

Recruitment and Retention of Patients into Emergency Medicine Clinical Trials

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Abstract

The emergency medicine (EM) and prehospital environments are unlike any other clinical environments and require special consideration to allow the successful implementation of clinical trials. This article reviews the specific issues involved in EM clinical trials and provides strategies from EM and non-EM trials to maximize recruitment and retention. While the evidence supporting some of these strategies is deficient, addressing recruitment and retention issues with specific strategies will help researchers deal with these issues in their funding applications and in turn develop the necessary infrastructure to participate in EM clinical trials.

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The United States spends \$2 trillion annually on health care, with as much as 15%–20% being spent in acute care and emergency situations.¹ Evidenced-based medicine is dependent on information gained from well-run clinical trials to provide the answers needed to guide efficient and cost-effective patient care. Clear evidence is lacking for many treatments, but research efforts are growing, especially in emergency medicine (EM). Projects and funding for research in this setting are not limited to the specialty of EM, but often involve the collaboration of multiple specialties such as orthopedics, cardiology, pediatrics, and neurology, both individually and as part of networks.

A recent search of ClinicalTrials.gov for “emergency department” clinical trials resulted in 691 open and closed studies, 312 currently seeking volunteers, and 59 that are listed as being funded by the National Institutes of Health (NIH) or other U.S. federal agencies.² A similar search of the Research Portfolio Online Reporting Tool listed 153 new research grants in 2009 supported by the NIH.³ There are several well-funded existing emergency research networks, such as the Neurological

Emergencies Treatment Trials network (NETT) and Resuscitation Outcomes Consortium (ROC), both funded by the NIH. The Pediatric Emergency Care Applied Research Network (PECARN) is another emergency network funded by the Health Resources and Services Administration/Maternal and Child Health Bureau’s Emergency Medical Services for Children Program and Division of Research, Training, and Education.^{4–6} Both the NETT and the ROC networks offer opportunities for numerous locations to participate in clinical trials in the emergency department (ED) setting; NETT has four current projects and 17 centers, and ROC has four current projects and 11 clinical centers (Table 1). The PECARN network has four research centers, each with multiple affiliated EDs, totaling 21 hospitals that serve approximately 900,000 acutely ill and injured pediatric patients annually.⁶ In addition, the National Institutes of Neurological Disorders and Stroke (NINDS) has launched the Clinical Research Collaboration, a project designed to encourage academic- and community-based neurologists and neurosurgeons to participate in clinical research through access to multiple clinical research protocols. Many of these protocols are relevant to EM and will need collaboration from emergency physicians to help enroll patients, such as those with epilepsy, headaches, stroke, and transient ischemic attacks.⁷

Essential to the success of any network is the recruitment and retention of subjects into studies. Although recruitment and retention may seem straightforward, issues unique to the ED environment need to be considered. This article highlights these issues and discusses how to incorporate strategies into the study design and one’s research infrastructure (Table 2).

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Table 1
Networks With Ongoing Emergency Research

Network	Primary Focus	Year Started	Organization	Ongoing Projects	Website
NETT	Conduct large simple trials to reduce the burden of very acute injuries and illnesses affecting the brain, spinal cord, and peripheral nervous system and to improve outcomes of patients with acute neurologic problems through innovative research focused on the emergent phase of patient care.	2006	Seventeen regional hubs, SDMC, CCC, NINDS advisory group	3	http://www.nett.umich.edu/nett/welcome
ROC	Clinical trial network focusing on research in the area of prehospital cardiopulmonary arrest and severe traumatic injury.	2006	Eleven regional clinical centers, DCC	4	https://roc.uwctc.org/
PECARN	Conduct multi-institute research into the prevention and management of acute illnesses and injuries in youth and children.	2001	Four research nodes, 20+ hospital ED affiliates, DCC	11	http://www.pecarn.org/pecarnnetwork/index.html
EMNet	Respiratory and allergy emergencies; health policy and other public health projects.	1996	Nine U.S. divisions, one international division, 201 hospitals, CCC	8	http://www.emnet-usa.org/emnet_details.htm

CCC = clinic coordinating center; DCC = data and coordinating center; EMNet = Emergency Medicine Network; NETT = Neurological Emergencies Treatment Trials; NINDS = National Institutes of Neurological Disorders and Stroke; PECARN = Pediatric Emergency Care Applied Research Network; ROC = Resuscitation Outcomes Consortium; SDMC = Statistical and Data Management Center.

