RESUSCITATION OUTCOMES CONSORTIUM REGISTRY

PROTOCOL (EPISTRY)

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RESUSCITATION OUTCOMES CONSORTIUM REGISTRY

A. SPECIFIC AIMS

Overview

Out-of-hospital cardiac arrest and life-threatening traumatic injury are common, serious, debilitating and costly public health problems. The Resuscitation Outcomes Consortium (ROC) consists of ten Regional Clinical Centers and a Data and Coordinating Center (DCC). The University of Washington Clinical Trial Center serves as the DCC. The Consortium was funded by the National Heart Lung Blood Institute and other government agencies to conduct a series of large randomized trials to evaluate the effectiveness of interventions for these disorders. Additional funding has been obtained from the American Heart Association to offset the cost of extending ROC activities to include a registry to define the true burden of cardiac arrest. Also, the National Center for Injury Prevention and Control, Centers for Disease Control and Prevention will provide in-kind scientific expertise during the first year and may provide additional funding in subsequent years to define the true burden of life-threatening traumatic injury. These burdens are, at best, only crudely known. Whether and how EMS process, geographic, socioeconomic and periodic variation are associated with differences in outcome is unknown. This can be largely attributed to the absence of any internationally–representative epidemiologic database that includes outcome. Since patients at higher risk of poor outcomes are often excluded from clinical trials, estimation of the burden of illness based on those enrolled in ROC trials is subject to bias. Knowledge of factors related to specific episodes, together with regional factors including EMS system factors and outcome is a first step toward the development, implementation and evaluation of interventions to improve outcomes associated with these illnesses.

The overall goal of the proposed study is to supplement our existing DCC grant to implement a comprehensive and ongoing data infrastructure during the remaining four years of ROC activities, and to extend the work of ROC to include an EMS-based registry of out-of-hospital cardiac arrest and life-threatening traumatic injury in participating ROC sites to facilitate the ROC interventional trials. The DCC was aware of the potential value of a ROC Registry (and discussed it in our original coordinating center application) because of our previous experience with the use and value of registries alongside clinical trials (e.g., CAST trial, AVID trial). In both cases, the registries facilitated the efficient conduct of the trials, interpretation of their results, and were a rich source of data for hypothesis generation. However, the necessity of a ROC Registry has only become apparent since the sites and coordinating center for this trials network were selected and began to work out the details for proposed intervention trials. It has become clear that the effort required to set in motion the infrastructure for conducting and collecting EMS data is far more complex than that of other clinical trials and once in place is far more efficient to continue between protocols.

Aims of the Registry are to establish whether the results of ROC trials can be generalized to the population at large that experiences cardiac arrest or traumatic injury; to more fully establish the burden of these illnesses; the relationship between variation in EMS structure and process, regional factors such as geographic area or socioeconomic status, periodic factors and outcome. Included will be patients who experience out-of-hospital cardiac arrest or life-threatening traumatic injury and are evaluated by organized emergency response personnel at any level. For the purposes of this study, the designation Emergency Medical System (EMS) includes any and all levels of organized emergency response. We anticipate that participating sites serve a population of about 24,500,000 and will enroll about 17,500 cases of cardiac arrest and about 13,000 cases of trauma with impaired physiology in the field annually. Estimated survival to discharge will be 5.57% after cardiac arrest. Estimated mortality will be 16.55% after trauma with impaired physiology in the field. With these incidence and outcome rates, we will have 88%, 90%, 99% and 91% power to detect risk differences of 2.5/100,000 in the annual rate of cardiac arrest, 2.5/100,000 in the annual rate of traumatic injury, 1% in survival to discharge after cardiac arrest, and 1.5% in mortality after traumatic injury.

SPECIFIC AIM 1

To establish a comprehensive ongoing data infrastructure to facilitate the design, implementation and interpretation of ROC trials.

Hypothesis 1: The null hypothesis is that the characteristics of enrolled and non-enrolled patients are identically distributed.

SPECIFIC AIM 2

To define the incidence and outcome of out-of-hospital cardiac arrest and life-threatening traumatic injury.

Hypotheses 2a: The null hypotheses are that the EMS-based incidence of cardiac arrest and injury are identically distributed from year to year.
Hypotheses 2b: The null hypotheses are that the survival to hospital discharge after cardiac arrest and for injury are identically distributed from year to year.

SPECIFIC AIM 3

To describe the relationships between resuscitation performance and EMS structure, adjusting for episode-specific factors.

Hypotheses 3a: The null hypotheses are that the EMS process of care and structure for cardiac arrest and injury are identically distributed from agency to agency, both before and after adjustment for episode-specific factors.
Hypotheses 3b: The null hypotheses are that the EMS process of care and structure for cardiac arrest and injury are identically distributed from year to year, both before and after adjustment for episode-specific factors.

SPECIFIC AIM 4

To evaluate the relationships between outcome and patient, EMS, regional, and periodic factors.

Hypotheses 4a: The null hypothesis are that EMS structures will not be predictive of outcome, after adjustment for episode-specific factors including resuscitation performance.
Hypotheses 4b: The null hypotheses are that geographic and socioeconomic factors will not be predictive of outcome, after adjustment for episode-specific factors.
Hypotheses 4c: The null hypotheses are that circadian and seasonal factors will not be predictive of outcome, after adjustment for episode-specific and regional factors.

B. BACKGROUND AND SIGNIFICANCE

Overview of the Resuscitations Outcomes Consortium (ROC)

The Resuscitation Outcomes Consortium was established in 2004 by the National Heart Lung and Blood Institute of the National Institute of Health, in partnership with the Institute of Circulatory Respiratory Health of the Canadian Institutes of Health Research and other agencies. The goal of the ROC is to conduct clinical research in the areas of cardiopulmonary arrest and life-threatening traumatic injury. The ROC has the necessary infrastructure to conduct multiple randomized trials to aid rapid translation of promising scientific and clinical advances to improve resuscitation outcomes. Our focus on prehospital interventions recognizes the common epidemiology and physiology of cardiac arrest and trauma, as well as the time-dependent nature of treatment of these disorders.

Clinical trials will evaluate existing or new therapies (such as pharmacologic interventions, strategies of fluid resuscitation, or the use of immune modulators), clinical management strategies (such as bleeding control strategies, the use of cerebral protection, metabolically-directed therapies, and alternative CPR approaches), or a combination of the two. Consortium investigators will conduct trials of variable size and duration (equally

directed towards the cardiac and trauma populations). The ROC has an initial commitment of five years of funding, with a possibility of renewed funding.

Need to Facilitate ROC Intervention Trials

Baseline data submitted by the participating ROC sites demonstrate large and potentially important variations in the incidence and outcome of cardiac arrest and major trauma as well as EMS practices used to treat them. Failure to control for factors that account for some of these differences will increase the sample size of and may bias or confound the results of ROC intervention trials. For example, ROC investigators are currently designing a trial to assess the effect of an impedance threshold valve that is intended to increase venous return during cardiopulmonary resuscitation (CPR). Provision of good CPR is likely necessary to optimize the effect of the valve, but some ROC sites train their providers to analyze and defibrillate as quickly as possible whereas others train them to provide CPR for at least 90 seconds before analysis and shock. Non-random distribution of early analysis versus late analysis, or other differences in EMS process, among patients participating in the trial of the valve would reduce our ability to detect whether it is effective. Randomization of individual episodes of cardiac arrest to early analysis versus late analysis is not feasible due to the emergent nature of the event. The loss of compliance caused by the confusion of having an EMS provider alternate between the basic concept of assiduously assessing rhythm and defibrillating initially or aggressively doing CPR initially can be easily appreciated. Indeed a previous trial in the out-of-hospital setting confirmed that individual randomization of episodes to alternate treatment strategies can be associated with a high rate of protocol violations due to contamination or crossover.(1)

An alternate approach to controlling for differences in EMS process across ROC agencies is to allocate the same intervention(s) to clusters or groups of patients. For example, ROC investigators are currently designing a cluster randomized trial to assess the effect of an early analysis versus late analysis using EMS agencies as the cluster unit. Cluster randomization or randomization of individual episodes both require unbiased identification of whether patients are eligible. Since all episodes in a cluster receive the same intervention, ascertainment of 100% of episodes is necessary to prevent such bias. Similar arguments can be made for ascertainment of major trauma episodes. At present no ROC EMS agency has the infrastructure in place to capture all out-of-hospital cardiac arrest and major trauma episodes. Therefore a registry is necessary to establish a streamlined and persistent method of episode notification to reduce the potential for bias in ROC intervention trials.

