**Chapter 47
Trauma-related research methodology**

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**Introduction**

Trauma is a very common EMS response. According to the National Emergency Medical Services Information System (NEMSIS) database, inuries accounted for 14.6% of EMS calls in 2012 [1]. Despite advances in the management of injuries over the last several decades, trauma remains the most frequent cause of death for Americans aged 1–44 and the fifth largest overall cause of death nationwide. Nearly 120,000 Americans died from unintentional injuries in 2010 [2].

Improvements in trauma care require research. Many of our beliefs and practices over the years have changed as a result of research that has challenged conventional medical wisdom. There are many examples of trauma therapies that were previously used but later were no longer considered to be the standard of care following research. These include pneumatic antishock garments, aggressive fluid resuscitation, and certain forms of airway management. Our recent wars in Iraq and Afghanistan have provided a new venue for observational trauma research that has yielded valuable insights. Of note, many of these trauma therapies can be used both in military and civilian trauma settings.

**Prehospital trauma study types**

There has been great interest in the last decade in providing evidence-based care in the EMS setting. This requires ongoing research efforts to establish a knowledge base that will support reliable conclusions regarding optimal EMS care and the development of valid and verifiable clinical treatment guidelines for providers.

Similar to any clinical research, prehospital trauma studies can be of a variety of types [3]. These include (in descending order of rigor):

* prospective randomized clinical trials (RCTs) (double-, single-, or unblinded)
* prospective/retrospective observational/cohort trials
* retrospective reviews/database analysis/case–control studies
* case series/case reports.

The “gold standard” in clinical research has been the prospective randomized double-blind clinical trial. In this type of study, patients are randomly assigned to one treatment arm or another and the outcomes of each treatment group are analyzed. If the clinical trial is designed so that the only difference between the two arms is the treatment modality being randomized, it makes it possible to know if the therapy provides patient benefit. The “blinding” ensures that the patient, the researchers, or both do not know into which group each patient is assigned. This blinding minimizes bias that could change other ways in which the patients in the two study groups are treated.

Randomized and blinded trauma clinical trials are difficult to conduct in the EMS setting because the consent and randomization procedures in this emergency situation are often not feasible. One early example of a prehospital trauma RCT is the 1994 study by Bickell et al. looking at the effects of the administration of IV fluid in trauma patients [4]. In this trial, hypotensive trauma patients who had sustained penetrating trauma were randomized on even days to receive standard infusions of IV fluid and on odd days to receive no IV fluids until mechanical control of hemorrhage was achieved in the operating room. In this study, consent to participate was “implied,” therefore informed consent requirements were waived, greatly simplifying enrollment in this study. (This approach to consent is no longer permitted in the United States.) A more recent example of a prehospital RCT is the 2009 study by Moore et al. of human polymerized hemoglobin in the treatment of traumatic hemorrhagic shock patients in the EMS setting [5]. This trial randomized patients to be resuscitated with either crystalloid or Polyheme, and was conducted using an exception to informed consent as per the federal regulation 21§CFR50.24 [6].

Cohort/observational studies provide clinical information despite the possibility of treatment and/or observational bias. In these studies, there is no “active” treatment intervention being randomized and evaluated. Instead, one or more groups (cohorts) are defined and patient outcomes evaluated based on the use of specific treatments. It is important to note that cohort/observational studies can be either prospective or retrospective. In a prospective cohort study, the study parameters, patient cohorts, and outcomes are defined before each group undergoes the treatment. In a retrospective observational study, the information being studied has already been collected but the study questions and outcomes of interest have not been established. In order to minimize bias in these retrospective studies, the researchers must define the patient cohorts and study outcomes prior to analyzing the database. Retrospective studies, although more prone to bias than prospective studies, are often easier to conduct because the data already exist, for example in a state trauma registry. An example of cohort analysis in trauma is a study by Holcomb et al. [7]. In this multicenter study, several groups of trauma patients receiving various transfusions of blood products were followed and their outcomes analyzed.

There are multiple databases available for analysis to EMS researchers. Because of the popularity of electronic patient care records, many EMS agencies now have databases available for research analysis of the patients to whom they have responded. Many states require hospitals to report to a state-wide trauma registry. In addition, many state EMS offices collect EMS data and provide a state-wide view of EMS activities. The NEMSIS database is a national compilation of EMS data, supplied by participating state EMS offices, and offers the broadest overview of EMS nationally.

