies.
Promote awareness among researchers and the public of network activities. Keep national emergency medicine and emergency care specialty organizations informed of the existence of these networks and have them posted on their websites (e.g., ACEP, SAEM Web sites) for members and public to access links.

ACEP = American College of Emergency Physicians; ECRN = Emergency Care Research Network; SAEM = Society for Academic Emergency Medicine.

clinical context, as opposed to laboratory-based surveillance, which is limited by evaluation bias and inaccurate assessment of clinical data based on retrospective record review. Syndromes should neither be so rare that the studies are easily forgotten or so common such that enrollment is overly burdensome in a busy ED. For example, ''fever'' as a screen to study the prevalence of indigenously acquired malaria is too common a symptom for a target disease that is too rare to detect. Data are collected relatively completely in real-time during patient care encounters, and ED logs are audited and reviewed to collect data on missed eligible cases to identify potential biases. Arrangements are often made with affiliated microbiology laboratories to save and send specific isolates to reference laboratories, such as those at CDC.

Investigations A range of infectious diseases have been studied, including Shiga toxin–producing Escherichia coli among patients with bloody diarrhea; neurocysticercosis among patients with new-onset seizures; uropathogen antimicrobial resistance among patients with acute pyelonephritis; use of tetanus and rabies prophylaxis among patients with wounds and animal exposures; inappropriate antibiotic use for bronchitis, diarrhea, and lacerations; and the identification of tuberculosis and use of hospital isolation beds among patients admitted for pneumonia. The research has been published in Academic Emergency Medicine, Annals of Emergency Medicine, Clinical Infectious Diseases, Emerging Infectious Diseases, the Journal of the American Medical Association, and The New England Journal of Medicine.[11,12]

In addition to studying infections that have recently emerged, ideally, EMERGEncy ID NET will also rapidly detect disease emergence. The best recent example is EMERGEncy ID NET's role in the recognition of the emergence of community-associated methicillin-resistant Staphylococcus aureus or CA-MRSA.[13] Following the observation of an increased frequency of MRSA skin and soft tissue infections at one EMERGEncy ID NET site, a study protocol was written with institutional review board (IRB) approval within 6 months. Demographic, epidemiologic MRSA risk factors, and clinical data were collected on standardized forms in real time, and within 1 month, the study was completed after enrolling 422 patients. ED patient logs were reviewed and evaluable, but missed cases were compared to enrolled cases. Staphylococcal isolates were initially identified at site laboratories and then sent to the CDC for further analysis. CA-MRSA was found to have become the most common cause of community-acquired skin and soft tissue infections. Members of the EMERGEncy ID NET group were awarded a National Institutes of Health (NIH) contract to conduct clinical

Table 4
Summary of Five Emergency Care Research Networks

Name	Year Established	Goal/Mission	Setting	Websites
EMERGEncy ID NET Emergency Infectious Disease Network	1995	To conduct surveillance and research of emerging infections in the United States.	There are 12 geographically diverse, academically affiliated urban EDs with an annual visit census of approximately 1 million.	http://www.emergencyidnet.org
EMNet Emergency Medicine Network	1996	To advance public health objectives through multicenter, emergency department-based research. EMNet focuses on three areas: 1) respiratory/allergy emergencies, 2) health policy, and 3) other public health projects.	There are 198 medical centers (166 United States, 32 international); additional sites have completed EMNet surveys.	http://www.emnet-usa.org
PECARN Pediatric Emergency Care Applied Research Network	2001	To conduct high-priority, multi-institutional research for the prevention and management of pediatric acute illnesses and injuries, including the full spectrum of diseases that may be encountered in the pediatric out-of-hospital setting, in the ED, or in the pediatric critical care unit.	The four nodes of PECARN comprise 22 EDs in 10 states and the District of Columbia. Together, these sites evaluate more than 800,000 children annually and comprise a diverse population, with a high percentage of minority patients.	http://www.pecarn.org
ROC Resuscitation Outcomes Consortium	2004	To conduct multiple, collaborative, out-of-hospital clinical research trials and other types of studies to evaluate strategies to treat patients with cardiac arrest or severe injury and to expedite the translation of promising laboratory-based findings to clinical emergency care.	There are 268 EMS and fire agencies covering 35,000 square miles and serving almost 24 million people participating in ROC protocols. Approximately 30,000 EMS personnel staffing 3,500 vehicles will carry out ROC interventions.	http://www.uwctc.org
NETT Neurological Emergencies Treatment Trials Network	2006	To create a research network of clinicians in EM, neurology, and neurosurgery to promote efficiency in the design, implementation, and analysis of clinical trial therapies for patients with acute neurologic disorders, including ischemic stroke and intracerebral hemorrhage, subarachnoid hemorrhage, traumatic brain injury, spinal cord injury, and epilepsy.	Clinical Coordinating Center, Statistical and Data Management Center and 17 hub sites.	http://www.nett.umich.edu