Burden of Illness

Sudden Cardiac Arrest (SCA) **–** It is unclear how often cardiac arrest occurs. Most sources state about 400,000 to 460,000 Americans per year.(2, 3) However many of these are not treatable. Among participating ROC sites, there is a two-fold variation in the incidence of cardiac arrest. These differences may reflect lack of a commonly applied definition of cardiac arrest, or incompleteness of episode identification. A community-wide study in Oregon suggests that 0.53 sudden deaths occur per 1000 population annually.(4) The incidence of cardiac arrest treated by emergency medical services (EMS) is 0.57 per 1000 population in Canada.(5) Together these data suggest that about 180,000 treatable cardiac arrests occur each year in North America (US population 295,483,056 X 0.53 per 1000 population X 1.05 since 5% survive + Canadian population 31,127,234 X 0.57 per 1000 population).

Globally, cardiovascular disease contributes 30.9% of overall mortality and 10.3% of the burden of disease.(6-8) It is responsible for more deaths than any other disease in industrialized countries, and three-quarters of mortality due to non-communicable diseases in developing countries. Eighty per cent of deaths due to cardiovascular disease occur in low- and middle-income countries. In the United States, cardiovascular disease is the leading cause of death among individuals of any age, as well as those aged greater than 65 years, second leading cause of death among individuals aged 0 to 14 years and 45 to 64 years, and fourth leading cause of death among individuals aged 15 to 24 years (www.americanheart.org/downloadable/heart/1103834819155FS23LCD5.pdf accessed on March 2, 2005). Cardiovascular disease is projected to cost $368 billion in 2004 (http://nhlbi.nih.gov/about/03factbka.pdf accessed on October 22, 2004).

There has been a steady decline in morbidity and mortality from most cardiovascular diseases over the last 30 years.(9-11) The majority of this reduction has been attributed to risk factor modification.(12) Unfortunately, there has been little improvement in survival from SCA.(13, 14) Only 6.4% of affected individuals survive to discharge.(15) In summary, cardiac arrest continues to be a common, lethal, debilitating and costly disorder in North America and the rest of the world.

Life-Threatening Trauma- The true incidence of traumatic injury is also elusive. Among participating ROC sites, there is a four-fold variation in the incidence of major trauma and five-fold variation in the incidence of trauma with impaired physiology in the field. These differences may reflect lack of a commonly applied definition of trauma, or incompleteness of episode identification. Hospital-based data from the Centers for Disease Control suggest that in the United States the incidence of fatal injuries due to any injury is 55 per 100,000; the incidence of non-fatal injuries is 10,500 per 100,000 (http://webappa.cdc.gov/cgi-bin/broker.exe accessed on October 22, 2004) 13,750 Canadians died due to injuries in 1999 (**http://www.phac-aspac.gc.ca/injury-bles/facts_e.html accessed on February 16**, 2005). Together these data suggest that about 175,000 fatal injuries occur each year in North America (US population 295,483,056 X 55 per 100,000 population).

Globally, injury contributes 10% mortality.(16) It is the leading cause of death among individuals aged less than 24 years in industrialized countries,(17) and in over half the countries that report statistics.(7) In the US, injury is associated with greater years of potential life lost than any other target disorder. Trauma is the leading cause of death among individuals aged one to 44 years, and third leading cause among individuals aged 44 years to 54 years (http://webappa.cdc.gov/cgi-bin/broker.exe accessed on August 23, 2005). Injuries were responsible for 2.6 million hospitalizations, and 37 million emergency room visits.(18) The majority of these are due to either motor vehicle accidents or intentional injury with firearms. Among patients treated in level I-V trauma centers in the US and reported to the National Trauma Registry, 65% suffer minor injuries, 1% die in the emergency department and overall the mortality is 4.6% (http://www.facs.org/trauma/ntdb/ntdbannualreport2004.pdf accessed Oct 26, 2004). The actual societal burden from trauma is likely to be substantially higher when estimates include deaths at the scene of injury,(19) deaths in the emergency department and during hospitalization, deaths following hospitalization that are attributable to injury (20) as well as morbidity and reduced quality of life among certain survivors. (21) Societal costs of vehicular injury-related morbidity and mortality is projected to cost $257 billion in fiscal year 2005.(22)

Previous reports suggest an overall decline in mortality due to trauma.(23, 24) However, recent American data suggest that mortality from blunt trauma through motor vehicle accidents has increased since the national maximum speed limit was repealed in 1995,(18) especially in rural settings.(19) By the year 2020, injury is projected to be the third leading cause of morbidity worldwide.(25) In summary, traumatic injury continues to be a common, lethal, debilitating and costly disorder in North America and the rest of the world.

Variation in Cardiac Arrest and Trauma Incidence, EMS Process and Outcome

There is a wide variation in outcomes after the onset of cardiac arrest.(15, 26) Among participating ROC sites, there is a three-fold variation in survival after cardiac arrest. This is attributable in part to regional differences in the availability of out-of-hospital and hospital-based emergency cardiac care throughout the US.(26) Interventions for cardiac arrest include: bystander CPR, lay responder defibrillation programs(27), experience of EMS providers (28), and interventions provided by EMS providers (29, 30) or at receiving hospitals (31, 32). However, only lay responder defibrillation and therapeutic hypothermia have been shown in randomized trials to improve significantly outcomes to hospital discharge after cardiac arrest.

There is substantial regional variation in EMS structures and processes, e.g., EMS service level provided, number of EMS providers responding, use of procedures or drugs in field, training, quality assurance/feedback, and response time intervals. Some of these factors have been associated with differences in survival or quality of life after resuscitation,(15, 33-36) although no analysis has had adequate power to detect independent effects of all factors. Recent technology can quantify individual episodes on such parameters as defibrillation attempts, chest compression rate, ventilation rate, and other prehospital procedures performed.(37) However, there are no published data that demonstrate significant associations between these factors and patient outcomes. Feedback of this knowledge is essential to care delivery since

improved quality assurance has been associated with improved outcomes after resuscitation.(33) Also it is essential to efficient trial conduct since low baseline rates of survival are associated with larger sample sizes to detect a clinically important difference.

There is a wide variation in outcomes after the life-threatening trauma.(24, 38) Among participating ROC sites, there is a three-fold variation in mortality after major trauma and more than two-fold variation in mortality after trauma with impaired physiology in the field. This is attributable in part to differences in the regional availability of out-of-hospital and hospital-based trauma care throughout the US.(39) For trauma patients, out-of-hospital interventions may include: airway management, fluid resuscitation, hemorrhage control and rapid transport to a trauma center. Standard treatments used in trauma centers focus on limiting blood loss, restoring perfusion, limiting secondary brain injury, and modulating the inflammatory response that leads to multiorgan failure. The effectiveness of each component of trauma resuscitation is unclear.(23, 40-47) Experts have advocated full implementation of regional trauma systems(48) that triage patients with out-of-hospital characteristics predictive of poor prognosis(49-54) to trauma centers with special expertise.

Disparities in incidence and outcomes for cardiac arrest and trauma are observed across socioeconomic gradients as well as across geographic region.(55-61) Cardiovascular disease is the leading cause of income-related differences in premature mortality in the United States,(62) and Canada,(63) Also the burden of injury is greatest among individuals of low socioeconomic status.(64) Non-Hispanic blacks bear a disproportionate burden of morbidity and mortality due to cardiovascular disease and injury.(65) These disparities may be caused by differences in genetic risk, health behaviors, educational attainment, socioeconomic disadvantage, access to preventive care, or other yet to be identified variables. As understanding of the magnitude and cause of these disparities increases, potential interventions include culturally-appropriate public health initiatives, community support and equitable access to quality care.

The incidence and outcome of cardiac arrest and trauma vary by time of day, day of week or season.(66-70) Potential interventions include raising awareness about falls or vehicular accidents and promoting safety practices during the high-frequency seasons, or resource allocation of EMS and hospital resources to match anticipated need.

In summary, cardiac arrest and trauma incidence and outcome vary widely; adequately-powered analyses of observational data can identify promising EMS interventions for these disorders. Such analyses can also yield insight into the cause of geographical, socioeconomic or time-dependent gradients in cardiac arrest or trauma, and interventions to reduce these gradients.

