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Recruitment and Retention of Patients into Emergency Medicine Clinical Trials

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Abstract

The emergency medicine and pre-hospital 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 Emergency Medicine Clinical Trials (EMCT), and provides strategies from emergency medicine and non-emergency medicine 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 emergency medicine clinical trials.

Introduction

The United States spends 2 trillion dollars annually on healthcare 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. Projects and funding for research in this setting are not limited to the specialty of emergency medicine but often involving the collaboration of multiple specialties such as orthopedics, cardiology, pediatrics, and neurology both individually and as part of networks.

A search of ClinicalTrials.gov for “Emergency Department” clinical trials resulted in 691 open and closed studies, 312 currently seeking volunteers and 59 which are listed as NIH or other US Federal Agency funded[2]. A similar search of the Research Portfolio Online Reporting Tool (RePORT) listed 153 new research grants in 2009 supported by 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 National Institutes of Health (NIH). The Pediatric Emergency Care Applied Research Network (PECARN), is another emergency network funded by Health Resources and Services Administration/Maternal and Child Health Bureau’s (HRSA/MCHB) Emergency Medical Services for Children (EMSC) Program and Division of Research, Training, and Education (DRTE) [4–6]. Both the NETT and ROC networks offer opportunities for numerous locations to participate in clinical trials in the emergency department setting; NETT has 4 current projects and 17 centers and ROC has 4

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current projects and 11 clinical centers (Table 1). The PECARN network has four research centers each with multiple affiliated Emergency Departments (ED), comprised of 21 individual hospital that serve approximately 900,000 acutely ill and injured pediatric patients annually [6]. In addition, the National Institutes of Neurological Disorders and Stroke has launched the Clinical Research Collaboration (CRC), a project designed to encourage academic-based 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 emergency medicine 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 manuscript highlights these issues and discusses how to incorporate strategies into the study design and one's research infrastructure (Table 2). By understanding and addressing these issues we hope investigators can 1) increase the likelihood of funding and 2) implement successful emergency medicine clinical trials.

The Setting

The most recent public data from 2006 show that the volume of ED patients has increased by 36 percent 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 have a primary care provider [9]. ED's are also the gateway for the sickest patients who enter the hospital and healthcare system, being responsible for about 20% of hospital admissions[10]. The crowding and volume seen in emergency departments make them challenging environments to provide effective and timely care, apart from trying to incorporate clinical research [11,12].

However, the challenge and funding of research in the ED is 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 neurological and orthopedic imaging modalities when ordered by emergency department physicians[13].

Emergency medicine researchers will be called upon more to participate in this type of research and in turn receive more funding to do research in the ED setting. For researchers, particularly those not practicing in the 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 GCRC (general clinical research center), caregivers have neither the time nor resources to help with research. With this in mind researchers have to 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 practically cannot

be done 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 available for enrollment into their studies they should focus on specific strategies to enhance recruitment into their trial. Recruitment into EMCTs has three important elements: identification, consent/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, tPA for stroke, blood substitutes, hypothermia for acute brain injury, etc.). Researchers cannot expect 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 is 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 emergency departments 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 respond to specific clinical alerts through central paging [23]. For other conditions that do not include clinical alert pages, students (undergraduates, graduate or post-doctoral 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 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 screened. 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 (PHI). 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 electronic medical record 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 EHR's 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 allows for real-time notification based on HL-7 data. These software programs allow for instant notification to investigators[26] and has 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 MRIs. 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 help 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; National Center for Infections 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 utilizing 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 emergency medicine given their proven ability to screen and recruit.

