

EMERGENCY PRESERVATION AND RESUSCITATION FOR CARDIAC ARREST FROM TRAUMA (EPR-CAT)

Correspondence:
Samuel A. Tisherman, MD
University of Maryland School of Medicine
Department of Surgery
R Adams Cowley Shock Trauma Center
22 S. Greene Street
Baltimore, MD 21201
Phone: (410) 328-9781
Fax: (410) 328-3665
E-mail: stisherman@umm.edu

I. PROTOCOL INFORMATION

Title: Emergency Preservation And Resuscitation For Cardiac Arrest From Trauma

Master Protocol

Award No. W81XWH-07-1-0682

Phase II

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II. SPONSOR INFORMATION

Sponsor: Department of Defense (DOD) Telemedicine and Advanced Technology Research Center (TATRC).

III. PRINCIPAL INVESTIGATOR'S INFORMATION

Samuel A. Tisherman, MD
University of Maryland
Department of Surgery, University of Maryland School of Medicine
R Adams Cowley Shock Trauma Center
22 S. Greene Street
Baltimore, MD 21201
Phone: (410) 328-9781
Fax: (410) 328-3665
E-mail: stisherman@umm.edu

IV. ROLES AND RESPONSIBILITIES

Principal Investigator

The project PI will be responsible for protocol development, fulfillment of regulatory requirements, oversight of training for team members, data analysis, and publication of study results.

Coordinator

The primary research coordinator for this study will be Leslie Sult, RN, Shock Trauma and Anesthesia Research Core. She can be contacted by e-mail (lsult@stapa.umm.edu) or phone (410-328-0288). The coordinator working with the PI will be responsible for assisting with training of team members, procurement of equipment, and assuring appropriate data acquisition.

Subcontractors

At each site, there will be a local PI who will be responsible for local training of key personnel, protocol implementation, and data acquisition. The local site coordinator will be responsible for equipment acquisition, assistance with training, and data acquisition. Local co-investigators will be responsible for implementation of the protocol. In addition to the University of Maryland, the other active site for the study is the University of Pittsburgh. Other potential sites include the University of Texas-Houston and Oregon Health and Science University.

Consultants

Consultants will be called upon to assist with decisions regarding equipment purchases and/or training of key team members.

Medical Monitor

Per DOD Directive 3216.2, all GREATER THAN MINIMAL RISK STUDIES require a Medical Monitor. This individual is a qualified physician, other than the Principal Investigator, not associated with the

protocol, able to provide medical care to research volunteers for conditions that may arise during the conduct of the study, and will monitor the subjects during the conduct of the study. The medical monitor plays a role in reviewing serious adverse events and unanticipated events. The medical monitors will be Jose Diaz, MD, at the University of Maryland and Scott Gunn, MD, at the University of Pittsburgh .

The medical monitor is required to review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths and provide an unbiased written report of the event. At a minimum, the medical monitor must comment on the outcomes of the event or problem and in case of a serious adverse event or death, comment on the relationship to participation in the study. The medical monitor must also indicate whether he/she concurs with the details of the report provided by the principal investigator. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation and reports of events resulting in death must be promptly forwarded to the USAMRMC ORP HRPO.

V. SITE INFORMATION

The University of Maryland, Baltimore will be the coordinating center for the study. The University and Principal Investigator will take responsibility for submission of an Investigational Device Exemption from the Food and Drug Administration. The Shock Trauma and Anesthesiology Research – Organized Research Center (STAR-ORC) of the University of Maryland will assist with database management, regulatory requirements, and establishment/maintenance of the Data Safety Monitoring Board (DSMB). The Shock Trauma Center of the University of Maryland Medical Center will be a participating clinical site for the study, and this study description represents the initial submission of the study to be implemented at the Shock Trauma Center of the University of Maryland Medical Center. This will serve as the master protocol. Sites will submit their informed consent forms to the Coordinating Center for approval before submission to their local IRBs. The other active clinical site is the University of Pittsburgh. Potential additional sites include the University of Texas-Houston and Oregon Health and Sciences University.

For all sites involved in this effort, approvals from respective local Institutional Review Boards (IRBs) and the USAMRMC Office of Research Protections Human Research Protections Office (ORP-HRPO) will be secured prior to implementation.

All clinical sites are Level I trauma centers with active cardiac surgical services.

VI. STUDY INFORMATION

The proposed study is an interventional, safety and feasibility trial of a resuscitation technique for trauma patients who have suffered a cardiac arrest, presumably from exsanguinating hemorrhage. The cardiopulmonary bypass (CPB) equipment and the saline used for the flush are all approved for human use by the US Food and Drug Administration (FDA), though not for this indication.

VII. STUDY DESIGN

Rationale

Cardiopulmonary resuscitation (CPR) with artificial respirations and external chest compressions has enabled initiation of life-saving interventions by laypersons as well as medical personnel, anywhere, anytime [1], in patients who have suffered normovolemic cardiac arrest, e.g., from an arrhythmia. During exsanguination cardiac arrest, however, external chest compressions are not physiologically effective.

Standard resuscitation of trauma victims who develop cardiac arrest (become pulseless) includes airway management, aggressive fluid resuscitation, and emergency department (ED) thoracotomy with open chest CPR [2]. The open chest approach is used in this circumstance, in contrast to the approach for normovolemic cardiac arrest, with the hope of finding an intra-thoracic injury that can be quickly repaired and to clamp the aorta to maximize blood flow to the most vulnerable organs, heart and brain.

Unfortunately, rapid attempts at fluid resuscitation and hemostasis lose the race against the tolerance limits for complete ischemia of 5 min for the brain [3] and about 20 min for the heart [3].

Rhee et al reviewed 24 studies of ED thoracotomies in the literature with 4,620 cases. Presumably this is a group of patients who had become pulseless in the ED and the clinicians felt that there was some hope for successful resuscitation. The overall survival, however, was only 7%, with >90% of survivors having normal neurologic outcomes. Several factors seemed to influence survival rates: 1) penetrating (9% survival) was better than blunt (1%) trauma mechanisms, and stab wounds (17%) were better than gunshot wounds (4%); 2) thoracic injuries (11%) were better than abdominal (5%) or multiple (1%); 3) signs of life on arrival at the hospital (12%) vs no signs of life (3%), and signs of life in the field (9%) vs no signs of life (1%). Based upon this type of data, Hall and Buchman have developed a timeline for decision-making in patients who have suffered a cardiac arrest from trauma based on mechanism of injury, vital signs and signs of life. Recognizing the frequent futility of resuscitative efforts in patients who have suffered a cardiac arrest from trauma, the National Association of EMS Physicians and the American College of Surgeons Committee on Trauma have published guidelines for withholding or terminating resuscitation in these patients. Though intentionally left up to local protocols, they did recommend termination of resuscitation after 15 min unsuccessful CPR or, once cardiac arrest has occurred, if >15 min is required for transport. These data have lead trauma specialists to seek novel approaches to management of trauma victims who suffer cardiac arrest.

In 1984, Colonel Ronald Bellamy, a U.S. Army surgeon, and Dr. Peter Safar reviewed military casualty data. The majority of soldiers killed in action in Vietnam without brain trauma had penetrating truncal injuries [4]. They exsanguinated internally over a few minutes. Such casualties are still considered unresuscitable though many have technically repairable injuries upon autopsy. Bellamy and Safar agreed that a novel approach was necessary, i.e., Emergency Preservation and Resuscitation (EPR).

EPR is defined as treatment to preserve the viability of the entire organism during ischemia, such as no flow (cardiac arrest) or low flow (shock). The goal is to induce EPR with hypothermia, drugs, and fluids. If instantaneous preservation of the viability of brain and organism could be achieved, one could “buy time” for transport and major hemostasis during circulatory arrest, to be followed by restoration of blood volume and resuscitation, using CPB.