By understanding and addressing these issues, we hope investigators can increase the likelihood of funding and implement successful EM clinical trials.

THE SETTING

The most recent public data from 2006 show that the volume of ED patients has increased by 36% over the past decade, to approximately 120 million visits annually.⁸ This includes acute care and preventive care visits, which comprise 20% of ED patients who are unable to get an appointment with or do not have a primary care provider.⁹ EDs are also the gateway for the sickest patients who enter the hospital and health care system, being responsible for about 20% of hospital admissions.¹⁰ The crowding and volume seen in EDs make them challenging environments to provide effective and timely care, apart from trying to incorporate clinical research.^{11,12}

However, the challenges and funding of research in the ED are being addressed. In addition to the NETT, ROC, and PECARN networks, the introduction of the Comparative Effectiveness Research Act of 2008 and America's Affordable Health Choices Act of 2009 puts the focus on cost-effectiveness in all areas of health care. Specifically, one of the top 100 Initial Priority Topics for Comparative Effectiveness Research is investigating the value of neurologic and orthopedic imaging modalities when ordered by emergency physicians.¹³

Emergency medicine researchers will be called upon more and more to participate in this type of research

and in turn will receive more funding to do research in the ED. For researchers, particularly those not practicing in the ED environment, it may be difficult to understand why it is difficult to recruit and successfully complete trials from the ED.¹⁴ Unlike the controlled environment of a clinic or general clinical research center, caregivers have neither the time nor the resources to help with research. With this in mind, researchers must optimize the design and implementation of trials to accommodate the ED setting to take advantage of the millions of ED patients who could be eligible to participate in clinical trials.

RECRUITMENT

Providing evidence that one can enroll patients in the numbers required is crucial to receiving funding. Pilot studies can be done to determine the number of eligible and ineligible patients.^{15,16} While pilot studies allow for the most precise determination of potential subjects and a preview of potential implementation problems, they require a significant investment of resources for a small number of participants and cannot be done practically without funding themselves. Prospective and retrospective screening through chart review are more practical and can be helpful to estimate recruitment capabilities.¹⁷ However, these reviews often fail to identify potential obstacles to recruitment, such as real-time identification of eligible participants, consent issues, and the complexities of implementing a protocol. Once investigators can demonstrate that participants are

Table 2
Potential Problems, Solutions, Pros, and Cons Associated With Research in the ED Setting