trials of off-patent antibiotics to treat uncomplicated MRSA skin and soft tissue infections, and five of the 12 EMERGEncy ID NET sites are currently conducting this study. This is the first NIH-supported initiative to conduct clinical trials of off-patent antibiotics for common community-acquired infections, and it is anticipated that EMERGEncy ID NET will be able to compete for additional awards for similar initiatives. Investigations that are in the process of being completed or will soon be started include a reexamination of skin and soft tissue infections for changes in the prevalence, clonality, and antibiotic susceptibility of MRSA and evaluation of ED admission decisions and infection control management; an analysis of the prevalence of and risk factors associated with Clostridium difficile colitis among ED patients presenting with diarrhea, with particular attention to community-associated disease among patients without traditional exposures; and an investigation of

the bacteriology of cellulitis without drainage using advanced molecular diagnostic methods.

EMNet

Background The Emergency Medicine Network[3] was founded in 1996 and involves 198 medical centers (166 United States, 32 international); additional sites have completed EMNet surveys. The mission of EMNet is to advance public health objectives through multicenter, ED-based research. The network focuses on three areas:

1. Respiratory/allergy emergencies through the Multicenter Airway Research Collaboration (MARC). MARC is an international research network focusing on asthma, chronic obstructive pulmonary disease (COPD), anaphylaxis, bronchiolitis, and other airway disorders.[14]
2. Health policy research, which includes the National ED Inventories (NEDI), and the National ED Safety Study (NEDSS).[15]
3. Other public health projects, focusing on public health issues that affect the delivery and quality of emergency care, as well as the primary care needs of medically disadvantaged populations. The ED 24-hour Research Network, surveys, and analysis of federal data sets are the core activities of this program.[16]

EMNet plans to continue its focus on the areas of respiratory/allergy emergencies (e.g., bronchiolitis, asthma, COPD, anaphylaxis) and health policy (e.g., patient safety, workforce issues). The network also will delve into other important public health topics such as health literacy, language barriers, and mental health. To advance these diverse activities, EMNet investigators will continue to seek federal, industry, and foundation funding and to work with investigators from both inside and outside of EM. EMNet also will continue to encourage and develop independently funded academic emergency physicians (EPs) (e.g., through K12 and K23 awards, participation in K30 and T32 training grants, and other mechanisms).

Structure and Function All EMNet programs are based at the EMNet coordinating center (ECC) at the Massachusetts General Hospital in Boston. The director of ECC is also the chair of the EMNet steering committee. The deputy director of the ECC works closely with the members of the steering committee. Members of the steering committee include members from Children's Hospital Boston, Massachusetts General Hospital, Oregon Health and Science University, Summa Health Systems, the University of Colorado Denver, and the University of Pittsburgh. The network is funded by a combination of federal, foundation, and industry grants; the primary sponsors of EMNet have been the NIH and the Agency for Healthcare Research and Quality.

Investigations Over the past decade, EMNet has completed over 50 studies and compiled over 500 publications. Excluding abstracts, the network has produced at least 250 publications, and it now averages approximately 40 original research publications per year. By late 2008, EMNet publications included over 400 participating investigators as authors, from a total of approximately 120 EDs. EMNet was honored in 2000 by an Emergency Medicine Foundation Center of Excellence Award and in 2006 by selection for the NIH-funded Inventory & Evaluation of Clinical Research Networks Best Practices Study.

