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## COUNTY OF ORANGE HEALTH CARE AGENCY

### HEALTH DISASTER MANAGEMENT EMERGENCY MEDICAL SERVICES

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May 9, 2008

Dan Smiley, Acting Director  
State of California Emergency Medical Services Authority  
1930 9th Street  
Sacramento, California 95814-7043

SUBJECT: REQUEST FOR APPROVAL - TRIAL STUDY OF HYPERTONIC  
RESUSCITATION FOLLOWING TRAUMATIC INJURY

Dear Mr. Smiley: *Dean*

Attached is a Request for Approval for Trial Study application for a federally funded study titled, Hypertonic Resuscitation Following Traumatic Injury. This is a Resuscitation Outcomes Consortium (ROC) multicenter trial that is currently ongoing in San Diego County and is planned for initiation in Orange County. A copy of the EMSA letter of approval for the San Diego EMS participation in the trial is included with this application.

I appreciate your help with this matter. Please let me know of any questions or concerns you may have at [ssratton@ochca.com](mailto:ssratton@ochca.com) or by phone at (714) 834-2824.

With best regards,

*Stratton*  
Samuel J. Stratton, MD, MPH  
Medical Director  
Health Disaster Management/Emergency Medical Services

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EMS AUTHORITY  
08 MAY 14 PM 12:07

REQUEST FOR APPROVAL

Check One:  Local Optional Scope of Practice  Trial Study

EMS Medical Director: Sam Stratton Date: 5/09/2008

Local EMS Agency: Orange County

Proposed Procedure or Medication: Hypertonic Resuscitation following Traumatic Injury

Please provide the following information. For information provided, check "yes" and describe. For information not provided, check "no" and state the reason it is not provided.

Yes No

1. Description of the procedure or medication requested: IRB Protocol Narrative  
Provided - pages 1-15

2. Description of the medical conditions for which the procedure/medication will be utilized: Section 4 of IRB Protocol, pages 19-22

3. Alternatives (Please describe any alternate therapy[ies] considered for the same conditions and any advantages and disadvantages): Section 8 of IRB Protocol, page 35

4. An estimate of frequency of utilization: Estimated (per trauma registry)  
500 cases/year in Orange County.

5. Other factors or exceptional circumstances: This is a multicenter,  
randomized, controlled trial.

Please attach the following documents. Check "yes" for each document attached; for documents not attached, check "no" and state the reason it is not attached.

Yes No

6. Any supporting data, including relevant studies and medical literature. Refer to summary of data - Section 1, IRB Protocol, pages 1-15

7. Recommended policies/procedures to be instituted regarding:

Use Hypertonic Resuscitation is investigational

Medical Control Double Blind Study, hypertonic vs normal saline

Treatment Protocols Double Blind Study, hypertonic vs normal saline

Quality assurance of the procedure or medication Appendix S of IRB Protocol

8. Description of the training and competency testing required to implement the procedure or medication. Attached - Online Training Program

9. Copy of the local EMS System Evaluation and Quality Improvement Program plan for this request. Formal Federally funded study - blinded data with  
Outside Data Safety Monitoring Committee

**EMERGENCY MEDICAL SERVICES AUTHORITY**

1930 9<sup>th</sup> STREET  
SACRAMENTO, CA 95814-7043  
(916) 322-4338 FAX (916) 324-2875



July 6, 2005

Gary Vilke, MD, FACEP, FAAEM  
EMS Medical Director  
San Diego County EMS Agency  
6255 Mission Gorge Road  
San Diego, CA 92120

Dear <sup>Gary</sup> Dr. Vilke:

This is to advise you that your request for approval to conduct a Trial Study on Hypertonic Resuscitation following Traumatic Injury is approved by the EMS Authority once the study is approved by the Food and Drug Administration (FDA) and the local Investigative Review Boards (IRBs) of the five San Diego County trauma centers. Approval by the EMS Authority, however, is contingent upon your agreement with the following conditions: 1) The EMS Authority will be provided with the finalized research protocol prior to enrollment of any patients, 2) Immediate notification (by phone or fax) will be provided to the Director of the EMS Authority of any occurrence of a serious adverse event related to the prehospital portion of the study, and 3) a written trial study progress report, including a summary of patient enrollment, all serious adverse events, and any correspondence between an IRB and the independent safety committee, will be submitted to the EMS Authority every six months in lieu of the usual 18-month report.

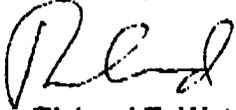
As you know, your request was reviewed by the EMS Authority's Medical Consultant, Dr. Steven Tharratt, in consultation with the members of the Scope of Practice Committee of the Emergency Medical Directors Association of California (EMDAC), on June 21, 2005. It was the recommendation of Dr. Tharratt and the Committee members that the study be approved with the conditions noted above.

Please advise the Director of the EMS Authority of the decision of the FDA and the local IRBs concerning this proposed study. If approved by the FDA and IRBs, please advise Ms. Nancy Steiner, Chief, EMS Personnel Division, of the initiation date of the study. Also, please advise Ms. Steiner of the termination date of the Polyheme Trial Study once the Hypertonic Resuscitation Trial Study is initiated as was discussed at the EMDAC Scope of Practice Meeting.

Gary Vilke, MD, FACEP, FAAEM  
July 6, 2005  
Page 2

If you have any questions regarding this matter, please contact Dr. Tharratt or Ms. Steiner by calling (916) 322-4336 or e-mailing [rstharratt@emsa.ca.gov](mailto:rstharratt@emsa.ca.gov), or [nancy.steiner@emsa.ca.gov](mailto:nancy.steiner@emsa.ca.gov).

Sincerely,



Richard E. Watson  
Interim Director

cc: Patti Murrin, EMS Administrator,  
San Diego County EMS Agency

David Hoyt, MD, FACS,  
University of California, San Diego

Joseph Barger, MD, Chair,  
EMDAC Scope of Practice Committee

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**PROTOCOL NARRATIVE**  
University of California, Irvine  
Institutional Review Board  
Version: July 2006

HS#: \_\_\_\_\_  
For IRB Office Use Only

**Lead Researcher Name:** David B. Hoyt, M.D.  
**Study Title:** Hypertonic Resuscitation following Traumatic Injury

**Important:** Please read the instructions before completing this protocol narrative.

**NON-TECHNICAL SUMMARY**

Provide a non-technical summary of the proposed research project that can be understood by IRB members with varied research backgrounds, non-scientists and community members. The summary should include a brief statement of the purpose of the research and related theory/data supporting the intent of the study and a brief description of the procedure(s) involving human subjects. ***This summary should not exceed more than ½ a page.***

Trauma is the leading cause of death among North Americans between the ages of 1 and 44 years. The majority of these deaths result from hypovolemic shock or severe brain injury. Patients in hypovolemic shock develop a state of systemic tissue ischemia with a subsequent reperfusion injury at the time of fluid resuscitation. Conventional resuscitation involves the intravenous (IV) administration of a large volume of isotonic (normal saline) or slightly hypotonic (lactated ringers, LR) solutions beginning in the pre-hospital setting. Although not conclusive, prior animal and human studies have suggested that alternative resuscitation with hypertonic saline (7.5%) solutions may reduce mortality in these patients. Furthermore, hypertonic fluids may have specific advantages in the brain-injured patient, as they may aid in the rapid restoration of cerebral perfusion and prevent extravascular fluid sequestration, thereby limiting secondary brain injury. In addition, recent studies have demonstrated that hypertonicity significantly alters the activation of inflammatory cells, an effect that may reduce subsequent organ injury from ischemia-reperfusion and decrease nosocomial infection.

