Volume 2

**Chapter 46
Cardiac arrest-related research methodology**

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**Introduction**

Each year, EMS professionals assess about 360,000 patients who are in cardiac arrest [1]. Resuscitation is attempted for about 60% of those assessed. Over the past decade, the median survival rate to hospital discharge for all patients with attempted resuscitation has slowly risen from about 5% to about 10%, with individual systems reporting rates between 3% and 16% [1–4]. Despite significant efforts devoted to improving survival from out-of-hospital cardiac arrest (OHCA) since 2000, a large gap remains between research on the disease and its effect on public health [5]. This chapter will review some of the issues that investigators should consider when developing OHCA clinical research.

**Consistent definitions**

Since its introduction in 1991, the Utstein style has become the gold standard for reporting data from OHCA [6]. This system of uniform terms and definitions for resuscitation reporting, last updated in 2014, allows useful comparison of outcomes among systems of out-of-hospital care across a plethora of countries [7]. Aspects of the Utstein style are controversial. For example, there is wide variation in classification of the etiology of cases. When hospital and autopsy information is available, investigators will discover that many patients have a diverse set of causes in addition to heart disease compared to a determination based only on the EMS records [8].

A challenge is differentiation of cardiac arrest from simple syncope. Cardiac arrest is the sudden onset of lack of blood circulation leading to unresponsiveness. Although patients are commonly apneic on EMS arrival, an agonal respiratory pattern is often present early in the evolution of an arrest [9]. A cardiac arrest event persists longer than several seconds and generally does not resolve spontaneously. Cases lasting only a few seconds most likely represent syncopal episodes rather than true cardiac arrest. Although rarely the patient is revived with only a brief period of cardiopulmonary resuscitation (CPR), therapy in addition to chest compressions and ventilation is typically needed to restore spontaneous circulation [10]. From a practical point of view, the simplest approach is to include cases in which EMS provided chest compressions or a shock with a defibrillator.

**Exclusion criteria**

There is wide variation in the reported incidence of EMS-treated cardiac arrest, ranging from 48 to 70 cases per 100,000 population per year [2]. This difference has been primarily attributed to variations in case ascertainment but real differences in incidence rates likely exist among communities, such as variations in prevalence of heart disease among populations and a general decline in the incidence of ventricular fibrillation (VF) outside the hospital [11]. Those patients obviously dead at the scene should ideally be tracked even though they have no chance of successful resuscitation, in order to verify case ascertainment approaches. These include patients with rigor mortis, decapitation, or dependent lividity on the arrival of EMS responders ([Table 46.1](https://jigsaw.vitalsource.com/books/9781118990827/epub/OPS/Vol2/c46.xhtml#c46-tbl-0001)) However, these cases are not included in the denominator of survival statistical analyses.

[**Table 46.1**](https://jigsaw.vitalsource.com/books/9781118990827/epub/OPS/Vol2/c46.xhtml#R_c46-tbl-0001) Possible exclusion criteria

| **Etiology independent** | **Etiology related** |
| --- | --- |
| Rigor mortis | Traumatic cause |
| Decapitation | Drowning |
| Dependent lividity | Accidental hypothermia |
| Do not resuscitate order | Asphyxia |
| Age <18 years | Toxic ingestion or overdose |
| Prisoner | Electrocution |
| Pregnant | Sepsis |

When the Utstein style was proposed, only arrests of cardiac etiology were included to maximize comparability between studies. Determination of cardiac etiology is often accomplished retrospectively through history obtained from family members, secondary survey physical examination, hospital chart review, autopsy reports, and EMS run records. Accurate determination of cardiac etiology is unlikely in some cases with only EMS records [8]. As a result, the Resuscitation Outcomes Consortium has chosen to track all cases without obvious trauma regardless of etiology.

With the declining incidence of VF, the proportion of OHCAs that are of non-cardiac etiology appears to be increasing. That may be sufficient reason to pay more attention to the care of these complex patients [12]. Some researchers point out that a patient who has a pulse following a shock by an automated external defibrillator (AED) used by a member of the public prior to EMS arrival and who does not receive any EMS CPR does not directly benefit from EMS cardiac arrest care; but most investigators include those patients.

Patients with advance directives indicating their desires to avoid any resuscitative efforts should also be excluded from research studies. Often these patients may initially receive treatment only to have resuscitation preemptively terminated once EMS learns about the advanced directive.

The pediatric population presents additional challenges for OHCA investigator. The incidence of cardiac arrest in this population is low; data suggest that fewer than 1,000 children experience out-of-hospital VF events per year in the entire United States [13]. Additional ethical and consent issues are raised when dealing with children younger than age 18, and accurate determination of age is not always possible during sudden cardiac arrest. The latest edition of the Utstein reporting guidelines includes a section on pediatric cardiac arrest [7].