Significance of Proposed Project

The ROC Registry will collate high-quality comprehensive EMS-based data using uniform standardized criteria to describe structure, process and outcome for consecutive cases of cardiac arrest and injury in the 11 diverse consortium sites providing a cross-sectional view of clinical and demographic characteristics of resuscitation in greater detail than could be obtained by single-center studies or national health statistics. The process of doing this and the resulting database will provide:

1) An ongoing data collection for efficient ROC trial design, implementation and interpretation

Enrollment in each ROC trial can be monitored with a streamlined and persistent method of cardiac arrest and injury episode notification in place. Timely identification of patients eligible but not enrolled in ROC trials will allow feedback to providers regarding missed patient enrollment and hence provide for timely corrective measures to enhance enrollment and shorten the time required to complete a given study. As well, comparison of the characteristics of patients enrolled and not enrolled in ROC trials will inform the generalizability of ROC intervention trial results to the community at large that experiences out-of-hospital cardiac arrest or major trauma.

2) Unbiased Estimates of Incidence and Outcome

EMS Structure and Process Factors

The Registry will facilitate comparison of outcomes relating differing resuscitation practices in the US and Canada. This information could inform standards and education policy, as well as local EMS agency decisions. Furthermore, participating EMS systems and hospitals will receive anonymized quality assurance reports at least quarterly that will allow them to compare their own patient population, interventions and outcomes with the range among others with similar or different characteristics. Collectively, these strategies will enable clinicians and centers to identify opportunities to improve quality of care and thereby improve outcomes after cardiac arrest or traumatic injury.

Geographic and Socioeconomic Factors

Population-level information from the Registry can inform public institutions of the efficacy of local education, safety enforcement and engineering initiatives and provide an evaluation of the impact of policy changes. Examples where epidemiological data could be helpful include: bystander CPR; distribution of AED programs; community education to encourage voluntary adoption of safe behavior; enforcement of safety regulations; efficacy of engineering interventions such seat belts, helmets or airbags, and mandatory reporting of domestic violence.

3) Relationships between EMS Structure and Process and Resuscitation Performance

Knowledge of such relationships will inform education and training as well as implementation decisions.

4) Prediction of Outcome based on Patient, EMS, Regional and Periodic Factors

Identification of prognostic or treatment factors accounting for variations in survival will generate hypotheses and result in the identification of novel interventions to evaluate in a subsequent trial by the ROC Investigators. The ability to predict variation in outcome will facilitate efficient (fewer numbers to obtain desired power) design and implementation (knowledge of key variables to control/collect) of ROC trials.

C. PRELIMINARY STUDIES AND PILOT WORK

Overview

The ROC Registry Working Group was formed in September, 2004. Activities to date have included: review of previous relevant registries; derivation of data sets that include mandatory, desirable and optional elements that describe structure, process and outcome related to EMS care for those with cardiac arrest or traumatic injury; development of consensus definitions for controversial elements in these data sets; assessment of baseline estimates of cardiac arrest and trauma incidence and outcome; and development of site-specific implementation strategies.

Relevant Cardiac Arrest or Traumatic Injury Registries

Existing cardiac arrest and trauma registries do not contain the necessary information to determine which interventions are effective in the out-of-hospital setting. For example, the National Registry for Cardio Pulmonary Resuscitation was developed in the United States to collate SCA data describing in-hospital events.(71) As of January 1, 2005, this registry describes more than 60,000 in-hospital events that required some form of resuscitation. More than 5,000 adult and 200 pediatric events are added to the registry quarterly by > 300 participating hospitals. However, events that occur out-of-hospital are excluded from this database.

For trauma, the American College of Surgeons supports a trauma registry that only collates data describing patients transported to Level I trauma centers. The Centers for Disease Control previously developed software to support a similar registry but this does not require inclusion of consecutive cases of patients in the out-of-hospital setting. Similarly, the Canadian Trauma Registry abstracts limited EMS data and collects data on patients who are treated at a designated trauma center. The Centers for Disease Control and Consumer Product Safety Commission jointly support the National Electronic Injury Surveillance System All Injury Program (NEISS) which is a national probability sample of hospitals in the U.S. and its territories. Patient information is collected from each NEISS hospital for every emergency visit involving an injury associated with consumer products. But this survey does not include those injured without consumer products. Data that have been previously collected in other settings lack detailed information about which

interventions were administered in the prehospital setting.(24, 46, 72-74) In addition, existing trauma registries have different inclusion criteria, are not population-based, usually only include trauma centers, lack detailed EMS information, have large variability in definitions for information that is collected, and do not capture out-of-hospital deaths, all of which contribute to selection bias, difficulty in interpreting results and underestimation of the true burden of injury. Due to these limitations in existing registries, there is insufficient data to describe variation in practice and outcomes after resuscitation in different EMS agencies.

The National Highway and Traffic Safety Agency (NHTSA) has supported the development of standardized data elements to describe structure and process related to EMS care (www.nemsis.org). Although each state's EMS director has committed to collecting these data elements, there is no secure and confidential method of collating information into a single dataset. The NEMSIS data elements do not include status at hospital discharge, which is critical to ascertain the burden of illness, the outcomes of interventions trials, or the quality of EMS practices.

International consensus panels comprised of resuscitation experts have developed templates for reporting outcomes after cardiac arrest (75) or trauma.(76) However these templates have not been universally applied in multiple sites. Until recently, the cardiac arrest template lacked simple and universal operational definitions of structure, process and outcome.(77)

In summary, existing registries contained insufficient data to describe out-of-hospital structure and process, lacked operational definitions for each variable, or lacked hospital outcome data.

Consensus Development of ROC Registry Data Elements

Using the information obtained through review of the above registries, the working group identified a comprehensive list of variables that potentially would be important for a registry of out-of-hospital cardiac arrest or traumatic injury episodes. Each variable was reviewed and identified as mandatory, desirable, optional or unnecessary. Consensus definitions and response options were developed by the working group for each of the mandatory, desirable and optional variables (Appendix 1). Since EMS agencies within the United States have committed to adopting NEMSIS data initiatives, its uniform definitions and response options were used where feasible. The Utstein glossary and template for uniform reporting of out-of-hospital cardiac arrest were also incorporated where feasible. The working group modified definitions where necessary for clarification and ease of data collection. Modifications made to key definitions are summarized below:

Arrest of Cardiac Etiology

The definition of this term was controversial because "presumed cardiac etiology" is frequently used as an inclusion or a priori subgroup criterion, but can only accurately be determined by conducting a post-mortem examination. Since it is impractical to perform an autopsy on every fatal arrest, classification must rely on information available to paramedics in the out-of-hospital setting. In the absence of precise definitions, use of the etiology of arrest as an inclusion criterion will create potentially large bias. Therefore, episodes will be enrolled regardless of etiology. The etiology will be presumed to be cardiac in origin unless the apparent cause is due to trauma, drowning, respiratory, electrocution, other non-cardiac, drug overdose, or non-traumatic exsanguination.

Life-Threatening Traumatic Injury

The definition of this term was controversial because the majority of existing trauma registries at ROC sites only enroll patients who die in the emergency room, are admitted to a level 1 trauma center for at least 48 hours, or meet specific triage criteria. All sites use local interpretations of the trauma triage criteria recommended by the American College of Surgeons to determine priority for transfer to a trauma center. If resources were unlimited, the ROC investigators would adopt a single interpretation of these criteria. As well, many patients identified by these criteria are stable in the field, would not be considered for inclusion in prehospital trials and do not have major injuries. Therefore the trauma cohort of the Registry will include patients who meet physiological criteria in the field by virtue of having abnormal vital signs, intubation, or died in the field. Age-based norms will not be used to determine abnormal blood pressure.(78-80) Inclusion of all

patients who meet standardized prehospital criteria rather than those transported or admitted to a trauma center allows for a true EMS-based sample, as a portion of trauma patients are not transported to trauma centers despite meeting criteria to do so (e.g., airway compromise, patient extremis, traffic, weather, hospital diversion status). This sample design is unique to this Registry, is a significant distinction from existing trauma registry data sources and directly supports the ROC trials. We are aware that exclusion of patients with normal vital signs in the field who are subsequently found to have major injury when evaluated in hospital underestimates the population-based burden of injury. As the ROC site investigators gain experience, expertise and efficiency in identifying and collating consecutive cases of major traumatic injury in the out-of-hospital setting, as well as additional resources, it is anticipated that these inclusion criteria may expand over time (Appendix 2).