This study seeks to address the impact of hypertonic resuscitation on two injured patient populations, those with hypovolemic shock and those with severe traumatic brain injury. The purpose of the study is to find out whether fluids with a high content of salt or fluids with a high content of salt and sugar will lead to an improved outcome following traumatic injury when given at the scene of an accident compared to balanced salt water (normal saline). The three fluid therapy studied are: high salt fluid (7.5% salt in water), high salt fluid plus sugar (6% dextran), or balanced salt water (normal saline). The study will last 28 days. During this time, medical records to see how patients are progressing will be collected.

The primary outcome for the hypovolemic shock group will be 28 day survival and the primary outcome for the TBI group will be neurologic outcome 6 months after injury based on the Extended Glasgow Outcome score.

**SECTION 1: PURPOSE AND BACKGROUND OF THE RESEARCH**

\_\_\_\_\_

1. Describe the **purpose of the research** project and state the overall objectives, specific aims, hypotheses (or research question) and rationale for performing the study.
2. Provide the **relevant background information** on the aims/hypotheses (or research question) to be tested and the procedures/products/techniques under investigation.
3. Include a description of the predictor and outcome variables, as appropriate.
4. Include a critical evaluation of existing knowledge, and specifically identify the information gaps that the project intends to address.
5. Describe previous research with animals and/or humans that provides a basis for the proposed research. Include references/citations, as applicable.

### **PURPOSE OF STUDY**

To determine the impact of hypertonic resuscitation on survival for blunt or penetrating trauma patients in hypovolemic shock (Study 1) and to determine the impact of hypertonic resuscitation on long term (6 month) neurologic outcome for blunt trauma patients with severe traumatic brain injury (Study 2).

### **AIMS AND HYPOTHESES**

#### **Study 1: Hypertonic Resuscitation for Hypovolemic Shock**

**Aim 1a:** To determine if prehospital administration of 7.5% hypertonic saline/dextran (HSD), compared to current standard therapy with normal saline (NS), as an initial resuscitation fluid affects survival following traumatic injury with hypovolemic shock.

- Hypothesis: Resuscitation of hypovolemic shock following injury with a single bolus of HSD as the initial resuscitation fluid will result in better 28 day survival when compared to conventional resuscitation with NS.

**Aim 1b:** To determine if prehospital administration of 7.5% hypertonic saline without dextran (HS), compared to current standard therapy with normal saline (NS) as an initial resuscitation fluid affects survival following traumatic injury with hypovolemic shock.

- Hypothesis: Resuscitation of hypovolemic shock following injury with a single bolus of HS as the initial resuscitation fluid will result in better 28 day survival when compared to conventional resuscitation with NS.

#### **Study 2: Hypertonic Resuscitation for Severe Traumatic Brain Injury**

**Aim 2a:** To determine if prehospital administration of HSD compared to current standard therapy with NS as an initial resuscitation fluid affects neurological outcome following severe traumatic brain injury.

- Hypothesis: Resuscitation of patients with severe traumatic brain injury with a single bolus of HSD as the initial resuscitation fluid will result in better neurological function 6 months from date of injury when compared to conventional resuscitation with NS.

**Aim2b:** To determine if prehospital administration of HS compared to current standard therapy with NS as an initial resuscitation fluid affects neurological outcome following severe traumatic brain injury.

- Hypothesis: Resuscitation of patients with severe traumatic brain injury with a single bolus of HS as the initial resuscitation fluid will result in better neurological function 6 months from date of injury when compared to conventional resuscitation with NS.

### **BACKGROUND AND RATIONALE**

Trauma is the leading cause of death among North Americans between the ages of 1 and 44 years. The majority of these deaths result from hypovolemic shock or severe brain injury. Patients in hypovolemic

shock develop a state of systemic tissue ischemia with a subsequent reperfusion injury at the time of fluid resuscitation. Conventional resuscitation involves the intravenous (IV) administration of a large volume of isotonic (normal saline) or slightly hypotonic (lactated ringers, LR) solutions beginning in the prehospital setting. Although not conclusive, prior animal and human studies have suggested that alternative resuscitation with hypertonic saline (7.5%) solutions may reduce mortality in these patients. Furthermore, hypertonic fluids may have specific advantages in the brain-injured patient, as they may aid in the rapid restoration of cerebral perfusion and prevent extravascular fluid sequestration, thereby limiting secondary brain injury. In addition, recent studies have demonstrated that hypertonicity significantly alters the activation of inflammatory cells, an effect that may reduce subsequent organ injury from ischemia-reperfusion and decrease nosocomial infection. The majority of previous clinical trials have focused on the use of a 7.5% saline solution coupled with 6% dextran-70 (HSD). Dextran was added to the solution in an effort to prolong the circulatory effect of hypertonicity. Subsequent to the early clinical trials, however, there have been several preclinical studies demonstrating reduction of inflammatory organ injury utilizing HS rather than HSD.<sup>1-5</sup> Removal of the dextran component may enhance the anti-inflammatory effects of this solution, which could reduce the risk of late complications after injury. The potential benefits of HS resuscitation have not been well studied in humans.

This study seeks to address the impact of hypertonic resuscitation on two injured patient populations, those with hypovolemic shock (either prehospital SBP  $\leq$ 70; or prehospital SBP71-90 AND HR  $\geq$ 108) and those with severe traumatic brain injury (prehospital GCS  $\leq$ 8). The primary outcome for the hypovolemic shock group will be 28 day survival and the primary outcome for the TBI group will be neurologic outcome 6 months after injury based on the Extended Glasgow Outcome score. In addition, this study will address the issue regarding whether dextran is a necessary component of this resuscitation strategy.

### ***Epidemiology and Physiology of Injury***

Traumatic injury is the leading cause of death among North Americans between the ages of 1 and 44 years, resulting in nearly 150,000 deaths per year in the United States.<sup>6</sup> The mortality following injury has classically been defined to occur in a trimodal distribution with 50% of deaths occurring at the scene, 30% in the first two days, and 20% following a prolonged intensive care unit (ICU) course.<sup>7</sup> Early deaths occur as a result of hypovolemic shock or severe head injury, while late deaths result from progressive multiple organ dysfunction or nosocomial infection.<sup>8,9</sup>

(Table 1). Early deaths resulting from traumatic brain injury may be exacerbated by inadequate cerebral perfusion, which leads to a secondary ischemic injury to the brain.

Late deaths are impacted by an initial systemic pro-inflammatory response that contributes to the

development of the Acute Respiratory Distress Syndrome (ARDS) and subsequent organ dysfunction leading to the Multiple Organ Failure Syndrome (MOFS). Whole body ischemia followed by reperfusion, upon resuscitation of hypovolemic shock, results in excessive, uncontrolled activation of the host inflammatory response resulting in organ injury. Following this initial excessive inflammatory response, many patients suffer a period of immunosuppression that is manifested, in part, by alterations in T cell responsiveness.<sup>10</sup> This results in increased susceptibility to nosocomial infection, which can provide the stimulus for a secondary aberrant immuno-inflammatory response that results in the development of ARDS and MOFS. Strategies designed to impact outcome following injury must target early deaths by focusing on the acute resuscitation of hypovolemia, while minimizing secondary brain injury for head-injured patients, and late deaths by the subsequent immunomodulation of the systemic inflammatory response.

TABLE 1: Epidemiology of Death following Trauma

	Acute (<48hrs)	Early (24hr to 7 days)	Late (> 7 days)
CNS injury	40%	64%	39%
Blood Loss	55%	9%	0%
MOFS	1%	18%	61%

CNS= Central Nervous System, MOFS= Multiple Organ Failure Syndrome

Adapted from Sauaia et al. (4)

HSD (7.5% saline with 6% dextran-70) has been investigated as an alternative resuscitation fluid in critically injured patients.<sup>11-15</sup> HSD results in an increase in serum osmotic pressure, which leads to the redistribution of fluid from the interstitial to intravascular space. This leads to rapid restoration of circulating intravascular volume, with a smaller volume of fluid required compared to isotonic or hypotonic crystalloid solutions and decreased accumulation of extravascular volume. The osmotic effect of HSD has been shown to reduce intracranial pressure in brain-injured patients. Thus, the combination of increased systemic perfusion, which increases cerebral perfusion, along with a decrease in the intracranial pressure will minimize the progression of secondary brain injury. In addition, recent studies have demonstrated an impact of hypertonicity on limiting the proinflammatory response of circulating inflammatory cells. Thus, hypertonic solutions may have additional beneficial effects by modulating the excessive immunoinflammatory response following systemic ischemia/reperfusion injury. Hypertonic resuscitation, therefore, has the potential to impact both early and late mortality following traumatic injury.