Potential Problem	Potential Solutions	Pros	Cons
Estimating eligible participants	Pilot study	Up-to-date estimate of available participants; preview potential study problems.	Significant investment for a small number of participants.
	Chart review	Estimate number historically available.	Does not identify barriers to recruitment, study interventions, and follow-up.
Identifying eligible participants in real time	Emergency physician/staff identify during treatment	Treating staff know the patient.	Not all staff aware of all studies; ED staff very busy; numerous providers and staff; motivation.
	Manual screening by research associates/students	Can often find subjects for cohort studies in real-time.	Need a critical number of studies/patients to keep staff engaged. For clinical trials needing intervention need more experienced staff to come in. Increase risk of HIPAA violations.
	Research coordinator/network	Familiar with studies; can access and identify participants in real time outside of treatment team.	Funding for position requires large study or multiple studies to be effective
	Central paging alerts	Alerts researchers to potential participants in ED through trauma activations, stroke codes, etc.	Only available for a limited number of conditions.
	Procedure-related alerts (procedure hold or checklists)	Treatment team made aware of trial prior to performing a procedure/ordering tests.	Could delay treatment for people not eligible. Still requires call to research team.
	Alerts through electronic health records	Alerts can be triggered on a variety of "trigger points" including orders or results.	Not available in all EHRs and requires expensive programming. Alerts usually require treating team to still call research team.
Obtaining timely consent	Alerts through HL-7 feed	Alerts can be triggered on a variety of "trigger points" including orders or results and be sent directly to research team for further screening.	Requires institutional IT costs, foreign software installation, and data sharing.
	Legally authorized representative	Allows for consent by someone other than patient.	May not be available; treating team may not have time to explain trial.
	Trauma teams with designated counselor	Time to spend with patient and/or LAR.	Cost and availability; may require multiple studies to be cost-effective.
	In-field cell phone	Limits time to first contact of LAR	No guarantee of contact, could take focus away from treatment time.
Implement protocol	EFIC	Allows for treatment when patient or LAR consent in unavailable.	Restrictions on use for emergency research.
	Protocol should be simple and easy to follow	Allows for easy execution of research.	Limits the number of outcomes and data points that can be studied and collected.
	Increased study related personnel/use a network	Decreases likelihood of errors/violations; guarantees knowledge of protocol specifics.	Large start-up cost of new networks; may require a large number of trials to be cost effective.
Attrition and follow-up retention	Reimburse for transportation	Alleviates issues related to transportation.	May not be allowed under all protocols.
	Out of area patients use local follow-up	Obtains follow-up information.	Local physician must be included in research plan and IRB approval.
	Out of area patients us self-reported follow-up	Obtains follow-up information.	Self-report may be less reliable or not a possible outcome.
	Follow for research during routine follow-up for condition	Obtains follow-up information.	Requires cooperation of follow-up care if not in ED or with ED physician.
	Offer no-cost, long-term follow-up	Obtains follow-up information.	Costly to trial.

Table 2
(Continued)

Potential Problem	Potential Solutions	Pros	Cons
	Shorten follow-up time Use hard endpoints like death Increase participant contact between visits with phone calls, e-mails, letters	Less likely to lose people. Can follow-up with death registries (SSDI, NDI). Keeps the participant engaged in trail and offers reminders of visits; allows for troubleshooting of potential barriers prior to a missed visit.	Limits to short-term endpoints. Not an appropriate outcome for many conditions. Cost and time involved can be high depending upon number of participants; must obtain IRB approval for all participant contact and materials.

EFIC = exception from informed consent; EHR = electronic health record; HIPAA = Health Insurance Portability and Accountability Act; HL-7 = Health Level Seven; IT = information technology; LAR = legally authorized representative; NDI = National Death Index; SSDI = Social Security Death Index.

available for enrollment into their studies, they should focus on specific strategies to enhance recruitment into their trials. Recruitment into EM clinical trials has three important elements: identification, consent and enrollment, and implementation.

Identification of Participants

A critical hurdle for clinical trials is the lack of a timely and efficient method for identifying participants who meet inclusion and exclusion criteria for entry into prospective studies. This is especially important in ED patients, where time from presentation to the need for treatment is short (e.g., cardiac catheterization, tissue plasminogen activator for stroke, blood substitutes, hypothermia for acute brain injury). Researchers cannot expect busy clinical practitioners to screen and identify eligible participants, nor can they expect participants to answer study advertisements themselves.^{14,18-20} While ED staff education and orientation are important, the study is unlikely to be successful if it depends on treating physicians and staff to identify eligible participants. The use of a research coordinator or a specific research staff member who is either dedicated to reviewing current patients in the ED or alerted to incoming patients is essential to capture all eligible participants.^{21,22} While research personnel are expensive, they can usually be written directly into the funding mechanism and can often be shared across multiple projects. Many academic EDs have invested in unfunded research personnel to develop a track record of success to help secure future funding. Such research personnel can work closely with clinical teams such as stroke and trauma teams and can respond to specific clinical alerts through central paging.²³ For other conditions that do not include clinical alert pages, students (undergraduates, graduate, or postdoctoral fellows) have been successfully utilized to be physically present in the ED to screen prospective participants.²⁴ However, the skill and experience of these individuals to enroll patients into interventional clinical trials is generally unproven. Furthermore, there needs to be a sufficient volume of patients and studies to justify the effort and cost of

their full-time presence.²⁵ Creating a network to manage multiple studies within the same clinical center may allow for the more efficient use of dedicated personnel.^{4,5}