While these databases can be a very valuable resource for trauma research, great care must be taken in study design to ensure valid conclusions can be drawn from the data. Database analysis can be prone to bias if the study parameters are not strictly defined before analysis takes place. “Data mining” is the analysis of a database for patterns prior to the formation of a hypothesis and strict study parameters. Although care must be taken to avoid unsupported conclusions, data mining can assist in developing hypotheses for future clinical trials if any observed differences in patient outcome are believed to be based on treatment differences.

Case–control studies compare two groups of patients whose outcomes differ. This research format is especially useful when the adverse outcome of interest is observed infrequently. The case group is matched to the control group only on a minimum number of variables, so that it is possible to examine which variables differ in the two patient outcome groups. These studies may quickly identify a characteristic or treatment that imparted the observed difference in patient outcomes between the cases and the controls. This format was used in the study by Shayne that examined the need for angiography in penetrating thigh trauma [8].

Case reports often are the starting point for the analysis of a case series or the initiation of a case–control study. The most important aspect of these reports is either the observation of a new disease or complication, or the potential benefit of a newly attempted therapy.

Data gathering and analysis of EMS patient care are performed as part of the quality assurance (QA)/performance improvement (PI) process needed to improve patient outcomes. In this process, a new protocol, medication, procedure, or device is implemented by the EMS agency after review of current medical literature and approval by its medical director, training officer, and other senior administrative personnel. After training of the EMS providers, this change is implemented and the outcome of the intervention is monitored as part of the QA/PI process. There is no control group, although sometimes the outcome may be compared to that of “historical controls,” a similar group of patients treated differently prior to the initiation of this new therapy. When studying the effects of a new therapy, it is often necessary to wait some period of time, after which it is likely that the new therapy being reviewed for quality has been fully integrated into the EMS system of care. This non-studied “wash-out period” helps to remove any inaccuracies that may influence the study outcome as a result of incomplete or inaccurate adoption of the treatment being studied as the system and providers become accustomed to it. This QA/PI process allows for the implementation of therapies with proven efficacy in the research setting. The subsequent QA/PI monitoring of patient outcomes allows EMS providers to compare current outcomes to those observed when other therapies were provided in order to establish that the new treatment approach enhances patient outcomes.

**Design issues in prehospital trauma studies**

**Patient informed consent**

Issues surrounding patient consent for participation in prehospital clinical trials are among the most difficult technical research issues to resolve. Federal law and investigational review board (IRB) policies regarding research on human subjects require that the patient provide informed consent before participating in a clinical trial in order to preserve the patient’s autonomy. This typically involves the patient being counseled about the medical issue being studied, the different therapies that may be provided, and the potential risks and benefits of participating in the clinical trial. This consent process allows the patient to make an informed decision about whether or not to participate in the clinical trial being proposed.

This issue is obviously problematic for emergency research in general [8], and especially in the prehospital setting, because the urgency of the patient’s condition often makes obtaining consent from either the patient or a legally authorized representative unfeasible. Trauma victims often are unconscious, in severe pain, or have unstable vital signs, all of which can impair their ability to make an informed decision about participation in a clinical trial.

Because the requirement for informed consent had the potential to prevent critical prehospital research from being performed successfully, the National Institutes of Health (NIH) and Food and Drug Administration (FDA) collaborated with clinicians interested in emergency research in establishing the rules that would allow for an exception to informed consent when it cannot feasibly be obtained. In federal regulation 21§CFR50.24, the United States government [8] has allowed for an exception to informed consent in certain emergency and prehospital studies. Once a patient who has been enrolled in such a study is stabilized, the study involvement can then be explained to the patient or legally authorized representative. At this later time, the patient or representative has the option to withdraw from the study but still be cared for by the clinicians who are the designated care providers. (See Volume 2, [Chapter 45](https://jigsaw.vitalsource.com/books/9781118990827/epub/OPS/Vol2/c45.xhtml) for details.) In the study of a hemoglobin solution in the management of traumatic hemorrhagic shock patients, the exception to informed consent rules were used for the first time [9]. Virtually all of the patients or family members agreed to continue participation in the trial [10]. The use of an exception to informed consent can be simplified with the use of scripts, algorithms, and a plan that allows patients to “opt out” of the study, even if they cannot provide informed consent to participate in the study [11,12].

**Inclusion and exclusion criteria**

Inclusion and exclusion criteria define the patient population being studied. The goal of these criteria is to establish a group of patients that is easily identified, clinically relevant, uniform in the expected outcome, and generalizable to patients treated in the clinical setting [13]. In many trauma studies, the initial decision must establish whether or not to limit the study population to patients with either blunt or penetrating injuries. This decision reflects the potential outcome differences that are seen in these two patient groups. Blunt trauma patients may have a greater spectrum of injuries (traumatic brain injury, chest contusion, pelvic fracture, and hepatic laceration, for example), whereas penetrating trauma patients may have multiple wounds based on the path of the projectile. In addition, the distinction can become blurred when a patient sustains combined penetrating and blunt injuries, such as may result from a blast injury.