### ***Resuscitation of Hemorrhagic Shock***

Early studies of resuscitation of hemorrhagic shock in dogs suggested that merely returning the shed blood to the animal was inadequate, and mortality was significantly improved by the addition of intravenous crystalloid solutions.<sup>16</sup> It was noted that approximately 3 times the shed blood volume of crystalloid was required to replete intravascular volume. These studies led to the current management protocol for hypovolemic shock which involves the rapid administration of LR or NS to the trauma patient.<sup>17</sup>

Recent studies have challenged this approach suggesting that aggressive fluid resuscitation in patients with uncontrolled hemorrhage will result in increased bleeding and coagulopathy. These studies are based upon animal models of uncontrolled hemorrhage from either major vascular or massive solid organ injury.<sup>18-24</sup> A recent clinical trial of fluid resuscitation in patients with penetrating torso trauma demonstrated improved survival among patients who received no pre-surgical resuscitation vs. conventional resuscitation (survival 70% vs. 62%).<sup>25</sup> These authors propose that the prehospital administration of fluids to these patients merely increases the rate of hemorrhage. This study population included only penetrating injuries with a rapid transport time to the hospital. The vast majority of traumatic injury in North America, however, results from blunt injury as a result of motor vehicle collisions. Furthermore, such patients often have multisystem injury including brain injury and may have a prolonged transport time. Thus, designing a prehospital fluid resuscitation strategy to optimize outcome for these patients is critical.

Some authors have advocated that no pre-surgical fluid be administered to the trauma patient. However, concern has been raised that this approach will lead to increased mortality in patients with a delay to definitive surgical therapy, as in the case of rural injuries requiring a prolonged transport time. In addition, these models do not account for the multisystem injury seen in the majority of blunt trauma victims including traumatic brain injury. Hypotension has been clearly associated with increased morbidity and mortality in brain injured patients. These concerns have led to the suggestion that the best approach may involve a controlled resuscitation with hypertonic fluids.<sup>20, 23</sup> Animal models of uncontrolled arterial and venous hemorrhage have demonstrated reduced mortality and no increase in pre-operative hemorrhage with hypertonic resuscitation.<sup>20, 26</sup> The use of hypertonic fluids allows a decrease in the total volume of fluid administered, while supporting adequate tissue perfusion for survival prior to definitive hemorrhage control.

### ***Systemic Ischemia with Reperfusion Injury***

Multisystem traumatic injury often leads to significant hemorrhage resulting in hypovolemic shock. Systolic hypotension (SBP < 90 mmHg) in adults results from a loss at least 30% of their circulating blood volume or Class III shock. This results in a compensatory peripheral vasoconstriction in an effort to preserve perfusion to the vital organs. As a result, the patient is in a state of systemic ischemia due to hypoperfusion. Upon initiation of intravenous fluid resuscitation, intravascular volume begins to improve and the body suffers from an acute reperfusion injury as a result of the reintroduction of oxygen to the ischemic tissues. This results in an increase in systemic oxidative stress, which can lead to direct tissue injury and the activation of inflammatory cells. Toxic reactive oxygen intermediates can result in the

activation of inflammatory cells by acting as intracellular second messengers in the nuclear translocation of a key transcription factor, Nuclear Factor B (NF- $\kappa$ B). NF- $\kappa$ B has been implicated in the transcription of a number of proinflammatory genes including: many cytokines (TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-8, IL 2), hematopoietic growth factors (GM-CSF, M-CSF, G-CSF), cell adhesion molecules (ICAM-1, ELAM-1, VCAM-1) and nitric oxide synthase (iNOS).<sup>27</sup> The up-regulation of adhesion molecules by the endothelium leads to the diapedesis of activated circulating neutrophils and monocytes into the interstitium where they are excessively activated and thus contribute to inflammatory organ injury.<sup>28</sup> This systemic, over expression of the host inflammatory response results in ARDS and MOFS. ARDS occurs in up to 50% of severely traumatized patients.<sup>29</sup>

### ***Hypertonic Saline and the Inflammatory Response***

Several studies suggest that HS can have profound effects on neutrophil function. In vitro studies have shown that HS prevents up-regulation of the important adhesion molecule CD11b on the surface of neutrophils and induces the shedding of L-selectin adhesion link from the surface of the neutrophil.<sup>30-32</sup> These adhesion molecules are critical to the adherence of neutrophils to the endothelium resulting in extravascular migration and activation of these cells during reperfusion injury. Furthermore, this effect appears to be transient and reversible, suggesting that the acute reperfusion injury could be attenuated without increasing the risk of subsequent infection from neutrophil dysfunction.<sup>33</sup> HS resuscitation has also been shown to significantly attenuate inflammatory lung injury in a two-hit animal model consisting of an initial hemorrhagic shock with reperfusion followed by and intratracheal endotoxin challenge.<sup>1</sup> Lung injury was also attenuated by HS resuscitation in a hemorrhagic shock model secondary to suppression of the hemorrhage-induced neutrophil oxidative burst.<sup>34</sup> Finally, the timing of HS administration appears critical, as lung injury is attenuated by administration at the time of reperfusion but was enhanced in animals given HS after partial resuscitation with crystalloid.<sup>35</sup> These data support the prehospital administration of this fluid as the initial fluid to resuscitate hemorrhagic shock.

The effect of HS on monocyte/macrophage activation is less well defined. A recent study suggests, that similar to the neutrophil effect, hypertonic preconditioning inhibits the macrophage responsiveness to inflammatory stimuli, such as endotoxin.<sup>36</sup> These studies demonstrated a significant reduction in TNF- $\alpha$  production in response to endotoxin following hypertonic saline pretreatment. Similar to the neutrophil data, this effect was transient with restoration of normal macrophage responsiveness after 20 hours. This reinforces our hypothesis that initial inhibition of macrophage and neutrophil function at the time of reperfusion may reduce the acute inflammatory response while preserving the ability of these cells to respond to a subsequent nosocomial infection in the ICU.

### ***Post-traumatic Immunosuppression***

Following the initial period of excessive systemic inflammation, which can contribute to direct organ injury, there follows a period of immunosuppression, which may increase the susceptibility to infection. Nosocomial infection rates among trauma patients admitted to the ICU are reported to range from 30 to 40%.<sup>37,38</sup> In addition, nosocomial infection in this population has been associated with a two fold increased risk of death.<sup>38</sup> Post-traumatic immunosuppression has been related to a shift in the cellular immune response of the patient. The identification of functionally distinct T helper cell populations, termed Th1 and Th2, have contributed to an understanding of the mechanisms involved.<sup>39</sup> Th1 cells secrete interferon- $\gamma$  (IFN- $\gamma$ ), TNF- $\alpha$ , and IL-2 and are involved in monocyte/macrophage mediated inflammatory responses. Th2 cells secrete IL-4, IL-5 and IL-10, which stimulate mast cell and eosinophil function but inhibit T cell proliferation and macrophage activity. IL-10 has been implicated as a suppressor of T cell proliferation and cytokine production and is thought to play a key regulatory role in the development of anergy.<sup>40</sup> Reduced production of IL-12 by monocytes from these patients may also contribute to this shift as IL-12 is an important in directing CD4 T-cells to the Th-1 phenotype.<sup>41</sup>

Several investigators have demonstrated a switch from the Th1 to Th2 phenotype in critically injured patients.<sup>41-43</sup> This shift has been demonstrated by monitoring the cytokine production of peripheral blood mononuclear cells (PBMC), isolated from trauma patients. The timing of the shift is towards the end of the first week following injury and correlates with the time of onset of the majority of initial nosocomial

infections.