**Population description**

The reader’s ability to compare results across different studies relies upon an accurate description of the patients included in the study, such as their age, sex, geographic locale, and EMS response. Factors such as previous cardiac disease, other comorbidities, tobacco use, and family history may also be useful, although they may be more difficult to obtain [14]. A standard approach to describing patients who were included and excluded can often by achieved by using the Consolidated Standards of Reporting Trials (CONSORT) patient flow diagram [15].

A description of the location (e.g. home or EMS vehicle) and witness status of the arrest should be included ([Table 46.2](https://jigsaw.vitalsource.com/books/9781118990827/epub/OPS/Vol2/c46.xhtml#c46-tbl-0002)). The description of the EMS system in which the study was conducted and the associated population density (rural, suburban, or urban) are relevant because these characteristics may affect the results of the study and will assist the reader with determining its generalizability. For example, a study of a device for supporting circulation likely will be doomed to failure if the trained responders cannot be at the patient’s side until 25 minutes after the patient’s collapse [16]. Ideally, the number of potential first responders and paramedics should be reported so that the frequency of exposure of individual EMS professionals to cardiac arrest events can be estimated [17].

[**Table 46.2**](https://jigsaw.vitalsource.com/books/9781118990827/epub/OPS/Vol2/c46.xhtml#R_c46-tbl-0002) Arrest characteristics

| **Location** | **Witness** |
| --- | --- |
| Home/residence | Spouse |
| Extended care facility | Family member |
| Medical/dental clinic | Bystander |
| Public/commercial building | Off-duty medical personnel |
| Workplace | On-duty fire/police personnel |
| Educational institution | EMS |
| Outdoors |  |

**Data collection and reporting**

Established in 1991 as the metaphor for describing emergency cardiovascular care, the “chain of survival” may assist the researcher in arriving at clinically relevant conclusions [6]. In 2010, a fifth link was added to the chain: immediate recognition and activation of help, early CPR, rapid defibrillation, effective advanced life support, and integrated postarrest care [12]. Many well-conducted clinical OHCA studies concentrate on one specific link in the chain in order to test the effectiveness of a particular intervention. Other investigators choose to test a “bundle” of interventions, affecting several links in the chain, that show promise of acting together to improve outcomes.

One of the primary challenges to implementing cardiac arrest research is the fact that the disease is exquisitely time-sensitive and time data are generated from multiple different sources. For example, the emergency medical dispatch center clock often displays a time that is different from the time on the responder’s watch or on the defibrillator used in the resuscitation [18]. Time synchronization of devices and clocks used in the EMS system allows for accuracy in the recording and reporting of relevant events. Most defibrillators currently available will synchronize their clocks automatically when ECG waveform data are downloaded from the defibrillator to a computer.

All results should be reported in terms of intervals (i.e. the difference between event times) in order to ameliorate any ambiguity regarding terminology. For example, the call receipt-to-first-shock interval represents the difference between the time the 9-1-1 call was received and the time the first defibrillation was attempted. Time points such as call receipt, EMS dispatch, defibrillator application, and shock delivery are reliably recorded electronically. Ideally, time intervals should be reported in minutes and seconds.

Defibrillators can be purchased with voice recording capability, and use of voice recording significantly enhances decoding of the events during a resuscitation attempt. If voice recording is available throughout the resuscitation process, times for arrival at the scene, EMS administration of CPR, return of spontaneous circulation (ROSC), invasive procedures and medication delivery, scene departure, and emergency department arrival may all be reliably extracted [19].

Bystander accounts of collapse time and administration of CPR are important data points. Unfortunately, these reports are unlikely to be synchronized or accurately recorded. Reliable information may be obtained through witness interview via the telephone after the event is over [20].

Electronic capture of cardiac rhythm information is relatively easy. When captured electronically, ECG information is available for in-depth digital signal analysis [21]. Ideally, the presenting rhythm should be ascertained through blinded review of rhythm strips. Specific methods for adjudicating differences in opinion should be explicitly outlined. For example, 1 mm of amplitude deflection is commonly used as the cut-off for fine VF versus asystole [7].

Electronic data capture also allows assessment of the quality of chest compressions and ventilations provided to the patient [22]. Given the important effect that chest compression quality has on patient outcomes, a research design that does not collect this information is substandard. Measuring and improving chest compression quality may make the difference between a positive and negative trial because medications given but not circulated will not be effective.

**Outcome assessment**

Relevant outcome measures in the study of OHCA include survival, ROSC, neurological status, and quality of life. For example, the researcher may be interested in different outcomes when judging defibrillator performance as opposed to testing prehospital administration of therapeutic hypothermia [23,24].