There may be several advantages to including all trauma patients in an EMS clinical trial regardless of the mechanism of injury, including the speed of patient enrollment and the ability to apply the results to both patient subgroups. However, because outcomes differ in these two groups, this may interfere with the ability of the study to establish with certainty the effect of the intervention being studied. As a result, it is often prudent to conduct parallel clinical trials, one for patients with blunt trauma and the other for those with penetrating trauma.

Another research consideration is how terms such as “traumatic hemorrhagic shock” are defined. An analysis of the published literature will reveal standard definitions, such as hypotension being defined as a systolic BP <90 mmHg. The exclusion of patients with blood pressures that are not measurable is an important consideration, as the outcomes of traumatic arrest patients may be so poor that the effects of the study intervention would not be possible. The best approach is to define a population of traumatic hemorrhagic shock patients who could improve with optimal care, including the study intervention, but that also includes patients whose outcomes could suffer without optimal care. This situation provides the “clinical equipoise” necessary to establish a compelling clinical question and the justification for the use of an exception to informed consent.

Another important definition is which patients are “pediatric” and which are “geriatric.” Decisions regarding inclusion of children and the elderly in prehospital trauma research should be carefully considered. The differences in physiological responses to trauma in very young children and the elderly are well documented [14,15]. To account for these differences, the Trauma Score-Injury Severity Score (TRISS) method for predicting outcome in trauma includes age as a factor in its calculation [16]. It is common in prehospital trauma studies to include only patients whose ages fall in the 18–65 range. The disadvantage to this approach is that the research generates inadequate knowledge about the potential benefit of the study interventions to children and the elderly. In order to most accurately evaluate the benefit of clinically effective therapies in these special populations, clinical trials can be subsequently conducted where efficacy is determined in the <18 and >65 age groups.

Researchers should consider excluding patients from clinical trials when injuries render them not likely to survive, regardless of treatment with the investigational therapy or standard therapy. Inclusion of these critically ill patients who have non-survivable injuries could bias the results towards showing no difference in outcome when one actually exists. Patients with these critical injuries include those with severe traumatic brain injury (Glasgow Coma Scale score less than 5), traumatic arrest with no recordable blood pressure, and other signs of likely demise.

**Randomization and blinding**

The ideal RCT incorporates rigorous randomization procedures to ensure that patients are not preferentially entered into one or the other treatment arm of the study. There are many techniques for randomization. One common technique is simple alternation of treatment based on the day of the week or even/odd dates. This method is simple and easily remembered by the EMS personnel performing the interventions. However, there is the possibility of a treatment bias by the medics in knowing ahead of time how a patient will be treated that day. A better technique is the opening of an envelope to reveal the treatment arm for a particular patient after the decision is made to enroll. Another method is to contact direct medical oversight or dispatch for random assignment of a treatment arm to a particular patient, eliminating possible bias by the treating personnel. Once randomization occurs, it is necessary to analyze the data using an “intention to treat” design, whereby all patients randomized to a therapy are analyzed as if they received that therapy, even if that therapy was not provided for some reason. This analysis method will allow for an adjustment in outcome that could occur due to bias in the delivery of the therapies in the clinical trial.

The ideal RCT also involves blinding of the trial participants. In a double-blinded trial, neither the patient nor the treating health care providers, including the EMS crew, know which treatment the patient is receiving. In a single-blind study, either the patient or the provider does not know which treatment is being provided. It is sometimes easier to blind a medication by using an identical-looking placebo or active medication that is provided by the research team. For example, a nebulized medication could be provided that is prepackaged and visually identical in both treatment arms, but half of the randomization packages contain standard therapy (for example, albuterol) and the other half contain the study medication, either in place of or in addition to the albuterol. It is often difficult to blind the treatment being studied in trauma clinical trials if a procedure such as intubation is involved or if the use of a blood product is being studied.

**Establishing the clinical therapy of standard care patients**

Another important aspect of clinical trials research is the establishment of how the care of those who are treated in the standard care group is provided. This is especially true if the providers are aware of which treatment group a patient has been assigned to. When there is not double-blinding, it is necessary to either establish how the standard therapy group is treated (e.g. infuse 3 L of normal saline for all patients whose initial SBP is <90 mmHg) or to what endpoint therapy will be provided (e.g. infuse normal saline until the SBP is >100 mmHg). This will ensure that the allocation of therapies that are not being studied does not bias the results such that the benefit of the therapy being studied is either obscured or enhanced.