The predominant paradigm regarding the development of MOFS is the "two hit hypothesis". This theory suggests that the initial reperfusion injury, following trauma or hypovolemic shock, results in the initial injury, and dysfunctional but primed inflammatory cells such that a second hit, such as development of a nosocomial infection, results in an excessive systemic inflammatory response leading to further direct organ injury and subsequent failure.<sup>29, 44</sup> The changes in the cellular immune response that increase the susceptibility of these patients to infection may provide that secondary insult contributing to organ failure and death. Strategies designed to reverse this immunosuppression may thus be beneficial.

#### ***Hypertonic Saline and the Cellular Immune Response***

The levels of hypertonicity achieved following HS resuscitation have been shown to double T cell proliferation of mitogen-stimulated human PBMC.<sup>45</sup> HS has also been shown to enhance mitogen-stimulated IL-2 production by both Jurkat T-cells and human PBMC.<sup>3</sup> Furthermore, T cell suppression induced by a series of post-traumatic immunosuppressive agents including IL-4, IL-10, transforming growth factor-beta (TGF) and prostaglandin E2 was reversed by HS, *in vitro*.<sup>46</sup>

These studies have been extended to an *in vivo* model of hemorrhagic shock in mice. Mice were bled to a mean arterial pressure of 35 mmHg and resuscitated with either 4ml/kg of HS or 2 times the blood loss in lactated ringers (LR). Twenty-four hours after hemorrhage and resuscitation, the delayed type hypersensitivity (DTH) response and splenocyte proliferation were significantly suppressed in the LR group but enhanced in the HS group.<sup>47</sup> Furthermore, HS was protective against a subsequent septic challenge in these animals with a mortality of 14% vs. 77% in the LR group, following cecal ligation and puncture.<sup>48</sup> Taken together, these studies suggest that HS resuscitation of the trauma patient may enhance cellular immune function and thus decrease susceptibility to subsequent nosocomial infection.

#### ***Dextran***

Since HS was first proposed for trauma resuscitation, it has been used in combination with a synthetic colloid, most commonly dextran. Dextran is very effective volume expander and augments HS intravascular fluid expansion, prolonging its hemodynamic effects from one to up to four hours.<sup>15, 49, 50</sup> Dextran is a polydisperse glucose polymer produced by bacteria growing in a sucrose-containing media. Commercially available 6% Dextran 70 solution has an average molecular weight of 70 Kda, providing an intravascular oncotic pressure of 70 mmHg and a reflection coefficient of 0.8 (similar to albumin).<sup>49, 50</sup>

A single study by Vassar et al. in severely traumatized and hypotensive trauma patients suggested that the addition of dextran to HS offered no additional clinical benefit in prehospital resuscitation.<sup>15</sup> This conclusion was contested by a meta analysis by Wade et al., where the authors demonstrated a survival benefit to the addition of dextran to HS compared to normal saline alone, in particular among head injury patients.<sup>51</sup> Meta analysis by the Cochrane group failed to determine whether the addition of dextran improves effectiveness or safety of HS therapy, mostly due to lack of acceptable evidence.<sup>52</sup>

Besides plasma expanding properties, dextrans also have mild anti-inflammatory effects. Dextrans are oxygen radical scavengers; they modulate microvascular permeability and attenuate neutrophil/endothelial activation.<sup>53, 54</sup> Even though such effects might enhance HS's potent anti-inflammatory effects; recent evidence suggests that the oncotic effect is the most clinically relevant contribution of dextran to HS. Dextrans' side effects include an anticoagulant effect (prolong bleeding time, enhance fibrinolysis and reduce von Willebrand factor levels), anaphylactic reaction, accumulation within tissues, interference with serum glucose measurement and an association with acute renal failure (by unclear mechanism). The effects have not been observed with the dose of dextran administered with a single bolus of HSD in prior clinical trials. Since complications are related to volume infused, the manufacturers recommend a maximum dose of 20 ml/kg.<sup>50</sup>

#### ***Traumatic Brain Injury***

In North America, Traumatic Brain Injury (TBI) is the most common cause of death and disability in young

adults. Each year, more than 1.6 million people sustain TBIs, resulting in 80,000 permanent severe neurological disabilities and 52,000 deaths.<sup>55-57</sup> Indeed, TBI is responsible for the greatest number of potential years of life lost from any cause as well as for the highest burden on quality adjusted life years lost in survivors.<sup>58</sup> In addition to the cost of human suffering, the total annual cost to the health care system is estimated to be more than \$37 billion.<sup>59</sup> Current evidence and clinical guidelines stress the importance of early and effective hemodynamic resuscitation following TBI and stress the deleterious effects of hemorrhagic shock complicating TBI.<sup>60</sup>

As expected, the highest mortality happens among patients with severe TBI (defined as a Glasgow Coma Scale (GCS) of 8 or less). More than 40% of the severe TBI patients die. It is encouraging to note however, that one third survive with minimal to moderate neurological deficits. In fact, even among the most severely brain injured patients, there is a wide variability in neurological recovery with significant numbers on both ends of the neurological functional spectrum. It would also be expected that an effective treatment for TBI would improve neurologic outcomes. Hence it is important to include outcome measures assessing neurologic function.

Hypotension has been associated with a dramatic increase in the morbidity and mortality following brain injury. Prehospital hypotension is associated with a two-fold increase in the incidence of adverse outcome (severely disabled, vegetative, or dead) following severe brain injury.<sup>61</sup> Likewise, hypotension on arrival to the hospital and in the operating room has been associated with adverse outcome.<sup>62, 63</sup> Inadequate cerebral perfusion from hypotension results in an ischemic insult that extends the primary injury, thus creating a secondary brain injury.<sup>57</sup> The goal of resuscitation, therefore, should be to minimize the development of secondary brain injury by optimizing cerebral perfusion.

Cerebral edema following injury results from extravasation into areas of microvascular injury, vasoregulatory dysfunction, and the interstitial accumulation of osmotically active substances.<sup>64</sup> The injured brain loses its ability to autoregulate the vasculature in response to changes in blood flow, thus increasing its sensitivity to hypotension.<sup>65</sup> Cerebral perfusion pressure (CPP) is determined by the difference between mean arterial pressure (MAP) and the intracranial pressure (ICP). Optimizing cerebral perfusion thus relies on systemic resuscitation with intravenous fluids, to manage hypotension from hypovolemia, while adding osmotic agents to decrease intracranial pressure from extravascular fluid accumulation. The most commonly used osmotic agent, Mannitol, decreases intracranial pressure by decreasing interstitial fluid in the brain, however, its diuretic effect on the kidneys can lead to volume depletion and exacerbation of hypotension. The treatment of hypovolemia associated with brain injury is critical, however, overzealous infusion of isotonic fluids can result in increased intracranial pressure and reduced cerebral perfusion. The ideal resuscitation fluid for patients with hypotension and traumatic brain injury is one that will have favorable systemic hemodynamic effects while decreasing intracranial pressure.