Background

Since the late 1980s, researchers at the Safar Center for Resuscitation Research of the University of Pittsburgh have been engaged in systematic outcome studies in dogs for the development of EPR [5]. These studies employed full time intensive care throughout the experiments. In the initial series of experiments, following a 30-60 min period of hemorrhagic shock, EPR was induced by closed-chest CPB with hemodilution by crystalloids. Circulatory arrest periods of 60-120 min were explored, with CPB for reperfusion and rewarming. These studies demonstrated that: 1) Profound cerebral hypothermia (tympanic membrane temperature, T_{ty} 5-7°C) induced at the beginning of exsanguination cardiac arrest of 2 hrs improved neurologic outcome compared to that with deep hypothermia (15°C) [6, 7], 2) Use of the University of Wisconsin solution (used for organ preservation for transplantation) did not improved cerebral functional outcome, and 3) use of a totally heparin-bonded CPB system was feasible and safe. In these studies, all animals survived, but the main outcome variable was neurologic function. In the final experiment of this series, the limits of the preceding shock period were explored to see if induction of EPR would still be feasible. Sixty min normothermic hemorrhagic shock at a mean arterial pressure (MAP) of 40 mmHg, followed by rapid cooling using CPB and 60 min circulatory arrest at T_{ty} <10°C, is survivable [8]. Survival decreased if MAP was 30 mmHg during hemorrhagic shock. Survivors had complete functional recovery, however; and, documented for the first time, the brains were histologically normal.

Clinically, CPB cannot be initiated within the critical 5 min of recognizable cardiac arrest. A different approach is needed. Rapid placement of an aortic catheter could allow targeting of the brain and heart with a flush of cold fluid. A double balloon catheter could allow differential flushing of the heart and brain while assisting with hemostasis.

Hypothermia strategies. Subsequent studies have utilized a catheter for flushing the aorta with isotonic saline, at a rate of 1-2 L/min, starting at 2 min no-flow. This flush at 0-4°C could lower T_{ty} by 3°C per min.

The outcome model used included rapid, controlled hemorrhage from aorta and vena cava over 5 min to cardiac arrest (which was assured by inducing ventricular fibrillation); and aortic cold saline flush started at 2 min of arrest, with drainage via the vena cava catheter (Fig. 1). The period of circulatory arrest was varied from 15 to 180 min [9-11], under preservative Tty levels decreasing from 34°C to 6-10°C. Reperfusion and rewarming were accomplished with closed-chest CPB. Post-resuscitation mild hypothermia (34°C) was continued to 12 hr, as this has been demonstrated to improve neurologic outcome in survivors of non-traumatic cardiac arrest [12, 13]. Intensive care was continued to 72-96 hrs.

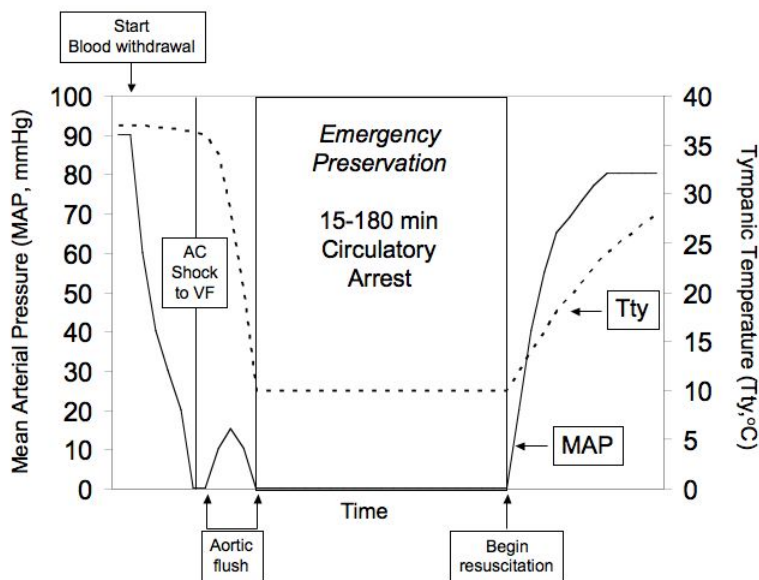


Figure 1. Emergency preservation and resuscitation model.

Lower temperatures were required to achieve longer arrest times. For EPR 15 min, a room temperature saline flush of 25 ml/kg via a balloon-tipped catheter placed via the femoral artery into the descending thoracic aorta decreased Tty to 36°C and resulted in survival with brain damage while ice-cold flush decreased Tty to 34°C, resulting in good neurologic outcomes. Similar results were achieved after 20 min EPR. Beyond 20 min, it seemed that spinal cord ischemia was a problem, manifest as hind-leg weakness. Total body cooling was needed. This could be accomplished with a flush via a large-bore cannula in the femoral or iliac artery to include the entire organism. To achieve good outcomes after 30 min EPR, 100 ml/kg flush into the abdominal aorta, achieving Tty 28°C, was required. Cooling to Tty 10°C with even larger amounts of flush was required to preserve the brain and organism to achieve intact survival after 60-120 min EPR [11]. Of concern clinically, however, is that this required 500 ml/kg of ice-cold fluid and ~15 min. Also, delaying the start of flush to 8 min arrest in the 30 min cardiac arrest model negated the preservation achieved with flush starting after 2 min or 5 min cardiac arrest [14].

Instead of the one-way flush described above, another approach would be to start with a single, small flush, to achieve mild cerebral hypothermia, and then, to recirculate diluted venous drainage blood, with or without an oxygenator, through a cooler-heat exchanger, to reduce Tty to profound hypothermia [5]. This needs further study.

Pharmacologic strategies. Pharmacologic approaches with novel drugs and solutions would be advantageous for induction of EPR by synergizing with hypothermia and, perhaps, decreasing the volume of flush that is needed [15-18]. A systematic exploration of pharmacologic cerebral preservation potentials of 14 different drugs was completed in 84 dogs using a model of 20 min exsanguination cardiac arrest, with a potentially portable volume of flush solution (25 ml/kg) at ambient temperature to achieve only mild cerebral hypothermia (34°C). In controls, saline flush started at 2 min cardiac arrest achieved survival with brain damage [9]. In groups of 3-6 experiments per drug, various doses were flushed into the aortic arch via a balloon catheter and, in some experiments, additional intravenous medication was given during

reperfusion with CPB. None of the 14 drug treatments resulted in a breakthrough effect [15-17]. Only an occasional dog achieved normal function (but with some histologic damage) after thiopental plus phenytoin or glucose plus insulin. The antioxidant tempol, however, gave a suggestion of benefit [18].

More recently, a study of an energy preservation strategy using oxygen and glucose added to the flush solution allowed some intact survivors after 3 h of circulatory arrest at Tty <10°C [19].

Solutions. In the studies described above, isotonic saline solution was used for flush and dextran 40/Ringer's solution for reperfusion via CPB. Special solutions, such as polynitroxylated albumin plus tempol (PNA-T) (Synzyme Co.) or "Unisol" (2 solutions: an 'intracellular fluid' with composition designed for no flow, and an 'extracellular fluid' designed for reperfusion) designed by Taylor et al [20, 21] (Organ Recovery Systems Co.), might have some benefit. This was suggested in pilot experiments with the Pittsburgh EPR model above (unpublished data). Unisol has been used successfully by the groups at Uniformed Services University of the Health Sciences and Massachusetts General Hospital (led by Drs. Rhee and Alam). Letsou et al, have shown that 2 hrs EPR can be achieved with good functional outcome using Hextend→ as a plasma substitute during the time of profound hypothermia [22]. Controlled studies comparing different fluids are worth considering.

Trauma. Exsanguinating hemorrhage in trauma patients does not occur without significant tissue trauma. Adding tissue trauma to the 60 min EPR model in the form of thoracotomy, laparotomy, and splenic transection, with splenectomy performed during arrest led to survival, but with evidence of coagulopathy and development of multiple organ dysfunction [23]. Animals that did not have the additional trauma survived neurologically intact. The encouraging finding was that brain histopathology was normal, suggesting that, with prolonged intensive care and rehabilitation (as could be utilized clinically), long-term intact survival would be expected. Using a model of low-flow CPB with profound hypothermia, Alam et al [24] have demonstrated that clinically relevant injuries can be repaired and normal outcome achieved with EPR.

Other approaches. Rhee et al [20] and Alam et al [25] have also explored EPR in a clinically relevant exsanguination model in pigs. Using readily available equipment, they induced profound hypothermia by aortic flush, both proximally and distally, via a thoracotomy and direct aortic cannulation. They used the Unisol solutions during cooling and rewarming, respectively. Repair of the aortotomy was accomplished during no flow. After total circulatory arrest of up to 30 min, normal neurologic recovery could be achieved [20]. Normal cognitive function after exsanguinating hemorrhage from a vessel injury and prolonged asanguinous low flow (by CPB) at 10°C can also be achieved even after prolonged shock prior to induction of hypothermia. They have explored the rates of cooling and rewarming and found a suggestion that best outcome is with the most rapid cooling [26] and moderately slow rewarming [27].