**Selection of outcome measures**

The proper selection of outcome measures is another aspect of trauma clinical trials that is essential to understanding the efficacy of a therapy under study. A study that identifies an outcome that is not clinically relevant may not lead to a change in the standard of care. Outcomes of interest may be those that are either globally relevant, such as 30-day survival, or incrementally important, such as survival to the emergency department, operating room, or intensive care unit. Although survival is a simple and non-biased outcome measure, its use may not allow for the future use of therapies that provide less dramatic benefit, such as improved 24-hour survival. When mortality is used in trauma studies, the survival of a patient treatment group can be estimated using the TRISS method, and this estimated survival compared to the survival of the treatment group that receives the intervention or therapy under study.

Another well-accepted and reproducible outcome measure, relevant to prehospital traumatic brain injury and stroke research, is the Cerebral Performance Category (CPC) [17,18]. This score has proven useful in measuring the outcomes of brain-injured patients. Other examples of common outcome measures in trauma clinical trials are endotracheal intubation and operative intervention rates, morbidity as measured by organ dysfunction scores, intensive care unit days, and total hospital days.

In retrospective studies, the goal is often to describe the outcome of a current practice, so that future prospective research can clarify the effect of a change in this practice. For example, how much saline is normally administered in the EMS setting or the ED for trauma patients who present with traumatic hemorrhagic shock? This information regarding *current* standard practice could allow prospective trauma studies to be better designed so that new therapies can be identified and tested against the current standard.

In an excellent discussion of clinical research study design, Hanson has the following recommendations regarding outcome measures [19].

* They should be directly tied to the specific aims and capable of measuring the outcomes of interest.
* They should be important to patients.
* Patient-reported outcomes should be considered.

The issue of outcome measures that are important to patients has become more prominent recently [20]. They have been described as qualitative outcome measures or patient-reported outcome measures (PROMs). This process often involves the patient completing a questionnaire or survey after participation in a clinical trial to get his or her perspective on the outcome. These qualitative outcome measures can be combined with the more common quantitative measures in a study. This approach can help ensure maximum clinical and therapeutic relevance to study outcomes.

**Other considerations for prehospital trauma research**

Considerations unique to prehospital trauma research, as opposed to research that occurs in a hospital environment, include issues related to the local, regional, or state trauma system; interactions between multiple EMS agencies; direct medical oversight; and transport of patients to facilities that are not part of the participating trauma system.

**Involvement of the EMS system**

Each EMS agency is part of a larger EMS system. This system includes the 9-1-1 dispatch centers, multiple EMS agencies, and the local trauma centers and non-trauma facilities. Together, these different entities participate to form the complex system of emergency care found in most parts of the United States. As a result, prehospital trauma research projects must account for the participation of all these separate components of the system. A prehospital trauma research project may well affect the dispatchers, multiple EMS agencies, and the receiving trauma centers, some or all of whom may participate directly or indirectly in the project. The researcher must anticipate the possible effects of the project on the involved agencies and, at a minimum, inform them of the project. Alternatively, representatives from each of the involved trauma system components may be brought in to participate in the project planning discussions to solicit ideas and support for the project, and discuss effects of the project on each segment of the system. Getting such “buy-in” from as many of the involved agencies as possible early in the project can help avoid problems and misunderstandings later, and help assure smooth execution of the research.

**Single versus multiple EMS agencies and trauma centers**

Similarly, the project researchers must decide early in the planning whether to involve one or more than one EMS agency and trauma center. Depending on the design of the local trauma system, possible study patients may be brought to a number of local trauma receiving hospitals. By including multiple EMS agencies and/or multiple trauma centers in the study, the researchers will be able to recruit patients from a larger population, thus speeding the execution of the project and increasing the number of patients studied. In addition, this broader population will increase the generalizability of the results and minimize the possibility of bias that is inherent in a single-facility study, where treatment protocols may be specific to that institution.

However, the management of the project is made more complicated by involvement of multiple facilities or EMS agencies. More personnel must be trained to carry out the project, and the possibility of protocol violations increases, as the study protocol may be interpreted slightly differently in each location. In addition, the logistics related to updating each site on any changes in the study protocol or any problems encountered are increased with the involvement of multiple sites. The best way to overcome these challenges is to establish an oversight committee, made up of dedicated coinvestigators at each agency and hospital. Each member of this committee would then be responsible for keeping his or her site up to date on the protocols and progress of the study and supervising the execution of the study locally.