### ***Hypertonic Saline and Traumatic Brain Injury***

A recent meta-analysis of studies involving the prehospital administration of HSD concludes that patients with traumatic brain injury in the presence of hypotension who receive HSD are twice as likely to survive as those who receive standard resuscitation.<sup>66</sup> Sub-group analysis of the individual trials also suggested that patients with traumatic brain injury (Glasgow coma score (GCS) <8) who received HSD had a significant survival advantage. Vassar et al. reported a survival to discharge for patients with severe brain injury of 34% for those receiving HSD vs. 12% for those receiving conventional resuscitation.<sup>15</sup> The mechanism of action of HSD in these patients is likely multifactorial. Hypertonic saline administration in animals and humans with hypovolemic shock results in rapid improvement in the mean arterial pressure.<sup>11, 67-74</sup> This effect is due to plasma volume expansion secondary to the increased osmotic load, along with centrally mediated effects on cardiac output.<sup>64</sup> Rapid restoration of mean arterial pressure results in improved cerebral perfusion pressure, which supports the injured brain.

In addition to the systemic effects of hypertonicity, HS has been shown to lower ICP in several clinical trials and animal models.<sup>75-84</sup> The effect of HS on ICP is thought to be due primarily to reduction of cerebral edema due to increased osmotic load in the intravascular space. During cerebral injury, organic

solutes that function as osmolytes are extruded into the extra cellular space by several mechanisms thus contributing to the rise in ICP.<sup>64</sup> Increasing extra cellular sodium levels by administration of hypertonic saline restores the active cellular sodium-osmolyte co transporters, which restore the osmolytes to the intracellular space thus restoring normal cell polarity. This may explain the prolonged effects on ICP seen in human trials in which a 10 to 15 mEq/L rise in serum sodium lowered ICP for 72 hours.<sup>82</sup>

In addition to its favorable effects on ICP, hypertonic saline has also been shown to have vasoregulatory, immunomodulatory and neurochemical effects on the injured brain that may be beneficial.<sup>64</sup> As discussed above, the injured brain loses its ability to autoregulate the cerebral vasculature thus increasing the risk of secondary ischemic injury to brief episodes of hypovolemia. Hypertonicity counteracts hypoperfusion and vasospasm by increasing vessel diameter via volume expansion. In addition, HS may have direct effects on the vascular endothelium. Reversing endothelial cell edema may prevent endothelial cell activation, thus leading to reduced leukocyte adherence and subsequent inflammatory injury.<sup>85</sup> HS infusion has also been associated with the release of nitric oxide, endothelins, and eicosanoids that alter vasomotor tone.<sup>86-88</sup> The systemic immunomodulatory effects of HS may also be beneficial in reducing the migration and activation of cerebral leukocytes that exacerbate acute cerebral injury. Finally, much research has focused on inhibiting the effects of excitatory amino acids, such as glutamate, released as a result of brain injury and ischemia. HS may be beneficial in this regard, as increasing extra cellular sodium reestablishes the normal direction of the sodium/glutamate transporters, which restore intracellular glutamate levels.<sup>89</sup>

In summary, hypertonic fluids meet the criteria outlined as an optimal resuscitation fluid for patients with traumatic brain injury. Their favorable effects on systemic perfusion, along with reduction of ICP results in protection of cerebral perfusion for the injured brain. Previous clinical trials support reduced mortality for patients with severe brain injury who receive HSD resuscitation. The more vital question, however, is whether there is an improvement in neurological outcome for these patients. Increased survival with devastating neurological dysfunction may not be ideal. Thus there is a clear need to not only confirm a survival benefit, but for further study of the impact of hypertonic resuscitation on long term functional outcome for patients with traumatic brain injury.

#### ***Previous Clinical Trials of Hypertonic Resuscitation***

There have been eight clinical trials of HSD for the acute resuscitation of hypovolemic patients (Table 2). In six of the trials HSD was administered in the prehospital environment, while in two it was administered upon arrival to the emergency department. In all trials there were no significant adverse events, attesting to the safety of this therapy. The six prehospital trials all demonstrated a survival benefit for patients treated with HSD vs. conventional isotonic resuscitation. The two emergency room trials showed no difference in survival, suggesting that the administration of this fluid at the time of initial reperfusion may be critical.

**Table 2: Human Trials of Hypertonic Saline as a Resuscitation Fluid**

Reference	Population	Design	N	Hypertonic Fluid	Outcome
Holcroft et al., 1987	Prehospital trauma patients	Prospective, randomized	49	7.5%NaCL/ 6% Dextran70	Improved SBP and overall survival
Holcroft et al., 1989	Hypotensive trauma pts in ED (SBP < 80)	Prospective, randomized	32	7.5%NaCL/ 6% Dextran70	No difference in survival
Vassar et al., 1991	Prehospital trauma patients (SBP < 100)	Prospective, randomized	166	7.5%NaCL/ 6% Dextran70	Improved SBP & improved survival for pts with TBI
Mattox et al., 1991	Prehospital trauma patients (SBP < 90) 72% penetrating inj	Prospective, randomized	359	7.5%NaCL/ 6% Dextran70	Improved SBP, Trend toward improved survival, decrease in ARDS
Younes et al., 1992	Hypovolemic shock in ED (SBP < 80)	Prospective, randomized	105	7.5% NaCl & 7.5%NaCL/ 6%Dextran70	Improved SBP, no difference in survival
Vassar et al., 1993	Prehospital trauma patients (SBP < 90)	Prospective, randomized	258	7.5% NaCl & 7.5%NaCL/ 6%Dextran70	Improved survival vs. predicted MTOS
Vassar et al., 1993	Prehospital trauma patients (SBP < 90)	Prospective, randomized	194	7.5% NaCl & 7.5%NaCL/ 6%Dextran70	Improved survival vs. MTOS & for pts with TBI
Younes et al., 1997	Hypovolemic shock in ED	Prospective, randomized	212	7.5%NaCL/ 6% Dextran70	Improved survival for pts with SBP < 70

In all prehospital trials, a 250 ml bolus of HSD vs. a standard crystalloid solution (LR or normal saline) was administered in a blinded fashion, followed by additional resuscitation with the standard crystalloid solution as required.

The largest evaluation of HSD resuscitation was a multicenter trial by Mattox et al. in 1991. This trial involved prehospital administration of HSD in three US cities. Although designed to be representative of the entire trauma population, this trial had a much higher percentage of penetrating trauma victims (72%) than seen in most studies. As a result, they were unable to evaluate any effect on traumatic brain injury. They did report a trend toward a decrease in the incidence of ARDS; however, only two patients in the cohort developed ARDS, which is a much lower incidence than seen in the average blunt trauma population.

There have been three subsequent meta-analyses by Wade et al.<sup>51, 66, 90</sup> The first was a traditional meta-analysis of all the trials using HSD or HS published as of 1997 and concluded that HSD offers a survival benefit for the treatment of traumatic hypotension while there was no benefit from HS alone. These authors acknowledged the limitations of including studies with significant differences in design and so went on to perform two individual patient cohort analyses. The first, which included 1395 patients from previous trials, demonstrated an improvement in overall survival to discharge in the HSD group (OR 1.47, 95% CI 1.04-2.08). Furthermore, patients who required blood transfusion or immediate surgical intervention for bleeding showed an even greater survival benefit from HSD. The second analysis focused on 223 patients with hypotension and traumatic brain injury. This paper concludes that HSD treatment in these patients resulted in a two-fold increase in survival compared to conventional resuscitation.

A recent study assessed the effect of hypertonic resuscitation on outcome for patients with both hypotension and severe traumatic brain injury.<sup>91</sup> This study enrolled 229 patients, randomized to 250cc 7.5% saline without dextran vs. LR as the initial prehospital resuscitation fluid and assessed neurologic

outcome using the extended Glasgow Outcome Score 6 months after injury. This trial failed to identify any difference in neurologic outcome, however there were significant limitations to this trial. Based on our estimates the trial was severely underpowered to detect a meaningful difference in outcome. In addition, as this trial was confined to TBI patients with prehospital hypotension there was a very high mortality (50%) thus limiting the number of subjects available for follow-up evaluation. There were also no attempts made to standardize the subsequent care of these patients. Interestingly, although not statistically significant, they did observe a trend toward improved survival at 6 months in the HS group (OR 1.17, 95% CI .9-1.5, p=0.23). Of the patients who survived to the Emergency Department, the long term survival was 67% for those receiving HS vs. 55% for the LR group (OR=1.72, 95% CI: 0.95-3.1, p=0.073).