The major EMNet studies at this time are 1) MARC-30, a multicenter study of severe bronchiolitis (U01 AI67693); 2) MARC-33, a multicenter study of smoking cessation (R21 DA20771); 3) NEDSS, a multicenter study of patient safety in the ED (R01 HS13099); and 4) NEDI, a series of databases with which to study EDs and ED-related health policy (unfunded).

Certainly one of the strengths of a multicenter ED network is that studies on diseases with rare presentations can be conducted relatively quickly and include adequate sample sizes for analysis.[17] One of the challenges in conducting multicenter research is the variability in local IRB assessments. Two studies were conducted as part of the EMNet to investigate the variability of IRB responses to multicenter studies, one observational protocol involving children[18] and the other a clinical trial involving adults.[19] In both studies there was substantial variation in IRB assessment of the standard protocols. For the pediatric protocol, the burden of the application process contributed to some investigators not participating, although the majority of investigators remained enthusiastic about multicenter research. For the adult clinical trial protocol, all IRB's ultimate gave approval.

PECARN

Background In 2001, PECARN[4] was created in response to a solicitation by the Emergency Medical Services for Children (EMSC) Program of the Health Resources and Service Administration's Maternal and Child Health Bureau (HRSA/MCHB) for proposals for four individual research nodes consisting of five to six sites each. The four successfully funded nodes were joined under the umbrella of PECARN, which is supported by cooperative agreements between the four nodal centers and HRSA/MCHB/EMSC. The year after PECARN was established, a cooperative agreement between the University of Utah and HRSA/MCHB/EMSC was established to create the Central Data Management and Coordinating Center (CDMCC) for the PECARN network. After more than a decade of deliberations and advocacy work by EMSC stakeholders, researchers, national organizations, and federal partners,[20,21] the need for PECARN was identified and resulted in the first federally funded national EMSC network.[22,23]

The mission of PECARN is to conduct high-priority, multi-institutional research for the prevention and management of acute illnesses and injuries in children and youths of all ages. This included the full spectrum of diseases that might be encountered in children in the out-of-hospital setting, ED, or in the pediatric critical care unit. Some of the strengths of PECARN are its infrastructure, dedicated and experienced investigators, large and diverse patient population, and collaboration and mentoring. Ongoing challenges include securing

ongoing funding, lack of an NIH institute focused solely on ECR, a substantial workload, equitable distribution of publications, coordinating leadership of the many committees, ensuring uniform standards of conduct of research at each site, coordinating IRB submissions to 22 distinct IRBs, and ensuring smooth leadership transitions at all levels to facilitate future success of the network.

Structure and Function The four nodes of PECARN comprise 22 EDs in 11 states and the District of Columbia. Together, these sites evaluate more than 800,000 children annually and comprise a diverse population, with a high percentage of minority patients. The population is 47% African American, 36% white non-Hispanic, 11% Hispanic, 2% Pacific Islander or Native American, and 4% other.[24] PECARN has an infrastructure[21,23] composed of four ''nodal centers,'' each with a nodal PI and administrator to organize, oversee, and support five to six hospitals within their node. Each nodal hospital has a funded site investigator and full-time research coordinator. Forging research partnerships among academic and community-based hospitals, each nodal center considers research concepts from investigators within the node, as well as from investigators outside of PECARN.

The PECARN steering committee serves as the primary governing body of PECARN. Each of the four nodes is equally represented (five members each) among the 21 members of the steering committee. The final member of the steering committee is the PI of the PECARN data center. The steering committee establishes and revises scientific and administrative bylaws, policies, and procedures; reviews and approves PECARN research proposals; formulates and monitors policies and procedures that guide the network; and establishes subcommittees to carry out specific tasks and activities. The five subcommittees created by the steering committee include the Protocol Review and Development Subcommittee, the Safety and Regulatory Subcommittee, the Quality Assurance Subcommittee, the Feasibility and Budget Subcommittee, and the Grant Writing and Publication Subcommittee. The subcommittees provide essential input into research design, organization, and implementation; assist with the development of network policies; and facilitate the timely publication of research studies. A critical component of the PECARN infrastructure is the CDMCC, which serves PECARN in a variety of capacities. These include assistance with research and grant development; training and educating research coordinators; preparation of operational manuals and study materials; study organization; technical expertise and support; site monitoring; and data collection, management, and analysis.