Early decisions must also be made regarding the enrollment of patients who are transported to non-participating hospitals or trauma centers. Depending on the degree of involvement of the hospital in the study, this may or may not have significant effect on the protocol. For example, if a study only involves the prehospital use of a new tourniquet, with the outcome measure being the estimated blood loss prior to arrival to the ED, then the study protocol can be completed and fully documented during the prehospital phase. In this case, which hospital the patient is delivered to would not necessarily be relevant to the study. However, if the study outcome is the rate of admission of the patients or length of stay in the ED, then involvement of the hospital is critical to protocol completion and recording of data. In such a case, the delivery of the patient to a hospital that is not participating in the study may result in that patient being lost to follow-up. Since it can be difficult to determine hospital destination, especially in a larger urban area with multiple trauma centers, it is generally best to have as many receiving trauma centers formally participate in the study as possible in order to maximize study recruitment.

**Roles of direct medical oversight**

Particularly in areas with centralized medical oversight for trauma patients, direct medical oversight can provide support for prehospital trauma research. This support can include assistance with destination decisions, randomization of participants, or contact with receiving hospitals to ensure protocol compliance and facilitate data gathering for study participants [21,22]. Recent developments involving telemedicine, still image transmission from the scene, and real-time video streaming hold new promise for the active involvement of direct medical oversight in the prehospital care of the trauma patient and associated research [23].

**Data analysis and trauma severity scoring**

Various techniques of data analysis are available to the prehospital trauma researcher. The general purpose of data analysis is to report the effects of a treatment or intervention under study or to define factors that are associated with improved patient outcomes [24]. In studies that involve survival as the outcome measure, logistic regression analysis can be used to establish the influence of other variables that affect patient survival, such as age, trauma mechanism, presence of head trauma, initial vital signs, overall injury severity, and other trauma outcome predictors. The Revised Trauma Score is often used to assess the initial physiological status of the trauma patient, as it is based on the initial Glasgow Coma Scale score and vital signs that are immediately available to EMS providers [25].

The standard method of adjusting for anatomical injury severity is calculation of the Injury Severity Score (ISS) for each patient. This score, originally described in 1974 [26], is an anatomical scoring system based on assigning an Abbreviated Injury Scale (AIS) score for each of six body areas. The three highest AIS scores are then used to calculate the overall ISS. The ISS correlates well with subsequent morbidity, mortality, and other measures of patient severity. However, it cannot be calculated in the field or ED.

Other measures of trauma severity have been reported that may be of value in prehospital trauma research. These include changes in vital signs [27], shock index [28], point-of-care lactate [29], and the field trauma triage guidelines developed by the Centers for Disease Control and Prevention [30].

**Military prehospital trauma research**

The military has always had a pivotal role to play in trauma research, including battlefield and out-of-hospital care. The concentrated trauma management experience available on the battlefield has helped physicians and surgeons develop better treatment strategies for centuries. Experiences from past wars, particularly World War II, Korea, and Vietnam, led to improvements in prehospital care concepts that were translated into civilian care systems.

A major improvement in military field research capability, the Joint Theater Trauma Registry (JTTR), was implemented during the Iraq war. This database of individuals injured or killed in battle in Iraq and Afghanistan has been a remarkable resource and allowed both military and civilian researchers to better evaluate therapies that were fielded. For example, the universal and aggressive use of tourniquets in these conflicts was controversial when introduced. However, the military experience with tourniquets was well documented in the JTTR. As a result, Kragh and colleagues were able to document a remarkable decrease in mortality and minimal morbidity with the widespread tourniquet use [31]. As a result of this positive and well-documented result on the battlefield, many civilian EMS systems have begun using tourniquets for severe extremity hemorrhage.

Another example of this use of the JTTR for evaluation of military trauma care resulted in discontinuation of what initially appeared to be a promising treatment: the use of factor VIIa for traumatic hemorrhage. Initial research demonstrated a potential for decreased bleeding and improved mortality in critically injured patients. However, after fielding VIIa to combat hospitals, patients were discovered to have an increased incidence of thromboembolic events, especially when undergoing long transport to Germany and the US. As a result of monitoring the outcomes of patients receiving factor VIIa in combat, made possible by the JTTR, as well as concurrent civilian trauma center experiences, updated recommendations were issued restricting the use of this treatment [32,33].

The use of the JTTR by the military has allowed for more accurate and timely changes in the treatment of soldiers and others on the battlefield. In addition, partnership with civilian trauma researchers, such as the American College of Surgeons Committee on Trauma, has given military medical leaders the information they need to regularly update field trauma treatment guidelines. These performance improvement efforts have contributed to the lowest battlefield mortality rates in history [34].