Assessment of Injury Severity

The definition of this term was controversial because "severity of injury" is frequently assessed based on information that can only be obtained in hospital after initial field treatment, and such ascertainment is frequently only performed in Level 1 trauma centers. Injury severity will be assessed by the International Classification of Disease-based Severity Score (ICISS) calculated from discharge administrative data when feasible.(81) The ICISS has good discrimination and calibration in predicting trauma mortality compared to alternate measures. It is similar to the Injury Severity Score, ISS (50, 51) but can be estimated for patients treated at trauma centers or other hospitals. Alternate measures such as the Revised Trauma Score, RTS (52) can be calculated from data available upon arrival of EMS providers at the scene, but change with treatment or the passage of time. Also the RTS requires component data to be recorded by EMS providers. Even in the best settings, this is not always done, and omission may be selective rather than random.(82) For similar reasons, we propose that the Trauma and Injury Severity Score (TRISS), which is calculated from RTS and other data,(83, 84) not be used to adjust for expected mortality. RTS will be calculated from EMS data; ICISS will be calculated from administrative hospital data when available; ISS will be obtained from hospital-based trauma registries when available. These measures of injury severity (i.e. RTS, ICISS, ISS) will be used as key covariates in the assessment of predictors of outcome after injury.

Mechanism of Injury

The definition of this term was controversial because "mechanism of injury" is frequently used as an inclusion or a priori subgroup criterion, but can only accurately be determined by conducting a post-mortem examination. Utstein, NEMSIS and CDC definitions used in the National Electronic Injury Surveillance System—All Injury Program (http://www.cdc.gov/ncipc/wisqars/nonfatal/helpfile.htm accessed on August 23, 2005) were evaluated. The Utstein variable definitions and response coding for mechanism of injury lacked specificity. However not all participating ROC EMS agencies code mechanism of injury by using the E codes employed in the NEMSIS code definitions. As well, the NEISS codes have been used to collect data in the emergency room setting but require validation in the out-of-hospital setting. Thus the working group developed a universal definition and response options for this variable that are applicable to both Canada and the United States. These consensus mechanism definitions are defined in Appendix 1.

Baseline Estimates of Incidence and Outcome of Cardiac Arrest and Life-Threatening Trauma

Each ROC site has applied the inclusion criteria of the registry to the best available data to estimate the annual number of cases and survival rate (Table 1). These are best estimates given that this data is not readily available in all sites. Note that there are wide variations in the incidence of cardiac arrest, incidence of trauma, survival after cardiac arrest and mortality after major trauma. These variations re-emphasize the need to develop comprehensive EMS-based estimates of incidence and outcome of cardiac arrest and trauma using uniform definitions.

Feasibility of Implementation

Each site assessed for each participating agency how to identify episodes, collate relevant data, assure its quality and transmit relevant information to the DCC. (Appendix 3) Some data elements will be by electronic transfer from existing databases and some data elements will be abstracted, with substantial variation in approach from site to site.

Table 1: Estimated Incidence and Outcome of Cardiac Arrest and Trauma in Participating ROC Sites

ROC Site	Year of Sampling	Population Served	Pt's Meeting Cardiac Arrest Inclusion Criteria (no.)	Cardiac Arrest by 100,000 Population	Cardiac Arrest Pt's Survival to Discharge (no.)	Cardiac Arrest Pt's Survival to Discharge (%)	Pt's Meeting Trauma Inclusion Criteria (no.)	Included Trauma per 100,000 Population	Included Trauma Pt's Survival to Discharge (no.)	Included Trauma Pt's Mortality Before Discharge (%)	Pt's Meeting Major Trauma Triage Criteria (no.)	No. Major Trauma per 100,000	Pt's Meeting Major Trauma Criteria Survival to Discharge (no.)	Major Trauma Criteria Mortality Before Discharge (%)
Dallas	2004	2,008,701	1,711	85	89	5.2	1,900	95	1,710	10.0	3,408	170	2,904	14.8
Iowa	2004	956,188	875	92	61	7.0	576	60	474	17.6	2,806	293	2,484	11.5
Milwaukee	2004	928,018	1,062	114	59	4.4	1,950	210	1,555	20.3	3,699	399	3,400	8.1
Ottawa / OPALS	2002-2003	3,000,000	2,600	87	72	2.8	500	17	450	10.0	5,000	167	4,750	5.0
BC	2004	3,280,000	1,984	60	96	4.8	1,116	34	896	19.7	3,355	102	3,040	9.4
Pittsburgh	2004	670,911	527	79	35	6.6	770	115	129	83.3	2,860	426	2,660	7.0
Portland	2003	1,444,219	632	44	40	6.3	526	36	441	16.2	2,310	160	2,201	4.7
Seattle / King Cnty	2003	1,763,000	1,600	91	140	8.8	1,600	91	1,350	15.6	4,700	267	4,151	11.7
Alabama	2004	1,278,936	688	54	19	2.8	842	66	760	9.7	3,108	243	2,808	9.7
Toronto	1999 - 2004	5,579,355	4,250	76	195	4.6	1,899	34	1,564	17.6	4,728	85	4,493	5.0
San Diego	2003-2004	2,800,000	1,537	55	123	8.0	1,404	50	1,003	28.6	10,290	368	9,852	4.3
Total		23,709,328	17,466				13,082		10,331		46,264		42,743	

Shaded boxes indicate data used only for expanded trauma inclusion criteria

Pilot Studies of Web-Based Data Capture

Several of the ROC investigators have participated in a pilot out-of-hospital cardiac arrest study.(85) This prospective cohort study was reviewed and approved by an Institutional Review Board with waiver of informed consent prior to any data collection. Included were 571 infants, children and adults who a) experienced cardiac arrest requiring chest compressions or external defibrillation, b) outside of the hospital in the study communities c) upon whom resuscitation was attempted by EMS personnel. Cardiac arrest was defined as lack of responsiveness, breathing or movement in individuals for whom the EMS system is activated for whom an arrest record is completed. All data were collated via a secure and confidential web-based method by using automated forms processing software with appropriate variable range checks, logic checks and skip rules similar to that proposed for the present study.

Recently the DCC used similar methods to collate data in a randomized trial of a band compression CPR device in more than 1300 patients with out-of-hospital cardiac arrest in five North American cities.(Personal communication, A Hallstrom, 7 July 2005) Out-of-hospital variables were mean 99% $\pm$ SD 3% complete. In summary, these studies confirmed the feasibility of using simple methods of web- data capture to facilitate the conduct of adequately-powered studies in diverse out-of-hospital settings.

EMS Structures Database

The ROC investigators developed data forms (Appendix 4) to capture the details of each site's EMS structure including dispatching, hospitals, and agency level characteristics such as geography, response numbers, and type of staffing/vehicles, and quality assurance procedures. These data are currently being assembled but will ultimately be linked to census tract information to be able to describe the demographics of the regions involved in ROC.

Strengths and Weaknesses

This study has several strengths. First, the Registry will apply simple and universal operational definitions of structure, process and outcome related to out-of-hospital cardiac arrest and traumatic injury to collate comparable data in multiple sites. Second, the Registry enables rapid and efficient collection of data on a large number of patients that will facilitate efficient conduct of randomized ROC trials while directly informing stakeholders about the robustness and generalizabilty of trial results. Third, our registry will be used to ascertain whether individual EMS agencies are managing resuscitation according to current guidelines.(2) If not, strategies could be developed and implemented to reduce the care gap between knowledge of effective or ineffective practices and actual care delivered. Fourth, ongoing collection of registry data and feedback of this data to participating EMS agencies could have direct effects on the quality of care by focusing clinician's attention on specific aspects of care that would otherwise be overlooked.

This study has some limitations. First, the results observed in participating ROC sites may not be generalizable to the community at large. However the catchment population of participating communities includes approximately 10% of the North American population and has diverse geographic and socioeconomic characteristics. To the best of our knowledge, this is a larger proportion than any other out-of-hospital registry. Second, it is plausible that structure, process and outcome data reported by each site will be subject to ascertainment bias since not all responses will be audited. However the participation of high-quality EMS systems, experienced clinical research staff, practical operational definitions, and audits during site visits, all of which will be substantially enhanced because of the ROC trials, suggest that this is unlikely to be so. Third, it is plausible that some episode may be missed and that some data elements may be difficult to abstract from patient care records (PCRs) that are completed by EMS providers during an emergent situation. However all sites will be required to validate the completeness of their episode notification by querying their EMS agencies' dispatch logs periodically. All sites have agreed to the data elements and will work over the next year to train personnel and alter existing paper or electronic data capture to be sure these elements are being collected. As well, our use of timely episode reporting by sites will facilitate quick feedback from the DCC to sites and to responders to reduce incomplete data.

D. RESEARCH DESIGN AND METHODS

DESIGN

Prospective cohort study.