These studies attest to the safety of HSD in the hypotensive trauma population and to the practicality of using this fluid in the prehospital environment. They also suggest that certain subgroups of patients are most likely to benefit from this intervention, including those at-risk for inflammatory organ dysfunction and those with traumatic brain injury. The major limitations of previous studies have been either the insufficient patient number to detect significant clinical differences in outcome or the lack of focus on the specific patient population most likely to benefit. These studies were also conducted prior to the evolution of the basic science literature demonstrating the effects of hypertonicity on the immuno-inflammatory response. Thus, critical evaluation of these effects in humans has not been undertaken.

**Summary of Results Phase 2 Trial: University of Washington (preliminary analysis, Sept 2005)**

A trial of hypertonic resuscitation following blunt traumatic injury was recently closed for futility at the University of Washington. Analysis of the first 200 patients enrolled in this trial has guided protocol changes for the hypovolemic shock cohort and thus the data analysis is summarized here. Twenty eight day survival, which was a secondary endpoint for this trial was assessed by using Cox proportional hazards methods. There was no overall benefit to HSD resuscitation with an unadjusted hazard ratio (HR) of 0.75 (95% CI 0.44-1.3). After adjusting for differences in baseline characteristics the HR was 0.98 (95% CI: 0.53-1.80) (Table 1)

**Table 1: Cox Regression for Survival Adjusting for All Univariate Baseline Factors**

Variable	p-value	Hazard Ratio	95% Confidence Interval	
Treatment (LR vs HSD)	0.940	0.98	0.53	1.80
Age ≥ 55	0.010	2.31	1.22	4.35
Head AIS ≥ 2	0.530	0.83	0.46	1.49
Chest AIS ≥ 3	0.850	1.07	0.54	2.11
Injury Severity Score ≥ 25	< 0.001	6.37	2.24	18.07
Air vs Ground transport	0.370	0.76	0.41	1.39
PRBC in the first 24 Hours (ref = 0)				
0 < PRBC < 10	0.980	1.00	0.66	1.51
PRBC ≥ 10	0.024	2.53	1.13	5.67

We noted that there was evidence of improved outcome for patients who were in severe shock as manifested by the need for ≥10 units of packed red blood cells (PRBCs) in the first 24 hours after injury. This was further evaluated using Cox proportional hazards methods with an interaction term to assess the effect of treatment by red cells transfused. Colinear covariates were excluded from this analysis. The hazard ratio for 28 day survival was 2.49, 95% CI: 1.1-5.6 (Table 2). This is consistent with analyses of prior phase 2 trials, which suggested that the patients requiring emergent operative control of hemorrhage had the greatest benefit.

**Table 2: Cox Regression for Survival Adjusting for Age, Chest AIS, and PRBC**

Variable	p-value	Hazard Ratio	95% Confidence Interval	
Treatment (Lactaed Ringers (LR) vs HSD)	0.074	0.30	0.08	1.13
Age ≥ 55	0.012	2.19	1.19	4.05
Chest AIS ≥ 3	0.048	1.92	1.01	3.67
PRBC in the first 24 Hours (ref = 0)				
0 < PRBC < 10	0.840	1.11	0.42	2.92
PRBC ≥ 10	0.080	2.30	0.90	5.86
Treatment x PRBC	0.012 (overall)			
Treatment LR and 0 < PRBC < 10	0.360	2.25	0.40	12.58
Treatment LR and PRBC ≥ 10	0.008	8.35	1.76	39.70
<b>Estimated Hazard Ratios of Treatment LR vs HSD</b>				
Within PRBC = 0		0.30	0.08	1.13
Within 0 < PRBC < 10		0.67	0.22	2.01
Within PRBC ≥ 10		2.49	1.11	5.59

We believe that the lack of an overall improvement in outcome is based on the enrollment of a significant number of patients who were transiently hypotensive in the prehospital setting but not truly in hemorrhagic shock. This is manifested by the fact that 45% of the patients enrolled did not receive any blood transfusions in the first 24 hours. Review of the prehospital vital signs for patients stratified by the amount of transfusion required suggests that changing the inclusion criteria from all patients with a SBP  $\leq 90$  mmHg to those with a SBP  $\leq 70$  mmHg or SBP 71-90mmHg with a heart rate  $\geq 108$  beats/min would reduce the number of patients that do not receive blood transfusions from 44.4% to 36.8% of the population. While this change would reduce the rate of patient enrollment by 25%, we believe that the ability to capture a better proportion of patients who are likely to benefit from this therapy would mitigate this concern.

As noted in table 2, the HR for patients who did not receive any blood transfusions in the first 24 hours was 0.30 (95% CI: 0.08-1.13). Although this did not reach statistical significance, it raises the concern for a trend toward harm in this group. The two reasons patients fall into this group are either transient hypotension without subsequent evidence of significant hemorrhage or immediately lethal injuries that result in death prior to significant medical intervention. We have reviewed each death in this category and find that there were a disproportionate number of patients with these early, fatal injuries randomized to the HSD group. This accounts for the trend toward an unfavorable outcome for this treatment arm and thus we do not believe that HSD treatment is inherently harmful to patients who were not in severe shock.

In addition to the changes in inclusion criteria, the sample size assumptions have also been modified as discussed in the section of the protocol referring to sample size.

### Significance and Study Implications

Despite the many previous clinical trials of HSD resuscitation, it has not been adopted in the U.S. or Canada as a prehospital resuscitation strategy. This is due, in part, to the fact that previous clinical trials have not shown a definitive survival advantage, overall, and that several key clinical questions remain regarding the appropriate target population. Previous trials have been limited in statistical power and have included a predominance of penetrating trauma victims with a very short transport to the hospital. In this population, the effect on survival may be less evident and the development of secondary outcomes such as ARDS is less common. Furthermore, it is evident that patients with traumatic brain injury may have the greatest benefit from HSD therapy and there has been inadequate evaluation of the long term neurological outcome for these patients. There is now compelling evidence from the laboratory that hypertonicity has significant effects on the responsiveness of inflammatory cells, yet the impact of HSD therapy on the incidence of ARDS and MOFS has not been addressed. This proposal brings to bear the resources of the Resuscitation Consortium to evaluate the effect of early administration of HSD and HS on outcome for patients in hypovolemic shock and those with severe traumatic brain injury. Furthermore this multi-institutional trial will allow for a three arm study thus determining whether the dextran component of HSD

is required for the anticipated therapeutic effects.

In addition, the laboratory evidence demonstrating the immuno-modulatory effects of hypertonicity stem from animal models and *in vitro* studies on human cells from healthy volunteers. These mechanisms need to be explored in the injured patient to better define the clinical relevance of these hypotheses. We anticipate that selected centers within the consortium will be able to conduct detailed laboratory studies of the immuno-inflammatory response of the patients enrolled in this trial. This proposal will be submitted separately. The data achieved from these studies will provide insight into the clinical and biological advantages of hypertonic resuscitation, and thus contribute to the development of a resuscitation strategy to improve clinical outcome. This study will address the major clinical questions remaining regarding the utility of this approach.

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## **SECTION 2: ROLES AND EXPERTISE OF THE STUDY TEAM**

**List all study team members below.**

1. Describe their **specific role and responsibility** on the study in the text box provided.
2. **Faculty Sponsors** - list as Co-Researchers and describe their role on the project; include oversight responsibilities for the research study.
3. Explain who will have access to subject identifiable data.
4. Indicate who will be involved in recruitment, informed consent, research procedures/interventions, and analysis of data.
5. Provide a description of their **qualifications, level of training and expertise**. Include information about relevant licenses/medical privileges, as applicable.