Comparison to standard therapy. Wu et al [28] compared 1 hour of EPR with standard care (CPR and fluid resuscitation) following cardiac arrest from prolonged hemorrhage (~2 hrs). In the CPR group, spontaneous circulation could not be restored without CPB, but long-term survival could not be achieved despite aggressive intensive care. Even with 1 hour of hypothermic no flow, however, almost all dogs survived in the EPR groups. Early in the study, several EPR animals developed seizures. They postulated that more prolonged post-arrest mild hypothermia might alleviate this deterioration and, therefore, added a third group with 36 hr cooling. This group had significantly better neurologic outcomes than the EPR group with 12 hrs hypothermia.

In summary, outcomes from cardiac arrest in trauma patients with current management strategies are dismal. Laboratory studies from the Safar Center, USUHS, and Massachusetts General Hospital suggest that EPR holds promise for improving these outcomes. Sufficient data are available to develop a clinical feasibility protocol. Additional laboratory studies prior to initiating this study are not justified at this time.

Clinical protocol

Per the request of the FDA, 10 subjects who undergo EPR will be entered and a detailed report will be submitted to the FDA prior to any further subject enrollment. Subjects entered into this trial will have had a left thoracotomy and right tube thoracostomy. Appropriate operative exposure for EPR may require

transection of the sternum and extension of the thoracotomy to the right, as determined by the attending surgeon. Additional bleeding caused by this maneuver will be documented. Arterial cannulation for the EPR flush will be via the aorta. A vascular clamps will already have been placed on the vessel distal to the anticipated location of the insertion. An arterial perfusion cannula (17-21 Fr) (FDA-approved) will be placed proximally via a Seldinger type needle, wire, dilator sequence. The perfusion cannula will be advanced 8-10 cms proximally. Air will be removed from the cannula by sustained compression of the left ventricle. The cannula will be connected to the pump and tubing system using saline submergence. A purse string suture will be added immediately after initiation of flow and the cannula will be secured via Rummel style slide. The immediate goal is to maximize flow to the heart and brain. (Fig 2) The flush will be with ice-cold 0.9% saline via a CPB roller pump at a minimum of 2 liters/min. Flow will be increased as tolerated, with an expected maximum of 5 liters/min. Once the flush begins, the right atrium will be opened. If possible, a venous cannula (36-40 Fr) (FDA-approved) will be placed into the right atrium and veno-arterial pumping will be initiated with a hollow-fiber membrane oxygenator/heat exchanger. Flow will be increased based on venous return to a goal of 4-5 liters/min. Veno-arterial recirculatory flow may not be possible if the infusion of cold saline cannot keep up with the subject's blood loss, thus not allowing venous return to the CPB system. If this is the case, the one-way flush will continue (Fig. 2). Venous drainage that leaks into the chest can be suctioned and, if possible, returned to the CPB reservoir. Once the Tty has reached 20°C, the aortic clamp will be released slowly, monitoring CPB flow, to allow whole body cooling.

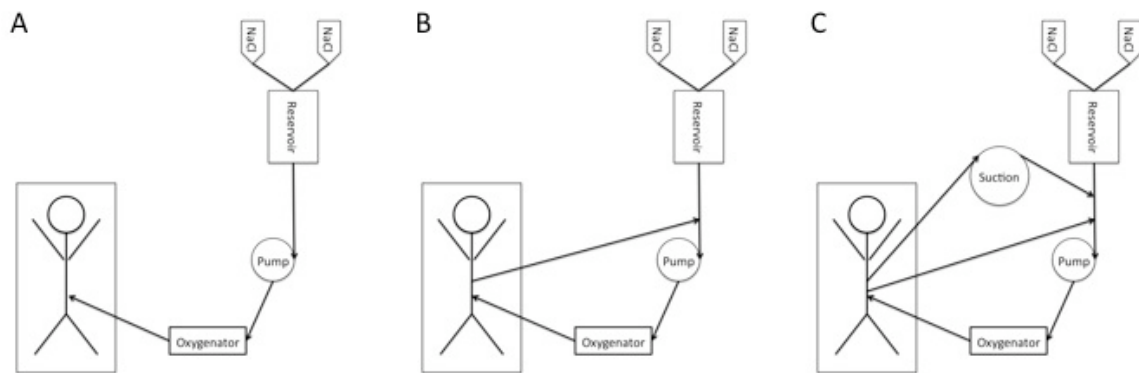


Figure 2. Straight flush and recirculation systems for cooling. Panel A = flush only. Panel B = recirculation. Panel C = recirculation with pump suction.

During cooling, Tty will be monitored utilizing infrared technology as a non-invasive estimate of brain temperature. A standard low-temperature rectal temperature probe will also be inserted to help assure a reasonable degree of total body cooling for EPR. Cooling will continue until Tty is <10°C and rectal temperature is <30°C. At this point, low flow CPB (10 ml/kg/min) will continue if possible. If not, circulation will be arrested until hemostasis has been secured.

The subject will be transported to the operating room (if not already in the operating room) for resuscitative surgery as soon as it is feasible. During the operation, if necessary, additional cannulae (FDA-approved) may be placed for CPB. The exact placement will depend upon the subject's injuries. A standard aortic arch approach may be appropriate. This will allow repair of the initial aortotomy.

The operative approach will be focused on damage control. Arterial bleeding will be managed with ligation or vascular repair. Venous bleeding will mostly be managed with packing, though direct repair or ligation may be needed. Contamination by enteric contents will be managed by rapid resection and bowel stapling, plus irrigation of the peritoneal cavity. All surgical fields will remain open for observation during reperfusion and rewarming to assure hemostasis. The abdomen and thorax are frequently packed and left open in these circumstances.

Although EPR should not be initiated in subjects with non-survivable injuries, it is possible that the severity of the injuries may not be evident until the patient has been cooled and undergoes operative exploration. If, at this time, non-survivable injuries are identified, the attending surgeon may elect not to continue resuscitative efforts.

Once hemostasis has been achieved, CPB will be initiated (if low flow CPB had not been continued throughout) for reperfusion and slow rewarming. The goal will be to keep the total time of circulatory arrest under 1 hour and to minimize the duration of low flow at profound hypothermia. The rewarming rate will be targeted at 0.5°C/min. During rewarming, transfusions of standard (i.e., for clinical use) packed red blood cells, fresh frozen plasma, cryoprecipitate, and platelets will be administered to achieve a hemoglobin of at least 8 gm/dl, normalized prothrombin time (INR <1.5) and activated partial thromboplastin time (PTT), fibrinogen level of 150 mg/dl, and platelet count of >100,000. Thromboelastograms may also be followed. Activated clotting times (ACT) will be monitored. If hemostasis is acceptable, the ACT will be maintained at >180 sec with intravenous heparin as needed until CPB is discontinued.

Rewarming will continue until Tty reaches 34°C. Mild hypothermia (Tty 34°C) may be maintained for 12 h to optimize neurologic recovery using external cooling plus sedation and paralysis as needed. If coagulopathy persists despite aggressive correction with blood products (to platelet count of 100,000 and normal PT/PTT and fibrinogen), rewarming to normothermia may be considered. More prolonged post-resuscitation hypothermia may be considered in selected subjects with poor neurologic function at 12 hours with no contraindication to mild hypothermia.

Shivering will be treated with sedation (propofol), analgesia (fentanyl), and, if necessary, neuromuscular blockade.

Decannulation should be performed as soon as the subject has sufficiently stable spontaneous circulation to be weaned from CPB. The thoracotomy should then be closed. If the subject requires more prolonged circulatory support, the use of Extracorporeal Life Support (ECLS) via extrathoracic (usually femoral or jugular) cannulation can be considered. ECLS may be appropriate for a subject who can not be weaned from CPB because of hypotension (despite inotropes/vasopressors or an intra-aortic balloon pump) or inadequate oxygenation (e.g., PaO₂ to FiO₂ ratio consistently less than 100), yet otherwise seems to have potential for long-term survival.

The experimental aspects of this protocol that are different from the standard of care for trauma patients include the rapid cooling with the saline flush, reperfusion/rewarming using CPB, post-resuscitation mild hypothermia, and the potential for long-term ECLS. Standard operative management of injuries will occur simultaneously with these components. The experimental treatment will be completed when the subject has been rewarmed to normothermia and is not on ECLS.