Setting

Out-of-hospital emergency medical services agencies, receiving institutions, and trauma centers in eight US sites and two Canadian sites participating in the ROC. One of the Canadian sites is composed of two geographically and functionally distinct units.

Population

All persons within the catchment area of any EMS agency participating in ROC, including infants, children and adults.

Inclusion Criteria

There will be no age-based eligibility criteria because: a) serious injury in infants or children is a particularly devastating public health problem with many potential life-years lost, b) cardiac arrest has devastating consequences in children even though it is less common than in adults, c) pediatric injury and cardiac arrest have been greatly under researched, d) children incurring serious injuries or cardiac arrest may be more amenable to new therapies than adults, and e) there is minimal risk associated with the study.

Pregnant women and prisoners will be included where permitted by local IRBs because: a) there is no scientific justification for excluding these patients, b) they represent a unique population rarely studied in resuscitation studies, and c) there is minimal risk associated with the study.

Sudden Cardiac Arrest

Included will be all individuals who experience cardiac arrest outside the hospital, are evaluated by organized EMS personnel and: a) receive attempts at external defibrillation (by lay responders or emergency personnel), or receive chest compressions by organized EMS personnel; or b) are pulseless but do not receive attempts to defibrillate or CPR by EMS personnel. This group will include patients with do not attempt resuscitation directive signed and dated by a physician, extensive history of terminal illness or intractable disease, or request from the patient's family.

Trauma

Included will be individuals of any age who experience injury outside hospital who are evaluated by organized EMS personnel and have any of: a) abnormal vital signs, b) intubation in the field, or c) died in the field (Table 2).

Table 2: Trauma Inclusion Criteria Based Upon Impaired Physiology in the Field

Systolic blood pressure ≤ 90 mmHg
Respiratory rate < 10 or >29
Glasgow Coma Scale score ≤ 12
Intubated in field
Died in field

Data Overview

The goals of the data management system are to maintain data accuracy, security, and quality; and to allow efficient access to the data for monitoring and analysis. The system is meant to adhere to recommendations and guidelines from Federal agencies, and academic medical center Institutional Review Boards (IRBs) on confidentiality and research data protection in light of the "Privacy Rule" under HIPAA.

Items

Eligibility, baseline information, EMS and hospital outcome data will be collected at each site. Data items are listed in Appendix 1. Draft dataforms are shown in Appendix 4. Past DCC experience suggests that these forms will undergo revisions approximately every 6 months at the beginning and at least yearly after that as new or different data elements are required.

Pre-hospital data points collected for all enrolled subjects will include: defined time points allowing for summary and analysis of response, treatment and transport times; demographic data such as incident location, birth year or age, gender, race and ethnicity; outcome data will include pre-hospital disposition (death, time of death, name of hospital transferred to); and vital status from any hospitalizations (e.g. alive or dead at discharge). For hospital outcome, patients who are transferred to another acute care facility (e.g. to undergo ICD placement or ongoing critical care) will be considered to be still hospitalized. Patients transferred to a non-acute ward or facility will be considered discharged.

Cardiac arrest events will be described in terms of initial rhythm, interventions such as time and number of shocks administered, and amount of CPR. CPR process data will include compression rate, ventilation rate and CPR flow fraction time. The latter is defined as the ratio of the time CPR is performed divided by the time patient is without spontaneous circulation.

Trauma patients will have their injuries described by type (penetrating vs. blunt), severity and mechanism. Information on the type of safety equipment in use at the time of injury (such as shoulder/seat belts, helmets, floatation devices, and eye protection) will be collected when available.

We will use **census tract** of the incident address to link to census tract poverty data (86) for socio-demographic measures. Census tract does not contain identifiable data and exhibits greater discrimination than zip codes. (87) Blocks(88) are undesirable because they contain potentially individually identifiable data. U.S. (http://www.ffiec.gov/geocode/default.htm accessed on April 25, 2005) and Canadian (http://geodepot.statcan.ca/Diss/GeoSearch/index.cfm?lang=E accessed on April 25, 2005) census tracts both contain populations of approximately 4000 individuals, have roughly similar permissible population ranges, and follow the same principles of trying to maximize socioeconomic status (SES) homogeneity within compact and clearly defined boundaries.

EMS structure data will be obtained from the EMS structure database (Appendix 4).

Coded patient identifiers for other related registries will be obtained if available (e.g. hospital-based trauma registry, NEISS and American College of Cardiology National Cardiovascular Data Registry [CathPCI Registry and ICD Registry components]).

Linkage

Linkage of various data sources to an episode will be accomplished at the site through use of the date the call was received at the dispatching center, the EMS responding agency identity, a site-determined incident number and personal identifiers. For this purpose, the date and time based on the call to dispatch is considered of fundamental importance and is required as part of any data transfer to the DCC. At no time will the DCC receive or accept personal identifiers. For those records that cannot be matched deterministically using patient identifiers, sites may use probabilistic linkage methods to match EMS records to hospital records using common variables between two or more datasets. The feasibility and validity of using probabilistic linkage methods to match EMS data to hospital data for cardiac arrest and trauma patients have been demonstrated.(89-91)

Multiple Episodes

Although knowledge of multiple episodes for a given patient is not important for the stated purposes of the Registry, such information could provide a rich and unique data set which may prove helpful for some research

questions. While there will not be many such multiple episode patients in any given year, the proportion of patients that may have had a previous episode in the last 4 years might be as high as 10 or 20%, especially for trauma patients. It will be impossible to capture all multiple episodes for a given patient with absolute certainty. However, individual sites may be able to link probabilistically on locally-retained patient identifiers, and, when able can include the link to any previous episode in the data base.

A separate but related issue is the concurrent occurrence of multiple episodes at the same location (i.e. a mass casualty incident). This can be linked by recording how many individuals were involved in each incident in the dataforms, as well as by matching by date, time and census tract.

Capture

Data capture will occur via several processes to maximize use of existing resources and develop new resources as required. Although we anticipate that some sites will eventually collect and collate data via record linkage to pre-existing hospital-based or other databases, this process may take some time to implement. All sites have indicated the capability to capture additional hospital outcome measures for trauma patients by linking to in-patient trauma registries where feasible. Therefore web-based data entry will be available to all sites prior to study initiation. The process will be different at each site and will evolve over time. The site-specific plans are included in Appendix 3. Generally, episodes will be identified by multiple strategies. Out-of-hospital data will be extracted from existing databases whenever possible. In most cases these will be reviewed locally and augmented with targeted review of the EMS run report to complete the required data elements and check for data errors. Where no appropriate database currently exists, processes will be put in place to funnel primary source materials to the Registry site coordinator.

Quality Assurance

Ultimate responsibility for the quality of data will reside with each site's Primary Investigator (PI). Site-specific plans for routine assurance of the primary source data are included in Appendix 3: Site implementation plans. These include ongoing assurance of existing resources, and sampling with re-abstraction. All sites will focus efforts on education to improve the quality of data collected in the field. In addition, range and consistency checks as data are being entered on the web, and similar checks on data sets transferred to the DCC, will provide immediate feedback which is known to substantially reduce errors. The DCC will perform additional consistency checks within and across data fields as the data accumulate. These checks will produce routine reports that will be distributed to the sites requiring correction and/or verification.

Site Audit

DCC staff will visit each site annually to evaluate the process for data collection. This will include an audit of randomly selected charts including primary data sources and supporting documentation. If the audit process identifies that the data do not conform to ROC Registry standards, as a condition of continued participation, the site shall submit within 45 days an action plan to correct such issues. Furthermore, non-conforming data submitted by the site will be withheld from the ROC Registry database until such data is brought up to standard and re-submitted to the DCC by the Site.

Security

All patient and site-specific data will be kept strictly confidential. No individual patient or site identifiers will be made public. No individually identifiable health information will be stored at the coordinating center. Security of data files and primary data materials at the site will be reviewed at each yearly site visit.

Data Management at Coordinating Center

Data Coordinating Center

The ROC DCC provides a powerful, secure, and reliable environment for the collection and analysis of research data generated by the consortium The ROC DCC Principal Investigator also serves as the Director of the Registry DCC. The staff of the ROC DCC is funded through this cooperative agreement to provide

methodological leadership, as well as develop the databases, verify, analyze and interpret the clinical and outcomes data generated from the consortium.