### **Lead Researcher:**

Dr. David B. Hoyt: Chair of the Department of Surgery at UCI Medical Center and co principal investigator. Dr. Hoyt will be the Principal Investigator of the study and will coordinate all aspects of

this project. Dr. Hoyt has a long-term interest in surgical aspects of trauma, and immunosuppression in trauma patients. He has been involved in extramurally funded basic research and mechanisms of immunosuppression throughout his career. He has extensive experience performing clinical trials and multi-center clinical trials. He also has been very involved in the development of large databases and overseeing the quality of data used in the care of trauma patients.

**Co-Researcher(s):**

Marianne Cinat, MD is a full time Attending Physician in the Department of Surgery/Critical Care and has extensive experience in the treatment of trauma patients and has been principal investigator and co-investigator on previous protocols conducted in the Department of Surgery. For this study, Dr. Cinat will assist with the trauma calls and will be attending to initial patient care and management.

Michael E. Lekawa, M.D., Associate Clinical Professor and Chief of the Division of Trauma and Surgical Critical Care, has participated in several prior investigational studies at UCIMC as Principal Investigator, including studies related to the treatment of patients with trauma. Dr. Lekawa has conducted many critical care and trauma related studies over the last 7 years. For this study, he will assist with the trauma calls and will be attending to initial patient care and management.

Matthew O. Dolich, M.D., Assistant Clinical Professor in the Department of Surgery: Division of Trauma and Surgical Critical Care. For this study, he will assist with the trauma calls and will be attending to initial patient care and management.

Darren J. Malinoski, MD., Assistant Clinical Professor in the Department of Surgery: Division of Trauma and Surgical Critical Care. For this study, he will assist with the trauma calls and will be attending to initial patient care and management.

Cristobal Barrios, MD., Assistant Clinical Professor in the Department of Surgery: Division of Trauma and Surgical Critical Care. For this study, Dr. Barrios will assist with the trauma calls and will be attending to initial patient care and management.

Bernardine Donato is a Clinical Nurse III with the Department of Surgery at UCI. She received her Diploma in Professional Nursing at Ellis Hospital School of Nursing in Schenectady, New York, her Associate Degree in Science at Long Beach City College, and her Bachelor in Health Administration at University of La Verne. She is a California Registered Nurse. For this study, she will assist with consenting subjects and data collection.

**Research Personnel:**

**SECTION 3: RESEARCH METHODOLOGY/STUDY PROCEDURES**

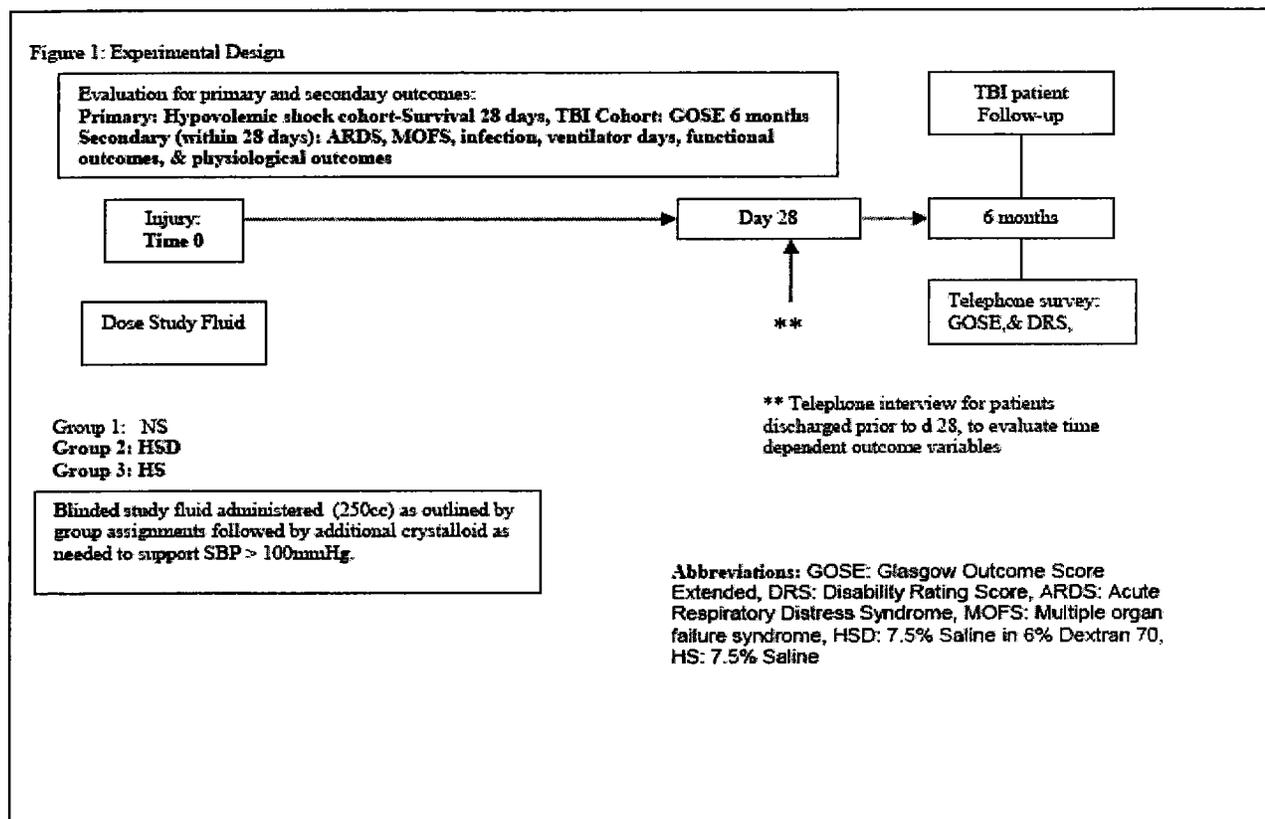
1. Provide a detailed chronological description of all study procedures (e.g., pilot, screening, intervention, and follow-up). Include an explanation of the study design (e.g., randomization, placebo-controlled).
2. Indicate the timing of **all study procedures** and the anticipated duration of the subject's involvement, if applicable.
3. Describe how the subject's privacy will be protected during the research procedures.

4. When applicable, provide information about the measures and outcome variables and the statistical methods of analysis.

**Additional information about completing this section is included in the Protocol Narrative instructions.**

### STUDY DESIGN AND PROCEDURES

These studies are randomized, double-blind, 3-arm controlled trials designed to evaluate the clinical outcome of trauma patients with either hypovolemic shock, as manifested by prehospital hypotension, or severe TBI as manifested by a prehospital GCS of 8 or less. Patients will be randomized to a single dose 7.5% saline in 6% Dextran-70 (HSD) (250cc), 7.5% saline (no dextran) (HS) (250cc), or crystalloid (250cc) as the initial fluid for prehospital resuscitation. The study design is illustrated in Figure 1 below.



### Randomization and Blinding:

The study fluids will be provided commercially from Biophausia Inc, Sweden. This company currently manufactures HSD and markets it in Europe as Rescueflow™. They will provide all three study fluids in identical IV bags suitable for blinding care providers to the treatment assignment. A randomly generated numeric code will be applied to each bag and a randomization list kept by the Data Coordinating Center. This means that the bags sent to the clinical sites are “pre-randomized.” Bags will be distributed to stations in variable size blocks to maintain sequential balance of the treatment arms within stations, and thus within sites and over time. When n treatment groups are compared against a common control, the most efficient design uses a 1:1:…:1:sqrt(n) allocation, so randomization will be 1:1:1.414 (HSD:HS:CTL).