Failure of EPR:

Technical issues may lead to inability to initiate adequate cooling for EPR. These issues could include (but are not limited to): inability to place the cannulae (most likely because of the subject's anatomy or specific injury pattern), displacement of cannulae after placement, and inability to establish adequate flow and thus adequate cooling. Minimal cooling rates are defined as achieving Tty 30°C within 15 min, 20°C within 30 min, and 10°C within 60 min. Failure of the pump is also a possibility, although this is unlikely as these devices are used routinely for CPB in the operating room. If EPR cannot technically be adequately induced, the investigator may elect to discontinue resuscitative efforts.

Personnel:

The trauma surgeon and the trauma team will perform the resuscitation. They will place the cannulae and initiate EPR. If possible, a perfusionist may assist with pumping for the cold fluid and with CPB. The cooperation of cardiac surgeons will be needed. A part-time coordinator will be involved in training, stocking the equipment needed for EPR, and collecting data. In addition, the coordinator may participate in EPR induction.

Because this is the first trial of EPR, subjects will not be enrolled when the trained team is not available.

Equipment for EPR:

Thoracotomy tray and standard trauma resuscitation equipment and supplies will be available per standard care of trauma patients. Specific equipment for this study that will be readily available in the ED will include: large volumes of ice-cold saline in a refrigerator (30 liters stored in a designated refrigerator for this trial), arterial and venous cannulae (various sizes and types), appropriate tubing, CPB pump, and hollow-fiber membrane oxygenator/heat exchangers. This equipment will be stored in a storage area near the trauma resuscitation rooms in the Emergency Department. It will be labeled at the site with the following warning: "CAUTION -Investigational Device/Drug. Limited by Federal (or United States) law to investigational use."

Concurrent Control Group:

We will collect data on concurrent patients who are appropriate candidates for EPR, but do not have EPR initiated because the team is not available. These data will include specifics of resuscitative efforts and the same outcome parameters as the EPR group. Per the request of the FDA, 10 concurrent control subjects will be entered and a detailed report will be submitted to the FDA prior to any further subject enrollment.

Historical Control Group:

Because of concern that bias may influence the selection of subjects who receive EPR, thus affecting the concurrent control group, outcome information regarding similar patients in the trauma registry of the respective institutions (Level I trauma centers) will be obtained. The most recent 100 patients who had undergone an ED thoracotomy will be reviewed. Additional subjects may be required in order to obtain at least 10 subjects who would have met criteria for entry into the study.

Consent:

Due to the emergency nature of the traumatic event and the need for immediate resuscitation, including initiation of EPR, this study must be performed under the Exception from Informed Consent for emergency research as outlined in FDA regulation 21CFR50.24. Once the subject has been stabilized, consent for continued participation in the study for collection of data and long-term follow-up, will be obtained from the subject's legal authorized representative (LAR). In addition, consent for follow up will be obtained for survivors in the control group. (See section X below for additional information regarding the exception from consent conditions, request, and justification.)

The research coordinator and one of the investigators will make every effort to contact the subject's LAR as soon as the subject is stable and the LAR seems prepared to understand the situation. There is no single time appropriate for notification of all subjects or LAR. We will notify as soon as appropriate for each case in the judgment of the treating team, recognizing that some families are dealing with end of life or similar issues. If the LAR is not immediately available, the research coordinator will continue to attempt to contact the subject's LAR. A summary of these efforts will be documented in the medical record. If the subject becomes competent to provide consent during the study period then he/she will be approached by the research coordinator and one of the investigators for consent. During the consent process, the details of the study will be reviewed along with potential risks and benefits, the endpoints of interest and the process by which these endpoints are evaluated.

For subjects who die before the research coordinator or an investigator has been able to discuss the study with the LAR, a letter will be sent to the LAR explaining the study and offering contact information if they are interested in discussing the study.

Outcome:

The primary outcome variable will be survival to hospital discharge without major disability (Glasgow Outcome Scale-Extended >5) after resuscitation with EPR in exsanguinating trauma patients, compared to concurrent or historic control patients. the ability (feasibility) and safety of inducing EPR. Secondary outcomes will include: 1) the feasibility and safety of rapidly inducing profound cerebral hypothermia for EPR in exsanguinating trauma patients, 2) 28-day survival, 3) 6-month neurologic functional outcome

(Glasgow Outcome Score Extended [GOSE]) and SF-36, and 4) the development of multiple organ dysfunction syndrome (MODS) (see Table: Multiple Organ Dysfunction Score) in the EPR group, as compared to a concurrent control group and historical controls.

For subjects who die, the coroner's office will be notified by the trauma service per routine policy.

The GOSE is defined as:

1. Dead
2. Vegetative state
3. Lower severe disability
4. Upper severe disability
5. Lower moderate disability
6. Upper moderate disability
7. Lower good recovery
8. Upper good recovery

Table: Multiple Organ Dysfunction Score					
Sum the worst scores of each of the individual systems over the course of the ICU stay					
	Score				
Organ system	0	1	2	3	4
Respiratory (PO ₂ /FiO ₂)	>300	226-300	151-225	76-150	≤75
Renal (serum creatinine - μmol/l)	≤1.1	1.2-2.3	2.4-3.9	4.0-5.6	>5.7
Hepatic (serum bilirubin - μmol/l)	≤1.1	1.2-3.5	3.6-7.1	7.2-14.1	>14.2
Cardiovascular (PAR*)	≤10.0	10.1-15.0	15.1-20.0	20.1-30.0	>30.0
Hematologic (platelet count –x 10 ⁻³)	>120	81-120	51-80	21-50	≤20

Primary objective

To demonstrate better survival to hospital discharge without major disability (Glasgow Outcome Scale-Extended >5) after resuscitation with EPR in exsanguinating trauma patients, compared to concurrent or historic control patients.

Secondary objective(s)

To examine the feasibility and safety of rapidly inducing profound cerebral hypothermia for EPR in exsanguinating trauma patients.

To examine 28-day survival, 6 and 12 -month neurologic functional outcome (Glasgow Outcome Score Extended [GOSE]) and SF-36, and the development of multiple organ dysfunction syndrome (MODS) in the EPR group, as compared to a concurrent control group.

Specific complications related to the implementation of EPR and CPB, such as vascular injuries, will be identified.

Data and Safety Monitoring Board.

This study will be monitored by a Data and Safety Monitoring Board (DSMB), which will include researchers with experience in resuscitation research from institutions not involved in the conduct of this clinical trial. At least one member of the DSMB will be a cardiothoracic surgeon.

At a minimum, the DSMB will be convened by teleconference or in person at least yearly. For the first 5-10 subjects enrolled in the trial (both EPR and control groups), the DSMB and the investigators will discuss each case by teleconference contemporaneously (within 30 days of subject enrollment). The DSMB will review each report submitted by the investigators to the FDA.

The DSMB will have the responsibility of making recommendations to the investigators and FDA regarding:

- Enrollment criteria, including inclusion and exclusion of subjects

- Technique used for induction of EPR and CPB for reperfusion
- Post-resuscitation mild hypothermia
- Outcome evaluations
- Patient safety
- Informed consent
- Performance of individual centers

The goal will be to enroll 10 subjects that undergo EPR and 10 concurrent control subjects. A detailed report will be filed with the FDA after the first 5 subjects in each group have been discharged or have expired. A final report will be filed after the hospital courses of 10 subjects in each group have been completed. All interim and outcome reports from the DSMB will also be sent to the USAMRMC ORP HRPO.

Outcome data and data analysis

Survival to hospital discharge without major disability, MODS scores, survival at 28 days, GOSE and SF-36 (at 6 and 12 months) will be compared between groups. Complications felt to be possibly or definitely associated with of the EPR technique will be specifically recorded. As with any cardiac arrest resuscitation trial, there is a risk that a subject will survive with a poor neurologic outcome (e.g., comatose, vegetative). Based on the current literature for survivors of cardiac arrest from trauma with standard care, this risk is small.

The decision to proceed with further clinical investigation of the EPR technique will depend upon the frequency of associated complications (in relation to the high risk of death and morbidity secondary to the original injuries) and lack of inferiority to standard care with regard to the secondary endpoints. Based on information learned during the course of the study, the entry criteria may be revised in order to select subjects most likely to benefit from the intervention. The technique for EPR may also be revised. Evaluating these new criteria or techniques may justify further investigation. If, despite revisions of entry criteria and technique, survival appears to be no better than (or worse than) standard care, the study could be stopped. The FDA, ORP HRPO, and reviewing IRBs will be notified of such revisions prior to their implementation.