General Policy Statement on Privacy and Confidentiality

The ROC DCC complies with and follows the principles of the privacy of health information outlined in the Health Insurance Portability and Accountability Act of 1996 (HIPAA Public Law 104-191). Security of the databases is maintained by the procedures outlined in HIPAA. These same procedures are applied voluntarily by the DCC for the data that are not individually identifiable. These procedures are as follows:

- Administrative procedures to guard data integrity, confidentiality, and availability;
- Physical safeguards to guard data integrity, confidentiality, and availability, including protection of physical computer systems and related equipment from natural hazards as well as intrusion;
- Technical security services to guard data integrity, confidentiality, and availability, including processes to protect, control, and monitor information; and
- Technical security mechanisms to prevent unauthorized access to data transmitted over the communications network.

Information Systems

Computer systems and other hardware were purchased during Year 1 of the consortium. DCC programming and analysis personnel were also hired for the research program or reallocated from existing University of Washington DCC projects.

Through collaboration of research, computer and clinical scientists within the consortium, several information systems have been developed to collect the trial data generated from approved human studies within the consortium. These systems will be refined during Year 2 through Year 5 of the ROC (i.e. Years 1 through Year 4 of the ROC Registry.)

Collection of clinical site information, describing their EMS agency organizational structure, physical assets, hospital and dispatch services is near completion. This information benefits the consortium trials and can aid in the establishment of the Registry.

Incident Identifiers

When a research subject is enrolled at a clinical site, ROC unique identifiers (randomly generated subject ID created independent of any patient characteristics) are generated through the ROC DCC information system to follow the patient throughout the course of the study. The EMS Agency run report numbers, local hospital medical record numbers and any local internal study number generated by the site principal investigator remain unknown to all participating investigators except the investigators at the clinical site that enrolls the subject. The clinical site that enrolls the subject is the only holder of a code matching an identifiable subject name or number. The privacy of that information at the clinical site is protected through the local hospital IRB approval for participation in the study.

The ROC DCC information system that generates the unique identifiers does not contain any information that directly identifies an individual subject. The DCC study databases do contain basic information about the conditions under which the sample was obtained, such as contributing site name, study name, collection date and time. Information on the contributing site, for example, is required in case any data appear erroneous or unreadable upon review of the case report forms.

Collation of Data

The DCC accepts data from the clinical sites by either batch data file upload or direct web-based entry. Both methods use a secure encrypted transport. Access to the web forms requires an electronic signature and valid username and password; users at a site must be authorized by the site's principal investigator.

Batch data files can come from a variety of sources, such as agency and county EMS run report databases, cardiac/trauma registries or site databases; they will need to match an export specification created by the DCC. This flexible specification will include Extensible Markup Language (XML) and several delimited text formats.

Data quality and consistency checks will be run at the time the data is imported; excluded records and error notices will be saved to a status log file for the source's reference.

Data may be entered directly and/or corrected using web-based HyperText Markup Language (HTML) forms. The forms will be programmed with interactive data checks as well as consistency checks across forms. Data may be entered or corrected in one or more sessions.

The batch and direct data entry methods are not exclusive; it is expected that some initial data will be batch imported and later edited or completed using the web forms. A history of each modification to the record will be stored for review and auditing purposes.

Electronic Data Storage

The DCC uses two data stores for managing study data. The first is an Internet-based online transaction processing (OLTP) database used for data collection, collation, reporting and maintenance. The second is a data warehouse used for analysis and reporting. Both systems are designed so that all new forms, changes to forms, and deletions are automatically tracked. By using a data warehouse, the DCC is able to better isolate sensitive data and provide consistency for analysis by creating frozen copies of the database; the database is archived at quarterly intervals.

SIR (Scientific Information Retrieval) database management software will be used as the data warehouse for the DCC databases. Although not as well known as some other packages, SIR possesses features that make it well-suited for this application. Among them are that it is a very stable product since enhancements to the database structure have been very conservative over its 25-year history. Most enhancements have been to ease of use and connectivity. SIR includes a standard Structured Query Language (SQL) interface and capabilities for writing system files for analysis packages (e.g., SAS and SPSS). The latest versions of SIR have also supported core and level 1 Open Database Connectivity (ODBC).

Physical Storage

The DCC servers and routers are located at 1107 NE 45th Street Seattle, WA 98105. The building uses card-key locks at the entrances after working hours and the offices are secured with a full-time combination lock as well as a key lock after working hours. The server and network room is secured with a bolt lock; the servers are rack-mounted in a locked cabinet.

All physical documents (paper forms, tapes and source documents) will be stamped upon receipt, logged in, and filed in fire-retardant cabinets. All documents should have patient identifiers removed prior to submission to the DCC. If these documents contain any patient identifiers upon receipt at the DCC, the Data Technician will black out these identifiers. Protection of files shall, at a minimum, include systems to protect against fire, flood, and vandalism. Backup copies will be made and maintained as appropriate.

Security

The DCC security policy provides data confidentiality and maintains data integrity while providing appropriate access. In addition, we have built extensive redundancy into our systems. The DCC provides access control and authentication in four domains: a) physical security, b) network access, c) database access, and d) data transmission.

Auditing and Tracking

The goal of our auditing and tracking procedures is to identify vulnerabilities and track changes to study databases. External security audits are performed once per year by a third-party service to identify possible methodology improvements and assess the network and database for vulnerabilities. Any findings identified are immediately addressed.

A change log is created of all edits to sensitive database information. This indicates who made the change, when it was made and the original and final values. Information is initially collected on the Production Internet Server and

checked for consistency before being stored in the data warehouse. The servers maintain web and shell account logs to track user activity.

Intrusion Detection and Prevention

The goal of our intrusion detection and prevention procedures is to monitor the network, application and database servers revealing performance bottlenecks or potential threats. Our system administrators use standard network packet scanners and bandwidth monitors to perform these functions. Our production and development servers automatically check for updates and run upgrades of the operating system and programs nightly. The system administrator patches the Microsoft-based Intranet workstations and servers as updates become available. Virus scanners are installed on all DCC workstations to prevent viruses, trojans or worms from being installed accidentally. The DCC requires all sensitive information be sent encrypted; faxes, e-mail and FTP all send information in the open and will not be used for sensitive information.

Quality Control

The DCC uses multiple levels of quality control, including interactive within-forms checks as data are entered, inter-forms checks for consistency across forms and source document checks during site visits. Range, error and intra-form consistency warnings can be corrected at submission or bypassed by providing a short explanation for the unusual data; these exceptions are later reviewed by the DCC.

REPORTS

A unique aspect of the ROC Registry database is that we will allow access to prescribed individuals at each participating EMS agency. These individuals will be able to access their specific agency data in the form of reports which will be pre-programmed according to requests approved by the ROC steering committee. It is anticipated that these reports would allow comparison of a specific agency with all other agencies combined. We believe this feature will help obtain and retain support and improved data acquisition from the EMS agencies. For example, a medical director would be able to compare process and outcomes in his EMS agency to the range of values observed in other participating agencies but would not be able to identify other individual agencies.

ANALYSES

Analytic methods are partially determined by the database structure which is outlined below.

Registry databases will contain the following covariate and outcome data for each episode:

Episode

- Patient-age, gender, and initial EMS reported rhythm and presumed etiology in the case of cardiac arrest, or initial vital signs, mechanism and severity of injury in the case of trauma.
- Site-date, time, location, witnessed status, bystander CPR or other care, and response times.
- EMS procedure and performance- number and skill level of EMS providers on-scene, fluids -type and volume, ventilation/airway - use of advanced airway, ventilation rate; CPR - defibrillation attempted, chest compression rate, CPR flow fraction, IV, drug type and some dosing, duration of field effort.
- Hospital admission and discharge status.

Regional

- EMS structure-number and type of EMS provider, number of episodes, number of vehicles, quality assurance procedures, etc.
- Hospital characteristics-trauma level, presence of coronary catheterization lab**,** presence of coronary electrophysiology lab etc.
- Population- distribution by age and gender
- Socio-demographic-Census tract variables; % poverty, median income, education level, population density, etc.