Manually screening ED admission logs for potential participants via medical records has been the method by which most participants have been recruited. However, manual screening of ED admission logs is not only inefficient and untimely, but also lacks the optimal privacy intended in the Health Insurance Portability and Accountability Act (HIPAA) for protected health information. Given the desire to better identify and screen participants, HIPAA-compliant electronic screening of existing medical information has been developed and used with some level of success.²⁶⁻²⁹ In a study using clinical trial alerts within an electronic health record (EHR), investigators were able to double enrollment.²⁸ In this example, an EHR triggered an alert to the patient's physician when study criteria matched the patient's medical record. While the doubling of enrollment was significant, the system was still inefficient and required the physician to be actively logged on to the patient's chart before any alert would fire, and once the alert was sent, the physician still had to call study investigators for the patient to be considered. To be successful in emergency research, alerts from EHRs must be timely and allow for programmed alerts directly to investigators so that the enrollment of participants does not depend on practitioners to notify the investigators. There are existing notification programs that allow for real-time notification based on Health Level Seven data. These software programs allow for instant notification to investigators²⁶ and have been used successfully to recruit participants in single institutions and small networks.³⁰ Overcoming data sharing and data management concerns could make these viable systems in large networks as this technology evolves.

Other ways to help remind or alert staff would be to include reminders on procedure kits for studies involving particular procedures or hard stops on orders such as x-rays or magnetic resonance imaging. The latter was used successfully at some centers to remind staff

to enroll participants into the National Emergency X-Radiography Utilization Study (NEXUS), where clerical staff at most centers could not order radiographs until the NEXUS imaging form was received as part of the order.^{31,32} For simple prospective cohort studies, having dedicated order sheets and documentation sheets that are built into the clinical workflow helps with compliance and enrollment. This is particularly true when using an EHR with dedicated order sets and documentation templates.

There are several examples where ED networks can identify and enroll participants into large databases for cohort studies. These include the National Center for Infectious Diseases and Centers for Disease Control EMERGENCY ID NET, for infections, and the Multicenter Airway Research Collaboration (MARC), originally for emergency asthma care, which is now the Emergency Medicine Network (EMNet), that includes MARC, the National ED Inventories (NEDI), National ED Safety Study (NEDSS), and ED 24-hour Research Network (ED24).^{33,34} Most of these types of networks have been successful in using the above screening techniques, but are not funded well enough to handle the complexity and treatment intervention as part of a clinical trial. Better funding and staffing of these existing networks may allow more trials to be done quickly in EM, given their proven ability to screen and recruit.

Consent and Enrollment

The time frame available to recruit participants in EM clinical trials is often far shorter than that for standard trials.³⁵ The unique time pressures affect the consent and enrollment process, with the further caveat that the patient may not be able to consent due to neurologic impairment accompanying the acute disease. Consent by a legally authorized representative of the patient is an option in these settings and is governed by various state laws and corresponding institutional review boards (IRBs). However, EM clinical trials are still faced with problems seeking consent when the family and/or the patient may not be available to consider participation in a clinical trial.³⁵ Furthermore, the providers and investigators seeking the consent often have no established relationship with the family or patient. This relationship and trust are what many potential participants depend on when making medical decisions, including whether to participate in clinical trials.^{36–38} Those obtaining consent in the ED can be aided by aligning themselves with members of a treatment team for support. This includes getting treating physicians involved and using specially trained social workers or trauma counselors. Social workers and trauma counselors have been helpful in obtaining consent for organ donations; however, availability and cost-effectiveness of such personnel will vary with the size and type of institution.³⁹ Although time is short, involving caregivers with existing medical relationships, such as primary care physicians, can be helpful.⁴⁰

Other studies have successfully used different techniques to improve enrollment time. In the Field Administration of Stroke Treatment–Magnesium (FAST-MAG) pilot trial, emergency medical technicians (EMTs) carried dedicated study cell phones for physician-investigator

phone elicitation of consent in the out-of-hospital setting.⁴¹ The study found that use of the cell phone during EMT prehospital treatment allowed for initiation of study procedures over 100 minutes sooner than prior trials than when consent was obtained after hospital arrival.