VIII. INCLUSION / EXCLUSION CRITERIA

Inclusion criteria

Subjects must meet all of the following inclusion criteria:

- Penetrating trauma with clinical suspicion of exsanguinating hemorrhage
- Age 18-65
- At least 1 sign of life at the scene (pulse, respiratory efforts, spontaneous movements, reactive pupils)
- Loss of pulse <5 min prior to ED arrival or in the ED or operating room
- Thoracotomy performed without immediate return of a palpable pulse in the carotid arteries after clamping the descending thoracic aorta

Exclusion criteria.

Subjects will be excluded for any of the following:

- No signs of life for greater than 5 min prior to the decision to initiate EPR. This time frame is defined as the time from loss of pulse to the decision to switch to EPR.
- Age is >65 years or <18
- Obvious non-survivable injury
- Suggestion of traumatic brain injury, such as significant facial or cranial distortion
- Electrical asystole
- Rapid external assessment of the injuries suggests massive tissue trauma involving multiple body regions (for example, a crushed limb, distorted chest anatomy, or pelvic instability).
- Pregnancy

- Prisoners
- Those with aortic arch injury that would preclude flush should be excluded from study participation.
- Active Military personnel

Based on clinical experience and published data, we believe that the most appropriate candidates for EPR would be subjects who have suffered a cardiac arrest from trauma, presumably from exsanguination, and do not respond to standard resuscitative efforts, including thoracotomy in the ED or operating room. Because of the need to conduct this study under the exception from informed consent, adults (>18 yo) will be included. To include subjects in this feasibility trial with the greatest potential for benefit, we will only include subjects with penetrating trauma. Subjects must be in cardiac arrest in the ED or operating room, as documented by the absence of a pulse in the femoral and carotid arteries. Standard resuscitation would include rapid fluid resuscitation and a thoracotomy with right tube thoracostomy. Subjects would become eligible for EPR if they do not respond immediately to these maneuvers and the injuries cannot readily be repaired via the thoracotomy (e.g., a stab wound to the heart for which the tamponade can readily be released and the wound quickly closed).

A checklist (Appendix A) will be utilized to quickly determine subject eligibility.

Subjects known to be prisoners upon admission will be excluded from the study. But if a subject is taken into custody after being enrolled in the study, we will continue to collect data (includes medical record review and review of their vital status).

IX. SUBJECT RECRUITMENT & SCREENING

Screening procedures

The decision to enroll subjects into this trial will have to be made promptly by the trauma team resuscitating the subject. Information available to them will include the mechanism of injury, time from injury and paramedic arrival to ED arrival, physical examination for signs of life (pulse, breathing, spontaneous movements, reactive pupils), cardiac rhythm, and response to standard resuscitative efforts. This information will be available from Medic Command and the paramedics who transport the subject. Since time is of the essence, little more information may be available. The most important information for screening will be the condition of the subject upon arrival in the ED or operating room and the response to the standard resuscitative efforts, i.e., with either no or only transient restoration of pulse. No other screening procedures will be performed.

The number of subjects in this initial feasibility trial will be 20 (10 EPR and 10 concurrent control). After review of these subjects by the investigators, DSMB, FDA, and ORP-HRPO, a decision will be made to either discontinue the study, proceed with another cohort of subjects with revised inclusion criteria or EPR technique, or consider a randomized, pivotal trial.

X. INFORMED CONSENT PROCESS

This clinical study qualifies for the “Exception from informed consent for emergency research” outlined in the FDA regulation at 21 CFR Section 50.24. Listed below are the respective regulatory criteria and corresponding justifications for the applicability of this clinical study.

(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

These potential subjects are clearly in a life-threatening situation with unsatisfactory available treatments, as evidenced by a <10% chance of survival based on current literature. The collection of valid scientific evidence is necessary to determine the safety and effectiveness of EPR.

(2) Obtaining informed consent is not feasible because:

- (i) The subjects will not be able to give their informed consent as a result of their medical condition;*
- (ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and*
- (iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.*

Since the subjects will be in cardiac arrest at the time of enrollment into the trial, they will be unable to provide consent for study enrollment. The LAR of potential subjects is usually not immediately available either at the injury scene or in the hospital or, if available, may also be undergoing trauma treatment. Time requirements for initiation of EPR and the need to continue resuscitative efforts for the subject preclude any discussion of consent with the LAR, if available and capable of providing consent. Trauma is unpredictable, thus precluding prospective identification of individuals likely to become eligible for participation in this EPR study.

(3) Participation in the research holds out the prospect of direct benefit to the subjects because:

- (i) Subjects are facing a life-threatening situation that necessitates intervention;*
- (ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and*
- (iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.*

Potential subjects are clearly in a life-threatening situation with <10% chance of survival with currently available treatments. Animal studies suggest that EPR may improve chances for survival in these patients, thus there is potential for direct benefit. Given the high mortality in this situation, the relative risk of EPR is reasonable.

(4) The clinical investigation could not practicably be carried out without the waiver.

Given the situation in which EPR is to be utilized, prospective informed consent of potential subjects is not possible. The medical condition of potential EPR subjects will preclude their ability to provide prospective informed consent. LARs of potential subjects are not routinely available and/or are undergoing trauma treatment themselves. The decision to enter the patient/potential subject into the EPR arm of this trial must be made as soon as it is determined that s/he has not responded to standard ED resuscitative efforts and thus does not permit notification of the potential subject's LAR or, if the LAR is present and mentally capable, an informed consent discussion with the LAR. The investigation can therefore not be carried out without the waiver.

(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

The therapeutic window for implementing standard resuscitative efforts in the proposed subject population, determining that such procedures have failed, and implementing the EPR procedures is only a few (i.e., 5) minutes. Attempting to obtain prospective informed consent of the potential subject's LAR or permission of a family member is not possible during this very short time period and may actually be detrimental to the subject. After resuscitation, the investigators will notify the subject or the subject's LAR of the subject's participation in the study as soon as this is feasible. Informed consent of the subject or the subject's LAR will be obtained for continued participation in the study to include the collection of the subject's medical record information and participation in follow-up interviews.

(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sec. 50.24. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.

An informed consent document for continued participation of the EPR subject in the research study will be developed and approved by the IRB.

- (7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:*
- (i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;*
 - (ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;*
 - (iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;*
 - (iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and*
 - (v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.*

Community consultation and public disclosure will be conducted as per local IRB guidelines. Community consultation will include public forums in affected communities. These meetings are open meetings at a non-clinical site that is open for community members to hear information about the study and to ask questions about the study. After IRB endorsement of each forum, we will work with Media Relations to advertise this forum. Opt out methods will be discussed with the public. Potential options may include a hospital style ID bracelets will be made available to persons who do not want to be enrolled in the study and would rather opt-out. Hospital personnel would be trained to check for these bracelets prior to enrolling any patients.

Investigators will also present this study to representatives of the communities involved. In Pittsburgh, these representatives will include the Human Relations Commission of the City of Pittsburgh and the Center for Minority Health Community Research Advisory Board. A website which can receive email will be created by the investigative team to solicit electronic feedback.

Public disclosure will be performed both prior to study enrollment and at the completion of the study in the form of multimedia press releases. These will include plans for the study including potential risks and benefits and a summary of the results of the study upon completion.

Locally, we will work with Media Relations to generate press releases about this study. We anticipate that this activity will result in radio, television and newspaper coverage of our study. We will specifically target the local newspapers for the involved communities. All advertising will be approved by the local IRBs and ORP HRPO.

An independent DSMB, consisting of experts in trauma and the ethical aspects of resuscitation research, will be formed to oversee this study.

Given the specific circumstances in which EPR will be considered, the “therapeutic window” does not permit the contact of a family member of the potential subject to ask if s/he objects to the potential subject’s participation in the EPR procedures.

Title 10 United States Code 980

Title 10 United States Code 980 states that "Funds appropriated to the Department of Defense may not be used for research involving a human being as an experimental subject unless- (1) the informed consent of the subject is obtained in advance; or (2) in the case of research intended to be beneficial to the subject, the informed consent may be obtained from a legal representative of the subject."

Even though there is intent to benefit patients enrolled in this study, the informed consent of the LAR is likely not going to be possible to secure in advanced, hence a waiver of 10 USC 980 will be requested.