Survival is one key endpoint in most cardiac arrest clinical studies. Alive at hospital discharge is the simplest survival data point to collect. Thirty-day, 6-month, and 1-year survival represent more rigorous endpoints because patients may be discharged to extended care facilities due to severe neurological impairment and then die within 30 days.

The use of ROSC is controversial as a patient-centered outcome. Spontaneous circulation is obviously necessary to achieve survival, but it is a less interesting outcome from the point of view of the patient compared to neurologically normal long-term survival. Nonetheless, it represents an important first step. If an intervention cannot improve ROSC, it is unlikely to improve 30-day survival. Clinically significant short-term survival may be defined as survival to 4 hours after the initial call for help.

When evaluating outcomes, the researcher must be aware of the potential effect of the intervention being tested. For example, what constitutes “successful” defibrillation? In the truest sense of the term, defibrillation means termination of VF, whether that results in asystole or more organized electrical activity. Survival may not be an appropriate endpoint when testing a defibrillator because multiple factors in addition to defibrillator function may affect a patient’s survival.

An important adjunct to survival as an endpoint is the neurological status of the patient, both short and long term. The clinical neurological examination including objective, functional, and cognitive assessments provides a useful tool for neurological evaluation. The Cerebral Performance Category is a simple standardized tool for the assessment of both cerebral and overall neurological performance ([Table 46.3](https://jigsaw.vitalsource.com/books/9781118990827/epub/OPS/Vol2/c46.xhtml#c46-tbl-0003)) [7]. This assessment can often be made via simple chart review. However, it lacks precision. More objective scales such as the modified Rankin Scale are more sensitive but require contact with the patient [25].

[**Table 46.3**](https://jigsaw.vitalsource.com/books/9781118990827/epub/OPS/Vol2/c46.xhtml#R_c46-tbl-0003) Cerebral Performance Category Score

| **Cerebral performance** | **Overall performance** |
| --- | --- |
| 1. Good performance | Conscious. Alert, able to lead normal life. May have minor psychological or neurological deficits. May have mild functional disability from non-cerebral organ system |
| 2. Moderate disability | Conscious. Sufficient cerebral function for part-time work in sheltered environment or ADLs. May have moderate cerebral disability alone or moderate disability from non-cerebral organ system. Performs ADLs |
| 3. Severe disability | Conscious with at least limited congition. Dependent on others for daily support because of severe brain dysfunction. May have severe cerebral disability alone or from non-cerebral organ system |
| 4. Coma, vegetative state | Not conscious. Unaware of surroundings. No interaction with surroundings |
| 5. Death | Certified brain dead or dead by traditional criteria |

ADLs, activities of daily living.

Quality-of-life evaluation is an excellent patient-centered outcome. Separating health-related issues from overall quality of life may be challenging because many confounders such as economic factors or interpersonal relationships may affect these assessments. While there have been studies assessing the quality of life among survivors of OHCA, much remains to be learned [26].

**Outcome sources**

Sources of outcome information are as widely variable as the outcomes themselves ([Box 46.1](https://jigsaw.vitalsource.com/books/9781118990827/epub/OPS/Vol2/c46.xhtml#c46-fea-0001)). When planning to access medical records and other data sources, researchers must clarify requirements regarding consent with respective institutional review boards. Once permissions are obtained, the researcher may access information in medical records, death registries in local communities or states, online obituaries, or the Social Security Death Index. Searching multiple sources may help ascertain all outcomes [27]. Researchers, with such approval, may contact patients, their families, or their primary physicians directly for outcome information.

**Box 46.1 Outcome sources**

* Medical record review
* EMS coordinator
* EMS run record review
* Social Security Death Index
* Community or federal death registry
* Coroner’s office
* Primary physician interview
* Patient/family interview

**Quality control**

Quality control is essential in a clinical study. Regular audits should be performed to ensure that the data collected are accurate. Sponsors of studies evaluating new drugs, biologics, and devices are required to monitor these studies.

Data and safety monitoring boards (DSMBs) monitor clinical trials involving interventions that entail potential risk to the participants. The primary responsibilities of the DSMB are to periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and efficacy when appropriate, and to make recommendations concerning the continuation, modification, or termination of the trial. The DSMB members consider study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study. If at any point during the study, profound benefit or detriment to patients is discovered, the DSMB will make a determination about terminating the study and reporting the data.

**Conclusion**

OHCA researcher has the opportunity to have an important effect on the lives of thousands of patients. Following well-established study design principles helps ensure that meaningful results are obtained and that patient outcomes are ultimately improved.