Consent and Enrollment

The time frame available to recruit participants in EMCTs is often far shorter than 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 neurological impairment accompanying the acute disease. Consent by a legally authorized representative (LAR) of the patient is an option in these settings and are governed by various state laws and corresponding IRB's. However, EMCTs are still faced with seeking consent when family and/or the patient may not be available to consider participation in a clinical trial[35]. Furthermore, providers/investigators seeking the consent often have no established relationship with the family or patient. This relationship and trust is what many potential participants depend on when making medical decisions, including participating in clinical trials [36–38]. Those obtaining consent in the ED can be aided by aligning them with members of a treatment team for support. This includes getting treating physicians involved and utilizing 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 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 FAST-MAG Pilot Trial, 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 pre-hospital 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 (EFIC) has been used successfully to enroll participants into research in the pre-hospital and ED setting[42,43]. While somewhat controversial, EFIC allows under federal law (FDA final rule 21 CFR 50.24) for enrollment of participants into studies without prior consent when 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. To be considered for EFIC, obtaining informed consent prior to treatment must not be feasible because: the participants will not be able to give their informed consent as a result of their medical condition, the intervention under investigation must be administered before consent from the participants' legally authorized representatives is feasible and there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation in order to get consent in advance of the trial. Furthermore, the trial must meet the following criteria: it must be a life-threatening situation, available treatments are unproven or unsatisfactory, participation in the research holds out the prospect of direct benefit to the participants and the clinical investigation could not practicably be carried out without the exception. The study would be required to follow further IRB 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 emergency medicine 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 wide spread implementation difficult [45] 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, so does the likelihood of protocol violations[14]. That risk can be minimized with strict oversight by specific study coordinators[22], but it requires a 24/7 presence to enroll. 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 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 make sure that proposed trials are designed optimally for the ED environment and that only key interventions and data points be 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 in the ED environment[4].

Finally, engaging emergency medicine 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 non-research clinical staff with

feedback and thank you cards regarding patients they cared for in the study helps develop awareness and good will for the trial within the ED.

Retention

Recruitment of participants is clearly a major hurdle for EMCTs, but if participants are enrolled and don't 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 non-random treatment termination. For example, participants in one treatment could consistently feel so ill as a result of drug adverse effects that they withdraw 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 are available follow up care. Some may be visiting and live out of state/country, others may be transient by nature, and over time people move. If a study is multi-center 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 that have the physical and logistical difficulties returning for follow-up. Furthermore the time and costs associated with return visits is a key reason 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 gender, lower education, functional impairment, poorer cognitive performance, lower verbal intelligence and greater co-morbidities/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 aged >70, had less than a bachelor's degree, and/or had poor perceived health 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-MI patients, a mean withdrawal rate of 21% has been reported in longitudinal studies [57–59]. It is implied that 5% or less attrition is unlikely to lead to bias, but that >20% poses serious risk to the study validity[60]. Perhaps of most relevance to emergency medicine 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 (SPOTRIAS), funded by cooperative agreements from NINDS, is a network of eight centers all running unique prospective EMCTs in major medical centers that serve

diverse populations[61]. Since 2002, seven centers have published results; five of the seven having post-discharge follow up of 90 days [41,62–65]. All of the studies report high levels of follow up at three 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 in 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 (OHRP), which allows these centers to cooperated with follow-up requirements and not become technically engaged in research, and thus bound by other IRB’s and institutional sub-contracts[39,69].

Summary and Limitations

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, emergency medicine researchers will have to develop such strategies to demonstrate that they can recruit and retain patients. This is a necessary component of ones application to receive funding and participate in emergency medicine trials and networks.

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Table1

Networks with Ongoing Emergency Research

Network	Primary Focus	Year Started	Organization[1]	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	17 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 pre-hospital cardiopulmonary arrest and severe traumatic injury	2006	11 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	4 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	9 US divisions, 1 International division, 201 hospitals, CCC	8	http://www.emnet-usa.org/emnet_details.htm

[1] SDMC – Statistical and Data Management Center, CCC – Clinic Coordinating Center, DCC – Data and Coordinating Center

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 heath records	Alerts can be triggered on a variety of “trigger pints” including orders or results.	Not available in all EHR’s and requires expensive programming. Alerts usually require treating team to still call research team.
	Alerts through HL-7 feed	Alerts can be triggered on a variety of “trigger pints” including orders or results and be sent directly to research team for further screening	Requires institutional IT costs, foreign software installation and data sharing
Obtaining Timely Consent	Legally Authorized Representative (LAR)	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 & 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
	EFIC	Allows for treatment when patient or LAR consent in unavailable	Restrictions on use for emergency research
Implement Protocol	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

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

Abbreviations: HL-7 (Hospital Language -7), EFIC (Exception From Informed Consent), LAR (Legally Authorized Representative), IT (Information Technology), EHR (Electronic Health Record), SSDI (Social Security Death Index), NDI (National Death Index), IRB (Institutional Review Board)