XI. DATA COLLECTION, ANALYSIS and COORDINATION

Data collection

Procedures to assess efficacy:

The primary outcome variable will be survival to hospital discharge without major disability (Glasgow Outcome Scale-Extended >5) after resuscitation with EPR in exsanguinating trauma patients, compared to concurrent or historic control patients. the ability (feasibility) and safety of inducing EPR. Secondary outcomes will include: 1) the feasibility and safety of rapidly inducing profound cerebral hypothermia for EPR in exsanguinating trauma patients, 2) 28-day survival, 3) 6 and 12-month neurologic functional outcome (Glasgow Outcome Score Extended [GOSE]) and SF-36, and 4) the development of multiple organ dysfunction syndrome (MODS) (see Table: Multiple Organ Dysfunction Score) in the EPR group, as compared to a concurrent control group and historical controls.

Once the EPR subject has been rewarmed and, if possible, weaned from CPB, there will be no additional invasive procedures performed on the subject for the specific purpose of the research study. The subject will continue to undergo standard medical procedures as indicated for the clinical care of his/her trauma injury.

For subjects in both arms of the study, the medical record will be utilized to determine the occurrence of multiple organ system dysfunction or death.

The MODS Score (Table) will be utilized to quantify the level of organ system dysfunction.

Neurologic functional outcome will be assessed in survivors using the GOSE and SF-36 at 6 and 12 months. If the subject is discharged from the hospital prior to either of these dates, GOSE information will be obtain via telephone calls to the subject or the subject's LAR.

Table: Multiple Organ Dysfunction Score					
Sum the worst scores of each of the individual systems over the course of the ICU stay					
	Score				
Organ system	0	1	2	3	4
Respiratory (PO ₂ /FiO ₂)	>300	226-300	151-225	76-150	≤75
Renal (serum creatinine - μmol/l)	≤1.1	1.2-2.3	2.4-3.9	4.0-5.6	>5.7
Hepatic (serum bilirubin - μmol/l)	≤1.1	1.2-3.5	3.6-7.1	7.2-14.1	>14.2
Cardiovascular (PAR*)	≤10.0	10.1-15.0	15.1-20.0	20.1-30.0	>30.0
Hematologic (platelet count –x 10 ⁻³)	>120	81-120	51-80	21-50	≤20
Neurologic (Glasgow coma score)	15	13-14	10-12	7-9	≤6

The GOSE is defined as:

1. Dead
2. Vegetative state
3. Lower severe disability
4. Upper severe disability

5. Lower moderate disability
6. Upper moderate disability
7. Lower good recovery
8. Upper good recovery

Procedures to assess safety:

The safety of the EPR procedures will be continually monitored during the subject's hospitalization. Although complications specifically associated with the EPR procedures will likely be difficult to differentiate from complications arising from the subject's trauma and/or standard resuscitative efforts, we will attempt to do so. These could include, but are not limited to, injuries to vascular structures, air or clot embolism, and hemolysis. Hypothermia can lead to coagulopathy.

Induction of EPR in a pulseless trauma victim bears the risk of survival with significant neurologic dysfunction after restoring circulation in a patient who would otherwise have expired. As this outcome is possible with standard care also, this will be difficult to assess, but will be monitored in relation to the concurrent control group.

Outcome data and data analysis.

The primary outcome measure is survival to hospital discharge without major disability (Glasgow Outcome Scale-Extended ≥ 5). Secondary outcomes include survival at 28 days, GOSE and SF-36 (at 6 and 12 months) will be compared between groups. Complications felt to be possibly or definitely associated with the EPR technique will be specifically recorded. The decision to proceed with further clinical investigation of the EPR technique will depend upon the frequency of associated complications (in relation to the high risk of death and morbidity secondary to the original injuries) and lack of inferiority to standard care with regard to the secondary endpoints. Based on information learned during the course of the study, the entry criteria may be revised in order to select subjects most likely to benefit from the intervention. The technique for EPR may also be revised. Evaluating these new criteria or techniques may justify further investigation. The FDA, ORP HRPO, and reviewing IRBs will be notified of such revisions prior to their implementation.

Data Coordination

Data will be collected at each site on the attached case report form (Appendix C). The information will be transmitted via a secure website to the data collection center at the University of Pittsburgh. Each subject will be assigned a unique code for the study. No patient identifiers will be transmitted to the data center. Links to personal identifiers will be maintained in locked filing cabinets at each site.

XII. LABELING & STORAGE OF DATA & SPECIMENS

A Case Report Form (CRF, see Appendix B) will be completed for each subject (both arms) enrolled into the clinical study. The responsible investigator for each study site will review, approve and sign/date each completed CRF; the investigator's signature serving as attestation of the investigator's responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic.

The CRF will be electronically transmitted to the data center at the University of Pittsburgh without patient identifiers.

The investigator-sponsor and study site investigators will maintain records in accordance with Good Clinical Practice guidelines to include:

- FDA correspondence related to the Investigational Device Exemption (IDE) application and Investigational Plan; including copies of submitted FDA Form 3500As, supplemental IDE applications, current investigator lists, progress reports, notice of device recall or disposition, and failure to obtain informed consent reports;
- IRB correspondence (including approval notifications) related to the clinical protocol; including copies of adverse event reports and annual or interim reports;

- Current and past versions of the IRB-approved clinical protocol and corresponding IRB-approved consent form(s) and, if applicable, subject recruitment advertisements.
- Signed Investigator's Agreements and Certifications of Financial Interests of Clinical Investigators;
- Curriculum vitae (investigator-sponsor and clinical protocol sub-investigators);
- Certificates of required training (e.g., human subject protections, Good Clinical Practice, etc.) for investigator-sponsor and listed sub-investigators;
- Signed informed consent forms;
- Completed Case Report Forms; signed and dated by study site investigators;
- Source Documents or certified copies of Source Documents;
- Monitoring visit reports;
- Copies of investigator-sponsor correspondence to study site investigators, including notifications of adverse effect information;
- Subject identification code list;
- Interim data analysis report(s); and the
- Final clinical study report.

The CRFs will be given an alphanumeric code. This code will be linked to the subject via a subject identification code list. The CRFs and the code list will be maintained in a locked cabinet in the local investigator's office. These identifiers will not be transmitted to the central data center at the University of Pittsburgh. Subject names or other directly identifiable information will not appear on any reports, publications, or other disclosures of clinical study outcomes.

The investigator-sponsor and study site investigators will retain the specified records and reports for up to 2 years after investigations under the IDE have been discontinued and the FDA so notified.

XIII. RISK AND INJURY

Anticipated risks of the EPR procedure itself include, but are not limited to, injuries to the vascular structures that are cannulated (aorta, femoral vessels, right atrium), air or clot embolism, and hemolysis. These risks will be minimized by extensive additional training of involved, experienced surgical and critical care personnel and the use of FDA-approved cannulae and equipment. Hypothermia carries the risk of coagulopathy. Aggressive replacement of clotting factors and platelets during rewarming will help minimize this risk.

In addition, as in any resuscitation trial, there is a risk of resuscitating a subject who would otherwise have died, but survives with significant neurologic deficits. This is complicated by the fact that some survivors of cardiac arrest from trauma also survive with neurologic deficits. The comparative risks are unknown. The risk of long-term survival with severe neurologic dysfunction will be minimized by consideration, with involvement of the subject's LAR, for withdrawal of care when the predicted chance for meaningful neurologic recovery is very low.

The expected mortality for the potential subjects to be included in this study, when treated with the current standard of care, is >90%. Based upon preclinical studies as described in the Background section above (section VII), EPR has the potential to improve outcome of these subjects. Thus, the benefit-to-risk ratio is favorable.

XIV. BENEFIT(S)

Potential subjects are clearly in a life-threatening situation with <10% chance of survival with currently available treatments. Animal studies suggest that EPR may improve chances for survival in these patients, thus there is potential for direct benefit. Given the high mortality in this situation, the relative risk of EPR is reasonable.

XV. COMPENSATION

There is no compensation for participation in this study. Emergency medical treatment for injuries solely and directly related to participation in this research study will be provided by the hospital. It is possible that hospital may bill insurance providers for the costs of this emergency treatment, but none of these costs will be charged directly to the subject. If any research-related injury requires medical care beyond this emergency treatment, the subject may be responsible for the costs of this follow-up care unless otherwise specifically stated. There is no plan for monetary compensation

XVI. CONFIDENTIALITY

Accurate and complete study records will be maintained and made available to representatives of the U.S. Army Medical Research and Materiel Command. These representatives are authorized to review research records as part of their responsibility to protect human research volunteers. Research records will be stored in a confidential manner so as to protect the confidentiality of subject information.

In unusual cases, these research records may be released in response to an order from a court of law. It is also possible that the University Research Conduct and Compliance Office may inspect these research records.