Circadian and Seasonal

- Day of week

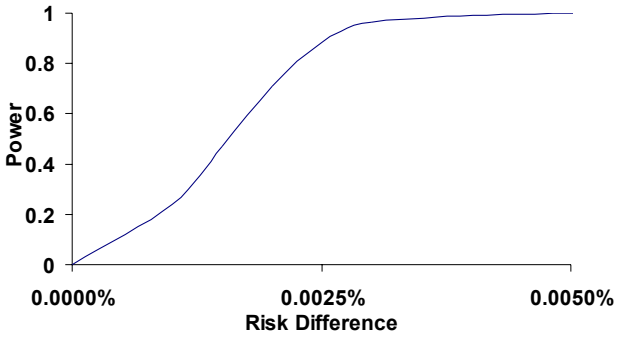


Figure 3: Power to Detect Difference in Overall Annual Major Trauma Incidence

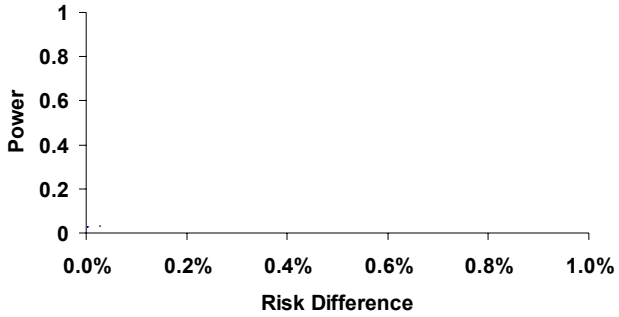
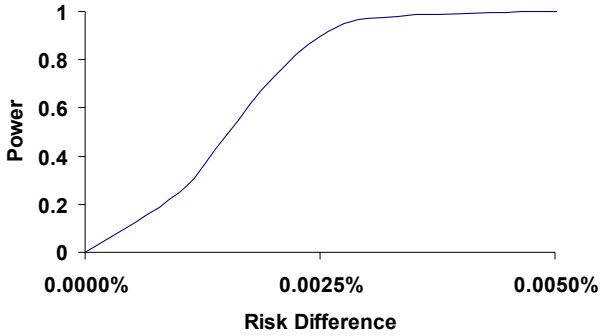
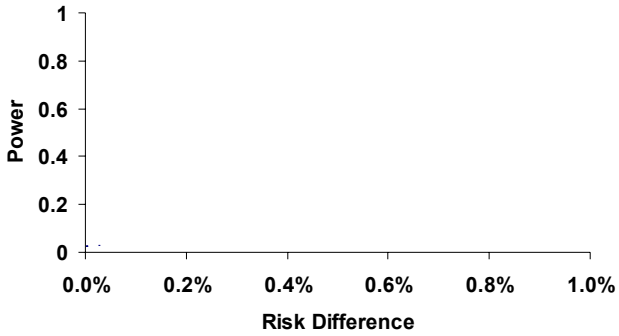


Figure 4: Power to Detect Difference in Overall Annual Major Trauma Survival





These powers are unadjusted for site or any covariates. Since patient- and location-specific variables have been shown to explain about 12%(100) of the deviation and socioeconomic status has been shown to be predictive as well(101) and assuming EMS process variables will explain a similar amount(102) power should be substantially increased by adjustment for covariates.

Special Precautions

Storage and Protection of Study Data- The Registry will be reviewed and approved by the University of Washington IRB prior to its initiation. This will include a review of the proposed mechanisms used to protect confidentiality of the data and the protection of the rights and interests of those enrolled. See page 138 for procedures in place for the storage and protection of study data.

Access to Study Data

Data Sharing with the ROC Funded Investigators- This proposal describes the establishment of a broad-based, epidemiological dataset that will help us better understand the individual, age-related, gender-specific and other population-specific responses to sudden cardiac arrest and trauma injury, including factors or therapies that influence stabilization and recovery. It will be used by our ROC Investigators to answer approved research questions. All data contributors will have obtained local IRB review and approval to submit study data for inclusion in the Registry. Data are created and used for data analysis within the Resuscitation Outcomes Consortium as a Minimum Data Set with a Data Use Agreement between the University of Washington and the local PI at each ROC site as the Data Contributor. The recipient investigators and study staff agree to insure the security of the data as well as not to identify the information or use it to contact any individual.

ROC Investigators and study staff gain access to the research data stored at the ROC DCC through industry standard security measures, as approved in the University of Washington IRB protocol for the Registry. The University of Washington Clinical Trials Center Core Information Systems Manager, Facilities Manager, Database Administrator and Director of Informatics as well as the Steering Committee for the ROC Registry

protect the data from improper use and disclosure. Once the ROC funded Investigator identity has been established, research data are made available for data analysis and reporting.

Data Sharing with External Investigators (Not Funded by ROC)- NIH awardee-investigators are expected to share the completed products of the research openly with the scientific community (that is, make them available) in accordance with the principles in (a) the competing grant application, (b) the Notice of Grant Award, and (c) Federal Register Notice 64 FR 72090 (December 23, 1999) Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources: Final Notice (**http://ott.od.nih.gov/NewPages/Rtguide_final.html**). The governing principles for sharing of results (Page 6 Section 4 of the Notice of Grant Award): (a) Unique research resources arising from NIH-funded research are to be made available to the scientific research community; (b) The collaborative effort will facilitate and optimize the timely placement of research results in the public domain; and (c) The results of the research will be made easily accessible to non-participating researchers and the public.

Guidelines for the release of program data have been prepared by the ROC Registry Steering Committee to balance the protection of the participating investigators' interests and maintain the intended spirit of the release policy. A Consortium Membership Program has been established to permit qualified individuals to apply for membership and agree to a code of conduct for responsible research. A Consortium Member who requests access to clinical data is required to fully execute a clinical data and methodologies distribution agreement that contains provisions to protect the confidentiality of clinical data. A Consortium Member is also required to submit to the Steering Committee the recipient's IRB letter of approval and IRB-approved protocol/ proposal to access patient data from the Registry. In the event that an individual and institution does not have an its own IRB or ethical committee, the Consortium Member is required to obtain IRB approval from an independent IRB, such as the Western IRB (WIRB). Upon ROC Steering Committee approval, Steering Committee directs the ROC DCC to provide access to the specific Resuscitation Outcomes Consortium Web page(s) at www.uwctc.org for a limited period of time that contains the requested Minimum Data Set(s).

When the ROC Registry data are ready to be made available to Consortium Members, the Registry data will be made anonymous by permanently removing the study's Subject Identification Number, which serves as the link back to subject's medical record number (maintained to facilitate the data quality assurance/quality control procedures of the study).

Study Data at the Conclusion of the Study

The future of clinical care for victims of cardiac arrest and traumatic injury depends on having a fundamental understanding of the structure, process and outcome of care fore these disorders. Scientists who understand the clinical issues faced by resuscitated patients can offer specific direction for future clinical and laboratory investigations. The establishment and use of a dataset that collects such information will be highly valuable to the critical care, cardiac, emergency medicine and trauma research community. It is our expectation that at the conclusion of the study (and its funding), the ROC Investigators will seek additional funding from other appropriate Federal agencies or private sources to retain this database and maximize its long-term benefits of serving as an important source of information to emergency medicine cardiac, trauma and critical care researchers**.**

E. Human Subjects Research

This human subjects research meets the definition of "clinical research."

Protection of Human Subjects Population

This prospective cohort study of individuals with out-of-hospital cardiac arrest or traumatic injury will be conducted in a manner consistent with federal regulations and local standards in Canada and the United States. We propose to enroll all patients with cardiac arrest or life-threatening traumatic injury meeting the inclusion criteria in the participating study communities. The study will recruit patients of any age and any gender, race or ethnic origin. We plan that the research will include sufficient enrollment of persons of both genders and diverse racial/ethnic backgrounds to insure that the benefits and burdens of research participation are distributed in an equitable manner.

Source of Information

The patient-related data will be obtained from out-of-hospital records that have already been previously collected during routine clinical care. Vital status and date of discharge will be collected from hospital records, by phone or review. Any other hospital data will come from existing records or databases (e.g. trauma registries). Patients will not be contacted.

Record to be Reviewed for Time Period

The study data will be collected from patients that meet the inclusion criteria and are treated from October 1, 2005 through April, 2009.

Use of Data

The ROC Registry data will be used as primary research data by the ROC Investigators in publications and oral presentations. Secondary use of the data is anticipated by external investigators. Such data shall be made available in a manner consistent with NIH policy and procedures.

Data to Be Collected

Please refer to the draft data forms attached to this protocol (Appendix 5, Draft Registry Data forms). To optimize subject privacy under the Privacy Act, the clinical data set for the study has been designed to meet the August 14, 2002 definition of a HIPAA 'limited data set' for research.

Recruitment of Subjects

This Registry is designed to satisfy the requirements for minimal risk research in the United States (Federal policy for the protection of human subjects. Final Rule. Federal Register 1991; 56: 28003-18) and Canada (TCPS Section 2.8).