Investigations The specific EMSC multicenter PECARN research agenda was developed using the Nominal Group Process and Hanlon Method of Prioritization,[25] resulting in a list of 16 EMSC topics. The top 10 items, in order of priority are as follows: 1) respiratory illness/asthma, 2) prediction rules for high stakes/low likelihood diseases, 3) medication error, 4) injury prevention, 5) urgency and acuity scaling, 6) race/ethnic/class disparities in health, 7) mental health, 8) infectious diseases, 9) best practices in patient care, and 10) pain and anxiety management. As of October 2008, PECARN had received nine federal research grants in addition to infrastructure funding and has 18 published or in-press publications; 50 presented research abstracts; and many more grants, manuscripts, and abstracts under preparation. Topics range from out-of-hospital care to the management of trauma, acute medical illnesses, and safety and quality of pediatric emergency care. One recent important randomized controlled trial on corticosteroid use in bronchiolitis was published in the New England Journal of Medicine.[26]

New research concepts, which may be submitted from investigators from both within and outside of PECARN, must first undergo comprehensive review at the nodal level prior to consideration by the PECARN Steering Committee. Recognizing the wealth of EMSC research expertise outside of PECARN, research proposals from outside of PECARN are encouraged, and outside investigators with specific expertise are invited to lead selected PECARN initiatives and projects. After the steering committee approves a preliminary proposal, the investigator develops a detailed protocol, with substantial support and input from the CDMCC and PECARN subcommittees. Most PECARN research projects require extramural funding.

ROC

Background In July 2000, the NIH sponsored a Postresuscitation and Initial Utility in Life Saving Efforts (PULSE) workshop, which focused on the time dependency of cellular injury mechanisms and emphasized that similar cellular processes occur whether the injury arises from physical trauma or cardiac arrest. Because these fundamental processes are treated best with early intervention, the ROC[5] was established to expedite the translation of promising laboratory-based findings to clinical emergency care. The ROC officially began in 2004, with $50 million of funding from the National Heart, Lung, and Blood Institute in partnership with the Institute of Circulatory and Respiratory Health of the Canadian Institutes of Health Research (CIHR) and other government and non-government funding partners. Three years ago, the American Heart Association became a funding partner and committed $500,000 per year for 4 years, and the CIHR and Heart and Stroke Foundation of Canada contribute additional funds to Epistry for the Canadian sites. Additional in-kind support is provided by manufacturers of monitors and defibrillators who donate new or modified equipment. ROC is composed of 10 regional clinical centers representing 11 distinct geographic regions in the United States and Canada. The University of Washington's School of Public Health in Seattle serves as ROC's Data Coordinating Center.

The general aim of ROC is to conduct multiple, collaborative, out-of-hospital clinical research trials and other types of studies to evaluate strategies to treat patients with cardiac arrest or severe injuries. Long-term objectives include 1) providing a knowledge base

that will improve therapeutic decision-making by testing treatment approaches for cardiopulmonary arrest and life-threatening trauma, 2) developing collaborations between community EMS providers and clinical research centers to permit efficient out-of-hospital resuscitation research, and 3) facilitating the training of EPs in resuscitation and clinical investigation.

Structure and Function There are 268 emergency medical services and fire agencies covering 35,000 square miles and serving almost 24 million people participating in ROC protocols. Approximately 30,000 EMS personnel staffing 3,500 vehicles will carry out ROC interventions. In addition to conducting community notification and consultation to fulfill the local IRB requirements for emergency research under exception from informed consent (EFIC), ROC sites confer with over 100 IRBs, representing 284 hospitals. To date, there are 25 ROC Epistry writing groups (16 cardiac arrest and nine trauma), exploring a wide range of scientific questions. The ROC investigators have already published, presented, or submitted 29 abstracts and 13 scientific manuscripts.[27,28]