XVII. ADVERSE EVENTS

See Appendix C

Adverse event definitions.

Adverse effect. Any untoward medical occurrence in a clinical study of an investigational device; regardless of the causal relationship of the problem with the device or, if applicable, other study treatment or diagnostic product(s).

Associated with the investigational device or, if applicable, other study treatment or diagnostic product(s). There is a reasonable possibility that the adverse effect may have been caused by the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Complications specifically associated with the EPR procedures will likely be difficult to differentiate from complications arising from the subject's trauma and/or standard resuscitative efforts. In this regard, we will take a conservative approach whereby any observed complication felt to be possibly or definitely related to the EPR procedures will be recorded as associated with this study treatment.

Anticipated adverse effects of the EPR procedures that will be specifically monitored in this study include:

1. Major vascular injury (requiring operative intervention) secondary to cannula placement.
2. Air or clot embolism either during the flush or during CPB.
3. Hemolysis
4. Excessive coagulopathy
5. Any death not explained by the injury severity and duration of cardiac arrest

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse effect. Any adverse effect that places the subject, in the view of the investigator-sponsor, at immediate risk of death from the effect as it occurred (i.e., does not include an adverse effect that, had it actually occurred in a more severe form, might have caused death).

Serious adverse effect. Any adverse effect that results in any of the following outcomes: death, a life-threatening adverse effect, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Hospitalization shall include any initial admission (even if less than 24 hours) to a healthcare facility as a result of a precipitating clinical adverse effect; to include transfer within the hospital to an intensive care unit. Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse effect (e.g., for a preexisting condition not associated with a new adverse effect or with a worsening of the preexisting condition; admission for a protocol-specified procedure) is not, in itself, a serious adverse effect.

Unexpected adverse effect. Any adverse effect, the frequency, specificity or severity of which is not consistent with the risk information described in the clinical study protocol(s) or elsewhere in the current IDE application, as amended.

Unanticipated adverse device effect. Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Anticipated risks of the EPR procedure itself include:

1. Injuries to the vascular structures that are cannulated (aorta, femoral vessels, right atrium)
2. Air or clot embolism
3. Hemolysis
4. Coagulopathy

Eliciting adverse effect information.

For surviving subjects (both arms), the research coordinator will visit the subject daily for two weeks to evaluate for any adverse events that were not recorded in the subject's medical record. Surviving subjects will also be routinely questioned about adverse effects at the 28 day and 6 and 12 month follow-up interviews.

Recording and assessment of adverse effects.

All observed or volunteered serious adverse effects, regardless of suspected causal relationship to the EPR or standard resuscitative procedures will be recorded in the subjects' case histories. For serious adverse effects occurring in the EPR subjects, sufficient information will be pursued and/or obtained so as to permit an assessment of the casual relationship between the adverse effect and EPR procedures.

Adverse effects will be treated consistent with standard medical practice.

Causality and severity assessment:

The investigator-sponsor will promptly review documented serious adverse effects to determine if the adverse effect was possible or definitely related to the study treatment.

If the investigator-sponsor's final determination of causality is "unknown and of questionable relationship to the EPR procedures", the serious adverse effect will be classified as *associated with the EPR procedures* for reporting purposes. If the investigator-sponsor's final determination of causality is "unknown but not related to the EPR procedures", this determination and the rationale for the determination will be documented in the respective subject's case history.

All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and subject deaths related to participation in the study should be promptly reported by phone (301-619-2165), by email (hsrrb@det.amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will

be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-PH, 504 Scott Street, Fort Detrick, Maryland 21702-5012

The DSMB is required to review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the DSMB must comment on the outcomes of the event or problem and in case of a serious adverse event or death, comment on the relationship to participation in the study. The DSMB must also indicate whether he/she concurs with the details of the report provided by the principal investigator. Reports for events determined by either the investigator or DSMB to be possibly or definitely related to participation and reports of events resulting in death must be promptly forwarded to the ORP HRPO.

XVIII. CHANGES TO PROTOCOL

Major modifications to the research protocol and any modifications that could potentially increase risk to subjects will be submitted to the ORP HRPO for approval prior to implementation. All other amendments will be submitted with the continuing review report to the ORP HRPO for acceptance.

Any deviation to the protocol that may have an effect on the safety or rights of the subject or the integrity of the study must be reported to the ORP HRPO as soon as the deviation is identified.

The University of Pittsburgh IRB stipulates that modifications to the protocol must be submitted in the following circumstances:

A minor modification is defined as a change that would not materially affect an assessment of the risks and benefits of the study or does not substantially change the specific aims or design of the study. Examples of minor modifications may include:

- the addition of research activities listed under sections 2.2 Exempt Review or 2.3 Expedited Review (University of Pittsburgh IRB Reference Manual)
- an increase or decrease in proposed human research subject enrollment supported by a statistical justification
- narrowing the range of inclusion criteria
- broadening the range of exclusion criteria
- alterations in the dosage form (e.g., tablet to capsule or oral liquid) of an administered drug, provided the dose and route of administration remain constant
- decreasing the number or volume of biological sample collections, provided that such a change does not affect the collection of information related to safety evaluations
- an increase in the length of confinement or number of study visits for the purpose of increased safety monitoring
- a decrease in the length of confinement or number of study visits, provided that such a decrease does not affect the collection of information related to safety evaluations 3 - 1
- alterations in human research subject payment or liberalization of the payment schedule with proper justification
- changes to improve the clarity of statements or to correct typographical errors, provided that such a change does not alter the content or intent of the statement the addition or deletion of study sites
- minor changes specifically requested by the IRB; Human Use Subcommittee, Radiation Safety Committee; Radioactive Drug Research Committee; or Clinical and Translational Research Center

A major modification is defined as any change which materially affects an assessment of the risks and benefits of the study or substantially changes the specific aims or design of the study. Examples of major modifications may include:

- broadening the range of inclusion criteria
- narrowing the range of exclusion criteria
- alterations in the dosage or route of administration of an administered drug
- extending substantially the duration of exposure to the test material or intervention
- the deletion of laboratory tests, monitoring procedures, or study visits directed at the collection of information for safety evaluations
- the addition of serious unexpected adverse events or other significant risks
- changes which, in the opinion of the IRB chairperson or his/her designee, do not meet the criteria or intent of a minor modification

XIX. CONTINUING REVIEW, FINAL REPORT AND NOTIFICATION OF COMPLIANCE INSPECTIONS

The protocol will be conducted in accordance with the protocol submitted to and approved by the USAMRMC ORP HRPO and will not be initiated until written notification of approval of the research project is issued by the USAMRMC ORP HRPO.

Accurate and complete study records will be maintained and made available to representatives of the U.S. Army Medical Research and Materiel Command as a part of their responsibility to protect human subjects in research. Research records will be stored in a confidential manner so as to protect the confidentiality of subject information.

All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study, and subject deaths related to participation in the study will be promptly reported by phone (301-619-2165), by email (hsrrb@amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RP, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the Sponsor, or regulatory agencies will be promptly reported to the USAMRMC ORP HRPO.

Any deviation to the protocol that may have an adverse effect on the safety or rights of the subject or the integrity of the study will be reported to the USAMRMC ORP HRPO as soon as the deviation is identified.

Major modifications to the research protocol and any modifications that could potentially increase risk to subjects will be submitted to the USAMRMC ORP HRPO for approval prior to implementation. All other amendments will be submitted with the continuing review report to the USAMRMC ORP HRPO for acceptance.

A copy of the approved continuing review report and the local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become

available. A copy of the approved final study report and local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available.

The knowledge of any pending compliance inspection/visit by the FDA, OHRP, or other government agency concerning this clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any Regulatory Agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements that relate to this clinical investigation or research will be reported immediately to USAMRMC ORP HRPO.