Since enrolment in the ROC Registry will involve the collection of personal health information, the relevant requirements regarding privacy and confidentiality must be met in both countries. No individually identifiable health information will be included in the ROC Registry. In the US, the main relevant provisions are the 1996 *Health Insurance Portability and Accountability Act* (HIPAA) (http://aspe.hhs.gov/admnsimp/pl104191.htm) and the Privacy Rule (http://www.hhs.gov/ocr/hipaa/finalreg.html). In Canada the relevant Federal legislation is the 2000 *Personal Information Protection and Electronics Document Act* (Recommendations for the interpretation and application of the Personal Information Protection and Electronic Documents Act (S.C.2000, c.5) in the health research context. Ottawa, Canada: Canadian Institutes of Health Research, November 30, 2001). In Ontario, new provincial legislation, the 2004 *Personal Health Information and Privacy Act* (PHIPA), applies and in British Columbia *Freedom of Information and Protection of Privacy Act* (http://mser.gov.bc.ca/privacyaccess/index_foi.html) applies. In addition to these laws governing privacy and personal health information, the regular research ethics requirements related to privacy also apply (Common Rule, Tri-Council Policy Statement).

Waiver of Informed Consent for Participation

A relevant Institutional Review Board in the United States (or Research Ethics Board in Canada) can approve a waiver of the usual requirements of informed consent, provided that it finds and documents that:

The research involves no more than minimal risk to the subjects. The proposed ROC Registry involves no intervention. All victims suffering sudden cardiac arrest or traumatic injury will receive standard treatment by EMS personnel in the field.

There is no risk to the subjects, except possibly a breach of confidentiality. We have taken extensive steps to manage and minimize this risk according to a range of recognized best practices and in conformity with prevailing regulations, policies and laws in the United States and Canada. There is no direct contact with the research subjects during the course of the research. Their identity is anonymous except to the local PI and

research staff abstracting the data for the Registry. The collection of data for this study is limited to information in patient charts obtained during routine, standard care. IRB-approved standards and practices for study data collection, storage, and retrieval are in place through the Resuscitation Outcomes Consortium Data Center, University of Washington to minimize the loss of confidentiality and privacy with the data collected during this study. All study personnel involved in data collection and analysis will be required to sign a confidentiality agreement.

The waiver will not adversely affect the rights and welfare of the subjects. The study has not and will not affect patient care, as these patients have already had their recommended care and the study requires data collection only.

The research could not be practicably carried out without waiver of consent. Persons being enrolled in the ROC Registry cannot consent to participate because they have acute an life-threatening illness that requires immediate treatment. To avoid selection bias in creating a robust, epidemiological dataset that describes patients with out-of-hospital life-threatening illness, the characteristics of ***all cardiac arrest or trauma patients*** that meet the inclusion criteria must be determined. The act of obtaining consent will introduce significant bias in that survivors are available to provide consent, but those who die early following injury are unavailable. These high-risk patients are critical to provide an understanding of risk factors for death or disability after out-of-hospital life-threatening illness. Subjects and/or their legal next of kin might not be identified for days following injury almost assuring that this bias will occur should consent be a requirement for data collection.

Whenever appropriate, the subjects will be provided with additional pertinent information after participation. As there are no direct identifiers used in the performance and reporting of this research, it will not be possible to provide those subjects whose data are being utilized with any information about the research. Information gathered from this study will be shared with the community at large upon publication.

The waivered or altered consent does not involve a therapeutic intervention. (Tri-Council Policy Statement. Ethical Conduct for Research Involving Humans. Ottawa: Medical Research Council, Social Sciences and Humanities Research Council, Natural Sciences and Engineering Research Council, 1998, Section 2.1(c).)

In the data collection for the proposed ROC Registry, the research subjects will not receive any experimental intervention, but will receive standard care in the field.

Privacy and Confidentiality

The design and procedures of the proposed Registry are consistent with the U.S. “Privacy Rule”, which regulates the 1996 *Health Insurance Portability and Accountability Act*, as well as the Canadian Federal 2000 *Personal Information Protection and Electronics Document Act,* and the Ontario Provincial 2004 *Personal Health Information and Privacy Act* and the British Columbia *Freedom of Information and Protection of Privacy Act.* In general, these laws reflect the emerging consensus about “Fair Information Practices”, which are gaining international acceptance (Guidelines for protection privacy and confidentiality in the design, conduct and evaluation of health research: Best practices (Consultation Draft), March 22, 2004. Ottawa: Canadian Institutes of Health Research. Privacy Advisory Committee (http://www.cihr-irsc.gc.ca/e/20490.html)

Identifiers

Through the use of a Data Use Agreement between the DCC at the University of Washington, and the local Principal Investigator (PIs) contributing data, the local PI certifies that the local PI or the research team will not transmit to the Registry the following *specified direct identifiers* of the individual or of relatives, employers, or household members of the individual:

Names (individual, employer, relative, etc.)
Date of Birth
Address
Telephone Numbers
Social Security Numbers
Electronic Mail (email) Address
Web Universal Resource Locators (URLs)
Internet Protocol (IP) Address Numbers

Medical Record Numbers
Health Plan Beneficiary Numbers
Account Numbers
Certificate/License Numbers
Vehicle Identifiers and Serial Numbers (e.g., VINs, license plate numbers)
Device Identifiers and Serial Numbers
Biometric Identifiers (e.g., finger or voice prints)
Full face photographic images and any comparable images

The medical record number will be recorded by the local PI and stored separately by the local site PI with access only by local study staff listed in the protocol. The code key that links a study Subject Identification Number to an identifiable patient will remain with the local PI/study staff at each site. The local PI agrees never to disclose the identity or any Protected Health Information regarding the patient to the Registry or to any other person or entity or for other research. This link must be maintained to perform future data integrity checks on the study data stored at the Registry. The study staff requires the ability to re-abstract a subject's study data or confirm any outlier values that might be observed during the data analysis phase of the study.

The link to human subjects will be destroyed when the research has been complete and published, or when relevant research goals requiring links to individuals are accomplished. The link will not be retained indefinitely. The link to the human subjects is not recorded with the data in the Registry, so as to protect the privacy and confidentiality of the research subjects.

Minimum Necessary

The clinical data set is derived through expert consensus to insure complete capture of the critical parameters and physiologic derangement in sudden cardiac arrest and trauma patients. The information obtained has been limited to only that information needed for the research effort to describe the incidence, severity, and consequences of cardiac arrest or traumatic injury in the out-of-hospital setting.

Inclusion of Women and Minorities

The registry will include all patients meeting the inclusion criteria regardless of age, gender, race or ethnic origin. In order to minimize bias in data collection a waiver of consent will be sought as described above.

Inclusion of Children and Vulnerable Populations

In the United States, research involving children is subject to additional protections beyond the general provisions of the Common Rule (Subpart D. Additional Department of Health and Human Services Protections for Children Involved as Subjects in Research. 48 Federal Register 9818, March 8, 1983; 56 Federal Register 28032, June 18, 1991.). For research not involving greater than minimal risk to children, 45 CFR Part 46.404 allows an IRB to approve studies provided that adequate provisions are in place to solicit the assent of children and their parents or legal guardians. However, 45 CFR Part 46.408(a) authorizes the IRB to permit the use of the waiver of these consent provisions, even in circumstances in which the assent of children (and their parents) might reasonably be obtained, if the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research.

The circumstances surrounding the proposed ROC Registry are not directly addressed in these regulations, but principles reflected in the regulations provide a strong basis for the ethical acceptability of enrolling children in the proposed Registry: (a) the collection of data itself poses minimal risk to the children enrolled in the Registry; (b) any risks that might follow from the inappropriate use, or inadequate protection of the children's' personal health information, have been thoroughly addressed in our proposed protocol for the safeguarding privacy and confidentiality (see above); (c) there are strong arguments in favor of including children in research, and in specific epidemiological studies such as the one proposed here, and these arguments have been accepted as important and valid by the Food and Drug Administration and the Secretary of Health and Human Services. For example, the following argument from the American Academy of Pediatrics was included in the publication of the Final Rule: "it is important that children be included in research protocols, including those on emergency treatments, so that the safety and efficacy of various treatment methods can be determined in a scientific manner."(Protection of Human Subject; Informed Consent. Federal Register Sept 26-Oct 2, 1996. Department of Health and Human Services. Food and Drug Administration [Docket No. 95N - 0158]. Final Rule.)`

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See attached binder for Appendices:

Appendix 1: Registry Data Set

Appendix 2: Expansion of Trauma Inclusion Criteria

Appendix 3: Site Implementation Plans

Appendix 4: EMS Structure Dataforms

Appendix 5: Draft Registry Dataforms