ROC has access to an enormous number of patients with severe trauma and cardiac arrest. The Epistry[29] has allowed sites to develop and test data collection methods in advance of clinical trial initiation. ROC has special challenges, because it is one of the first attempts to perform large-scale out-of-hospital research with emergency patients who are physically unable to give consent.[30] A ROC working group approached this problem through community consultation, which included 1) well-publicized public meetings, 2) tracking of numbers of attendees by zip or postal code, 3) formal presentations with comments by attendees, and 4) oversight by local IRBs (attending these events). The ROC has used random-digit dialing telephone services, where a random sample of the population is asked to assess the degree of community acceptance of a protocol, yielding a 65% to 75% public acceptance rate. The additional challenge of working with multiple IRBs has been approached by approving an initial protocol/application and distributing it to other local IRBs, with input from local authorities such as city council, county board of supervisors, mayors, and other local leaders.

Investigations During the initial 4 years of funding, ROC investigators launched a major out-of-hospital cardiac arrest and trauma registry (Epistry) and are currently enrolling patients in a clinical trial (hypertonic saline and dextran) that will determine which of three frequently administered intravenous fluids yields the best outcome in severely injured patients. ROC has also begun enrollment in a cardiac arrest trial (ROC-PRIMED), comparing outcomes after a several-minute period of cardiopulmonary resuscitation (CPR) prior to defibrillation versus prompt defibrillation and (with a factorial design) whether a small, inexpensive CPR adjunct airway device that may improve blood flow during CPR can improve survival from sudden cardiac arrest. ROC investigators expect to enroll 10,000 patient episodes of major trauma and 17,500 cardiac arrests annually. More specifically, 2,122 patients with traumatic brain injury, 3,726 patients with shock, and 15,000 with cardiac arrest are expected in these interventional trials.

Awarded to one ROC investigator, a 3-year, $300,000 grant through the Robert Wood Johnson Foundation–Physician Faculty Scholar Program will be directed toward redeveloping the EMS field trauma triage guidelines and assessing its cost-effectiveness. Three ROC sites will be participating: Portland, Oregon; Seattle/King County, Washington; and Birmingham, Alabama. Investigators anticipate that approximately 250,000 injured persons will be enrolled over 3 years (35,000 have already been enrolled). Another ROC site has broadened its ROC training core to include a fourth-year medical student supported by a training award from the Oregon Clinical Translational Research Institute (Grant UL1 RR024140, one of 12 original CTSA awards). With guidance and mentoring from local ROC investigators, this student has conducted three studies exploring the use of opt-out bracelets in the ROC Hypertonic Saline and Dextran trial.

NETT Network

Background In 2005 and 2006, the NINDS issued requests for applications[31] for a clinical coordinating center, a statistical and data management center, and clinical hub sites to establish the NETT network.[6] The Clinical Coordinating Center and the Statistical and Data Management Center (SDMC) received funding in mid-2006, and the clinical hub sites were funded in 2007.

The overall goal of NETT is to create a research network of clinicians in EM, neurology, and neurosurgery to promote efficiency in the design, implementation, and analysis of clinical trial therapies for patients with acute neurologic disorders. Neurologic disorders, including ischemic stroke and intracerebral hemorrhage, subarachnoid hemorrhage, traumatic brain injury, spinal cord injury, epilepsy, and others, have a high morbidity and mortality. All of these disorders typically present as emergencies, and management of these disease processes in the first few hours or even minutes can be critical. The unique configuration of NETT enables it to focus on the emergent phase of treatment and to conduct Phase III clinical trials. NETT is funded through a U-type, or collaborative, agreement award at the Clinical Coordinating Center, SDMC, and 17 hub sites. Each hub site has multiple ''spokes,'' or community hospitals that are affiliated with the academic hubs. Combined, NETT has the ability to recruit patients at over 60 sites. The NINDS funding for NETT exceeds $30 million over 5 years and is subject to competitive renewal.

Structure and Function The primary decision making body in NETT is the Executive Committee, which is composed of the investigators from the Clinical Coordinating Center, the SDMC, and program directors from NINDS. There is also a NETT Operations Committee, which handles trial planning and conduct and is composed of members from the Clinical Coordinating Center, the SDMC, and the NETT steering committee. The

steering committee, which is responsible for overall approval of new projects within NETT and strategic planning, is composed of investigators from the Clinical Coordinating Center, SDMC, and all of the PIs at the 17 hub sites.