When informed consent is not possible, exception from informed consent has been used successfully to enroll participants into research in the prehospital and ED setting.^{42,43} While somewhat controversial, federal regulations (FDA final rule 21 CFR 50.24) allow for enrollment of participants into studies without prior consent when a number of very specific conditions are met.⁴⁴ However, even if consent is waived before enrollment, notification must be done and consent obtained from the patient or legal authorized representative as soon as possible after the intervention. Such studies are also required to follow additional guidelines including requirements for community consultation and public disclosure before, during, and after the study.

Implementation of Research Protocol

When implementing trials in the ED, investigators need to make sure the trial and intervention are not overly complex and can be started quickly, if not completed in the ED. Complex trials with prolonged and complex screening protocols can be difficult to implement even if they are well funded. The impact and time required for what appears to be simple or routine intervention should not be underestimated. Accordingly, most successful large trials in EM have been prospective cohort studies and not clinical trials.^{4–6} There are few complex trials that can be done in the ED. These trials often require special environments and investigators to complete them, making widespread implementation difficult,⁴⁵ and it is thus important to learn from relatively simple trials completed in the ED.^{46–48} The intervention should be simple or at least familiar for ED personnel to carry out. Cardiac thrombolysis trials are an example of how simple studies can rapidly recruit and complete the implementation of the trial in the ED.⁴⁹ As clinical trials become more complex, they become more difficult to complete. In addition to the increased time and cost of personnel training, the likelihood of protocol violations increases with complexity.¹⁴ That risk can be minimized with strict oversight by specific study coordinators,²² but it requires a 24/7 presence for enrollment. Paying teams to be on call to come in and care for patients is a solution, but it is a costly solution that requires a critical mass of ongoing trials. Networks such as NETT, PECARNS, ROC, and EMNet have addressed this critical mass by having a large number of ongoing studies with dedicated infrastructure and resources such as dedicated coordinators, collaborative teams of investigators, primary administrative coordinating centers, and central data collection and management.

To ensure that the ED operational perspective is included in the trial design, investigators should work with ED staff and include an ED investigator early in the protocol development. This will ensure that proposed trials are designed optimally for the ED environment and that only key interventions and data points

are included. For example, NETT has an executive committee and steering committees that determine the suitability of trials in the ED environment. They help to guide investigators during the trial design in an effort to maximize study efficiency.⁴

Finally, engaging EM staff and giving them some ownership over the trial (as co-investigators or with related potential publication opportunities) is an important way to improve successful implementation.¹⁴ Also, providing nonresearch clinical staff with feedback and thank you cards regarding patients they cared for in the study help develop awareness and good will for the trial within the ED.

RETENTION

Recruitment of participants is clearly a major hurdle for EM clinical trials, but if participants are enrolled and do not complete follow-up, attrition and bias become factors that affect study interpretation and eventual value. Attrition is defined as loss of numbers due to resignation or death and is problematic in clinical trials. Bias in terms of medical research refers to a systematic situation that could not be remedied by repeating a study over and over again. Attrition can contribute to bias when participants are not lost randomly, but reflect participants who have certain characteristics that sustain better or worse outcomes.⁵⁰⁻⁵² While randomization and intention-to-treat analysis should address issues due to termination, they cannot account for nonrandom treatment termination. For example, participants in one treatment could consistently feel so ill as a result of drug adverse effects that they withdraw from the study at a higher rate than another treatment group.