XX. LITERATURE REVIEW

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Appendix A: Subject Eligibility Checklist

Inclusion Criteria

The subject **MUST** meet all of the following criteria:

Yes	No	Criterion
<input type="checkbox"/>	<input type="checkbox"/>	Penetrating trauma with clinical suspicion of exsanguinating hemorrhage
<input type="checkbox"/>	<input type="checkbox"/>	Age 18-65
<input type="checkbox"/>	<input type="checkbox"/>	At least 1 sign of life at the scene (pulse, respiratory efforts, spontaneous movements, reactive pupils)
<input type="checkbox"/>	<input type="checkbox"/>	Loss of pulse <5 min prior to ED arrival or in the ED or operating room
<input type="checkbox"/>	<input type="checkbox"/>	ED thoracotomy performed without immediate return of a palpable pulse in the carotid arteries after clamping the descending thoracic aorta

Exclusion criteria

Subjects will be excluded for any of the following:

<input type="checkbox"/>	<input type="checkbox"/>	No signs of life for greater than 5 min prior to the decision to initiate EPR. This time frame is defined as the time from loss of pulse to the decision to switch to EPR.
<input type="checkbox"/>	<input type="checkbox"/>	Age is >65 years or <18
<input type="checkbox"/>	<input type="checkbox"/>	Obvious non-survivable injury
<input type="checkbox"/>	<input type="checkbox"/>	Suggestion of traumatic brain injury, such as significant facial or cranial distortion
<input type="checkbox"/>	<input type="checkbox"/>	Electrical asystole
<input type="checkbox"/>	<input type="checkbox"/>	Rapid external assessment of the injuries suggests massive tissue trauma involving multiple body regions (for example, a crushed limb, distorted chest anatomy, or pelvic instability).
<input type="checkbox"/>	<input type="checkbox"/>	Pregnancy
<input type="checkbox"/>	<input type="checkbox"/>	Prisoners
<input type="checkbox"/>	<input type="checkbox"/>	Those with aortic arch injury that would preclude flush should be excluded from study Participation
<input type="checkbox"/>	<input type="checkbox"/>	Active Military personnel

Appendix B: Case Report Form

OVERVIEW OF SUBJECT DATA

EPR ID	<input type="text"/>
DATE OF INJURY	<input type="text"/>
HOSPITAL	<input type="text"/>
AGE	<input type="text"/>
ETHNICITY	<input type="text"/>
GENDER	<input type="text"/>
MECHANISM OF INJURY	<input type="text"/>
TIME PULSE LOST	<input type="text"/>
TIME EPR DECISION	<input type="text"/>
OBVIOUS NON SURVIVABLE	<input type="text"/>
EVIDENCE OF TBI	<input type="text"/>
ASYSTOLE	<input type="text"/>
MASSIVE TRAUMA	<input type="text"/>
PREGNANCY	<input type="text"/>
PRISONER	<input type="text"/>
TRANSPORTATION TYPE	<input type="text"/>
AGENCY NAME	<input type="text"/>
VEHICLE #	<input type="text"/>
TIME 911 CALL	<input type="text"/>
TIME ARRIVAL AT SCENE	<input type="text"/>
TIME DEPARTING SCENE	<input type="text"/>
TIME ED ARRIVAL	<input type="text"/>

ED Resuscitation Summary

WORST SBP	<input type="text"/>
WORST DBP	<input type="text"/>
WORST HR	<input type="text"/>
WORST RR	<input type="text"/>
BEST GCS	<input type="text"/>
CRYSTALLOIDS	<input type="text"/>
COLLOIDS	<input type="text"/>
PRBC	<input type="text"/>
FFP	<input type="text"/>
PLATELETS	<input type="text"/>
CRYO	<input type="text"/>
HB	<input type="text"/>
WBC	<input type="text"/>
PT	<input type="text"/>
PTT	<input type="text"/>
PLT COUNT	<input type="text"/>
PAO2	<input type="text"/>
SAO2	<input type="text"/>
FIO2	<input type="text"/>
VENTILATOR RATE	<input type="text"/>
VENTILATOR TV	<input type="text"/>
CREAT	<input type="text"/>
BILIRUBIN	<input type="text"/>

Daily Followup

WORST SBP	<input type="text"/>
WORST DBP	<input type="text"/>
WORST HR	<input type="text"/>
WORST RR	<input type="text"/>
BEST GCS	<input type="text"/>
CRYSTALLOIDS	<input type="text"/>
COLLOIDS	<input type="text"/>
PRBC	<input type="text"/>
FFP	<input type="text"/>
PLATELETS	<input type="text"/>
CRYO	<input type="text"/>
HB	<input type="text"/>
WBC	<input type="text"/>
PT	<input type="text"/>
PTT	<input type="text"/>
PLT COUNT	<input type="text"/>
PAO2	<input type="text"/>
SAO2	<input type="text"/>
FIO2	<input type="text"/>
VENTILATOR RATE	<input type="text"/>
VENTILATOR TV	<input type="text"/>
CREAT	<input type="text"/>
BILIRUBIN	<input type="text"/>

ED Thoracotomy

EPR ID	<input type="text"/>
OPERATION TITLE	<input type="text"/>
OP DATE	<input type="text"/>
TIME START	<input type="text"/>
TIME CROSS CLAMP AORTA	<input type="text"/>
TIME UNCLAMP AORTA	<input type="text"/>
TIME AORTIC CANNULA PLACED	<input type="text"/>
TIME FLUSH STARTED	<input type="text"/>
TIME GOAL TEMP REACHED	<input type="text"/>
TIME FLUSH COMPLETED	<input type="text"/>
STERNUM TRANSECTED?	<input type="text"/>
BLOOD LOSS FROM STERNUM	<input type="text"/>
EBL	<input type="text"/>
OP CRYSTALLOIDS	<input type="text"/>
OP COLLOIDS	<input type="text"/>
OP PRBC	<input type="text"/>
OP UO	<input type="text"/>
TIME CBP STARTED	<input type="text"/>
TIME CBP STOPPED	<input type="text"/>

OPERATIONS

EPR ID	<input type="text"/>
OPERATION TITLE	<input type="text"/>
EBL	<input type="text"/>
OP DATE	<input type="text"/>
OP CRYSTALLOIDS	<input type="text"/>
OP COLLOIDS	<input type="text"/>
OP PRBC	<input type="text"/>
OP UO	<input type="text"/>

INJURIES

EPR ID
INJURY REGION
ABBREVIATED INJURY SEVERITY

COMPLICATION

EPR ID
COMPLICATION

INFECTION COMPLICATIONS

EPR ID
INFECTION
DATE OF ONSET

LONG TERM FOLLOW UP

EPR ID
ALIVE
GOSE
RESPONDENT

MANUFACTURER INFORMATION

CPB ARTERIAL CANNULA SIZE	<input type="text"/>
CPB ARTERIAL CANNULA SITE	<input type="text"/>
CPB ARTERIAL CANNULA COMPANY	<input type="text"/>
CPB ARTERIAL CANNULA TYPE	<input type="text"/>
CPB ARTERIAL CANNULA LOT	<input type="text"/>
CPB VENOUS CANNULA SIZE	<input type="text"/>
CPB VENOUS CANNULA SITE	<input type="text"/>
CPB VENOUS CANNULA COMPANY	<input type="text"/>
CPB VENOUS CANNULA TYPE	<input type="text"/>
CPB VENOUS CANNULA LOT	<input type="text"/>
SALINE COMPANY	<input type="text"/>
SALINE LOT	<input type="text"/>
HEPARIN SOURCE	<input type="text"/>
HEPARIN LOT	<input type="text"/>

Appendix C: Adverse Event Form
(To Be Completed by the Principal Investigator)

IRB #	Principal Investigator:
Event date:	Date event reported to PI:
Subject ID:	Protocol: Same Different
Event report: Initial Follow-up #	Enrollment site: XXXXX

Research Drug/Device/Intervention: _____

Brief Description of Event: _____

Action Taken: _____

<p>Causality:</p> <p>Definite</p> <p>Possible <i>(there is a reasonable possibility that the adverse event, incident, experience or outcome may have been caused by the procedures involved in the research)</i></p> <p>Unrelated</p> <p>Probability:</p> <p>Expected</p> <p>Unexpected <i>(in terms of nature, severity, or frequency in the consent form)</i></p> <p>Is this a gene transfer study? _____</p>	<p>Event Severity:</p> <p>Serious <i>(meets one of the following criteria) A modification should be considered.</i></p> <p>>Death</p> <p>>Life threatening <i>(places subject at immediate risk of death from the event as it occurred)</i></p> <p>>Results in inpatient hospitalization or prolongation of existing hospitalization</p> <p>>Results in a persistent or significant disability/incapacity</p> <p>>Results in a congenital anomaly/birth defect</p> <p>>Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition</p> <p>Non Serious <i>(suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized) A modification should be considered.</i></p> <p>No additional risk of harm to subjects</p>
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DECLARATION: I certify that I have reviewed the attached report and conclude that the risk-benefit ratio of the research continues to be acceptable, and that the risks are minimized to the greatest extent possible.

Principal Investigator's Signature: _____ Date: ____/____/____

Principal Investigator's Printed name: _____