The NETT SDMC is located at the Medical University of South Carolina and has developed a unique Web-based system for data management and document management by NETT (Web DCU; https://webdcu.musc.edu/NETT/index.asp). Web DCU performs trial management as well as regulatory document management for NETT. Randomization is also managed by Web DCU and trial data are entered online.

The PIs at the hub sites oversee the conduct of the research within their entire hub–spoke complex, which includes the clinical hub site and approximately four to 10 spoke hospitals. With the inclusion of community hospitals in the hub–spoke complex, this model allows for direct dissemination of research results from the academic research centers to community hospitals.

Investigations Although in existence for less than 2 years, NETT is already engaged in its first clinical trial evaluating the effects of high-dose albumin treatment within the first 5 hours of ischemic stroke (ALIAS trial). Another trial examining the prehospital treatment of status epilepticus with intravenous lorazepam versus intramuscular midazolam (RAMPART) has been approved by the Food and Drug Administration and began enrollment in spring 2009. Additionally, a trial evaluating the effects of progesterone in traumatic brain injury (ProTECT) has been funded and will start enrollment by spring 2010. NETT has been proactive in educating participating centers and IRBs about trials requiring EFIC. The RAMPART trial requires EFIC and has been approved by the FDA. ProTECT will also require EFIC. NETT has been proactive in soliciting and developing new trial proposals, and there are currently multiple other trials being developed, one of which has already been submitted for study section review.

NETT is open to individual investigators through the NIH RO1 mechanism. PIs are not required to be investigators within NETT. NETT is also open to industry-sponsored clinical trials, but the clinical protocol must be developed by NETT and then funded by the industry sponsor. NETT trial guidelines have been developed and NETT trials should 1) be Phase III clinical trials; 2) have patient-oriented primary outcomes; 3) be able to be conducted within the NETT network; 4) have their primary intervention in the prehospital or ED phase of care; 5) be large, simple, streamlined trials; and 6) the results of NETT clinical trials should be easily translated into clinical practice.

DISCUSSION

The consensus conference highlighted the strengths and weaknesses of current ECRNs. The five EM research networks described above differ in their scopes of study, methodologies, and research questions addressed, yet all five networks foster multidisciplinary collaboration and enroll large, diverse patient populations, thus increasing the power and the generalizability of results. For example, with 12 geographically diverse urban EDs, the large EMERGEncy ID NET infrastructure is critical in facilitating the rapid identification of emerging diseases and infectious disease surveillance. EMNet involves 198 medical centers, including 32 international sites. PECARN has access to data from over 800,000 annual pediatric ED visits, and ROC investigators expect to enroll 10,000 trauma patients and 17,500 cardiac arrest patients per year. NETT has 17 hub sites and each hub has multiple spokes, with over 70 enrolling sites altogether. Such enormous and diverse sample sizes would not be practicably achieved by a nonnetworked single institution. The network model also increases work efficiency; a network in which there is a leading site and smaller hub study sites may obviate duplication of work. Similarly, when several sites within a network call for implementation of a uniform standard, practical application of the policy or standard often happens more efficiently because of the network infrastructure.

The networks also face similar challenges and the following difficulties (among others): 1) the ability to oversee a large infrastructure and coordinating leadership among committees and subcommittees, 2) decreased availability and sustainability of federal funding, 3) coordinating several sites and their respective IRBs and ensuring uniform standards for training and data collection, and 4) distributing publications and authorship equitably. In addressing the difficulty of overseeing the large infrastructure, it appears that successful networks have utilized a governing structure that depends on a steering or executive committee. Similarly, each participating site within a network has a governing body whose goal is to adopt the network's standards and policies for training and data collection, while maintaining its own voice and independence. By being cognizant of the inherent challenges of distributing authorship of publications equitably, it is hoped that network leaders will act fairly and ethically.

CONCLUSIONS

Through a survey and structured discussion process involving multiple stakeholders, we have identified strengths and weaknesses that are consistent across a number of existing emergency care research networks. By leveraging the strengths and addressing these weaknesses, strategies can be adopted to enhance the scientific value and productivity of these networks and give direction to future emergency care research networks.

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