A key retention issue is time to follow-up of participants. Clearly, the longer the follow-up, the more participants will be lost. Selection of a short-term outcome (e.g., survival to hospital discharge) can alleviate some attrition, but concise short-term outcomes are not the focus of many trials. When long-term outcomes are needed, clear concise outcomes like death can often be accurately ascertained through the National Death Index and Social Security Death Index, even when participants appear lost to follow-up.³⁰

Due to the nature of acute conditions, not everyone presenting to the ED lives in the immediate area and is available for follow-up care. Some may be visiting and live out of state or the even out of the country; others may be transient by nature, and over time people move. If a study is multicenter, there may be an opportunity for patients to have follow-up at another site. If participants need to make study-specific visits, consideration should be made for participants who have physical and logistical difficulties returning for follow-up. Furthermore, the time and costs associated with return visits are key reasons for attrition and failure to recruit.⁵³ If participants are compensated for transportation costs and their visits are at no cost, they are more likely to remain in the study.⁵⁴

Other predictors of attrition include older age, male sex, lower education attainment, functional impairment, poorer cognitive performance, lower verbal intelligence,

greater comorbidities, and worse physical health.⁵⁵ Some examples of attritional factors in other NIH studies illustrate specific examples. The Baltimore Longitudinal Study on Aging is a longitudinal study initiated in 1958 to study physiologic, sociologic, and psychological changes with aging. Age, education, and distance from the center have the strongest association with attrition. Participants who lived 500 miles or more from the study center, were over 70 years of age, had less than a bachelor's degree, had poor perceived health, and/or had a greater probability of dropping out.⁵⁶

Despite attempts to minimize it, attrition will occur. Among large population-based epidemiology studies of older adults, attrition rates over 20% are frequently reported for those with multiple follow-up interviews. Among post-myocardial infarction patients, a mean withdrawal rate of 21% has been reported in longitudinal studies.⁵⁷⁻⁵⁹ It is implied that attrition of 5% or less is unlikely to lead to bias, but that >20% poses serious risks to study validity.⁶⁰ Perhaps of most relevance to EM clinical trials are the NINDS stroke trials that have shown how retention may be less of an issue for participants with more acute and severe strokes who stay locally for care. The Specialized Program of Translational Research in Acute Stroke, funded by cooperative agreements from NINDS, is a network of eight centers all running unique prospective EM clinical trials in major medical centers that serve diverse populations.⁶¹ Since 2002, seven of these centers have published results, with five of the seven having postdischarge follow-up of 90 days.^{41,62-65} All of the studies report high levels of follow-up at 3 months.

Factors that can help decrease attrition include informed consent that clearly conveys the full commitment required for participation in the trial; strong relationships between a study coordinator, care providers, and the participants; and consistency among research assistants in maintaining contact with the participants they have recruited.⁶⁶ The use of patient-centered techniques such as videotapes or parsimonious questionnaires that are not overly time-consuming and impart something interesting and of value to the participants can be helpful. The Women's Health Initiative is a study focused on the prevention of morbidity and mortality in declining quality of life in older women from diverse backgrounds. Issues of diversity and understanding clinical trials were essential. Basic communication and listening skills were studied, and strategies to improve retention were implemented, including careful data monitoring and feedback to centers, intensive staff training, psychological support, and educational workshops.^{67,68}

Participants should have follow-up and outcome assessments conducted at routine clinic visit times if possible. Office staff should be in close contact with participants and record telephone follow-ups in a log, keeping track of best times to contact the patient.⁵⁴ While it is generally ideal to have follow-up conducted in a controlled and consistent manner, participants may be seen by local physicians and have standard of care tests and assessments done remotely. This has been made easier with guidance from the Office of

Human Research Protections, which allows these centers to cooperate with follow-up requirements and not become technically engaged in research and thus bound by other IRBs and institutional subcontracts.^{39,69}

SUMMARY

The obstacles involved with recruitment and retention in emergency clinical trials are clear, and while we have outlined the best available strategies to address them, many of these are neither proven with evidence nor likely to work in all settings. Nonetheless, EM researchers will have to develop such strategies to demonstrate that they can recruit and retain patients. This is a necessary component of an application to receive funding and participate in EM trials and networks.

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