Bags will be placed at each base station where they can be retrieved by the medic or airlift. One bag of study fluid will be kept on each ambulance and two bags on each helicopter. Since there is only one study bag on a

rig and all randomization is being done off site by the CTC, there will be no delay of patient care. Study site personnel will keep inventory records for each EMS site and conduct EMS site visits to confirm inventory status. When a site has less than 3 bags of fluid remaining, an additional set will be distributed. Each bag will have several stickers denoting its number and these will be placed on the medic report and Emergency Department (ED) report. Each site must establish a notification process with their EMS system or Emergency departments to notify study personnel of patient enrollment. In this manner, the subjects, investigators, study coordinators, and all persons caring for the patient will be blinded to the study treatment assignment.

Although it would be ideal to blind subsequent hospital care providers to the serum sodium and chloride values, due to the number of hospitals involved and the acuity of these patients this is not a practical option. Previous studies of the prehospital administration of 7.5% saline solutions have demonstrated that the mean serum sodium on admission is 155mEq/L. This level should not prompt alterations in care by the trauma team. Prior to study enrollment, all physicians caring for trauma patients including ED physicians, anesthesiologists, surgeons, and intensivists will be notified of the onset of the trial and be advised that elevated serum sodium levels are to be expected in these patients and should not be treated unless there are signs of a serious adverse event such as seizure activity. Such an event should be reported to the investigators immediately.

### **Administration of Study Drug**

When a patient meets the entry criteria, study fluid will be hung in the pre-hospital setting. Subjects will receive a one time, intravenous dose of study fluid given as a bolus. The blinded study drug (25Occ of HSD, HS or NS) will ideally be the first fluid hung for resuscitation (it may be hung simultaneously with other fluids). Each bag of study fluid will have several peel-off stickers with its unique identification number and these will be placed on the medic report, the ED admission record and/or nursing admit form. Additionally, each subject will have a brightly colored, plastic arm band with the study bag number placed on his or her wrist. In this manner all persons caring for the patient will be alerted to the subject's enrollment into the study. RCC's will also have their EMS personnel place an information sheet in the chart. Each site must establish a notification process with their EMS system or Emergency Departments to notify study personnel of patient enrollment.

### **Baseline Assessment**

Since patient enrollment will occur at the scene of injury, there will be no opportunity for an immediate baseline assessment of the patient by the clinical research coordinator. This initial data, including demographics, mechanism of injury, prehospital and ED hemodynamic variables, time to definitive care, mode of transport, Injury Severity Score (ISS), presence of TBI, and total fluids in the first 12 hours will be obtained by the research nurse as soon as feasible. This will include review of the prehospital report, documentation of events in the ED and the first day of hospitalization. All trauma admissions during this time period will also be tracked to identify any patients meeting the entry criteria but not enrolled in order to identify any selection bias as well as address the ability to generalize the results.

### **Plan for Outcome Assessment**

For this study, we have prepared a telephone survey that includes the key components of the GOSE and DRS to be administered to patients or their caregivers at 6 months after injury.<sup>103</sup> In addition, the GOSE and DRS will be assessed at the time of hospital discharge to obtain a baseline assessment. Attempts will be made to contact the patient directly; however, for those who are severely disabled, information will be obtained from the primary caregiver. In some cases, the patient may be conversant but not reliable due to the brain injury. To assess this, the interviewer will screen patients for cognitive impairment by explaining the study to them at the 6-month phone contact and then asking them 2 questions: (1) Can you tell me what you will be asked to do as a participant in this study, and (2) Can you tell me what you can do if you no longer wish to participate in the study. If the patient is unable to answer these questions then a caregiver will be sought to complete the survey.

To obtain meaningful outcome data for this study we need nearly complete follow-up for the TBI cohort. The Data Coordinating Center for the Resuscitation Outcomes Consortium has extensive experience with long-term outcome assessment in other populations. We intend to use the model utilized for the recently completed Public Access Defibrillator (PAD trial) which includes a detailed contact list collected from the patient prior to

discharge and a log for tracking follow-up attempts by the study coordinators. (See Appendix E.) This approach resulted in 100% follow-up for the primary endpoint in this trial. Study coordinators will be encouraged to establish a relationship with the patient and family while in the hospital which will aid in compliance with subsequent follow-up. The neurologic assessment tools will also be administered prior to hospital discharge in the event that long-term follow-up is inadequate despite our efforts. We also will initiate telephone contact at 1 month post discharge to establish a relationship and firm up commitment for the 6 month interview as well as to begin fall back contact procedures for those unable to be contacted by phone at 1 month. For the later patients, once contacted, we will also administer the GOSE, since these patients likely will continue to have contact issues. Our goal is to have 99% success with the 1 month although we expect 9% of those to require fall back procedures. Of those 9% we expect 5 % will not be able to be contacted for the 6 month follow-up and will therefore use the (on average expected ) 1 month GOSE for the primary outcome measure. For the 1% with no follow-up we will impute within treatment arm from the baseline GOSE (using multiple imputation procedures) and will also consider the worst case analysis (i.e., best score for the control and worst score for the treatment group).

## STUDY OUTCOME MEASURES

### Primary Outcome Measure

#### **A. Hypovolemic Shock Cohort**

28 day survival

#### **B. Severe TBI Cohort**

Neurologic outcome: GOSE 6 months after injury

### Secondary Outcome Measures

#### **A. Hypovolemic Shock Cohort**

Physiologic parameters indicative of organ dysfunction:

- ARDS Criteria met during the first 28 days post injury
- Multiple Organ Dysfunction Score (MODS)
- Presence of nosocomial infection
- Total fluid requirements in the first 24 hours after injury

Resource Utilization

- Number of days on ventilator
- Duration of hospital stay

#### **B. Severe TBI Cohort**

Additional neurological outcomes:

Disability Rating Score (Discharge & 6 months) GOSE at discharge

- 28 day survival

Additional data will be collected for safety monitoring (see Protection Against Risks, page 32).

## **SECTION 4: SUBJECTS (PERSONS/CHARTS/RECORDS/SPECIMENS)**

### **A. Number of Subjects (Charts/Records/Specimens)**

1. Indicate the **maximum number of subjects to be consented** on this UCI protocol.
  - Include projected screen failures and early withdrawals.
  - For Mail/Internet surveys include the number of people directly solicited.

- If the study involves use of existing charts, records, specimens, specify the maximum number that will be reviewed to compile the data or the sample population necessary to address the research question.

All trauma patients in the UCI Medical Center Trauma area over the age of 14 or greater or equal to 50 kg. and seriously injured enough to be categorized as a Major Trauma Victim will be considered for entry to this study. The anticipated screening sample size at this site is 500. The expected proportion of women to men may be less than 50%, but will merely reflect the population of trauma patients over this time period. The same is true of minorities. There are no inclusion or exclusion criteria based on gender or ethnicity.

2. Of the maximum number of subjects listed above, indicate the **target sample size** for the study.
- The target sample size is the number of subjects expected to complete the study or the number necessary to address the research question.
  - If the study only involves use of existing records, charts, specimens, specify the target number needed to address the research question.

The anticipated target sample size for this site is 450.

3. Explain how your target sample size was determined (e.g., power analysis; review of related literature).

### Sample Size

#### *A. Hypovolemic Shock Cohort*

Survival to hospital discharge for trauma patients with a prehospital SBP <90mm Hg is reported to be 46%. If patients in that study who had ongoing CPR in the field are excluded then survival improves to 67%. The design outlined includes three study arms addressing the effectiveness of both a single dose of HSD and 7.5% saline without dextran to conventional resuscitation. Previous meta-analyses by Wade et al. suggest that HSD is associated with a 47% relative improvement in survival (OR 1.47) but this includes studies with the endpoint of survival to hospital admission.

However, a previous study (refer to pages 15 to 17) found a much more conservative difference between HSD and control in the trauma patients with a prehospital SBP  $\leq 70$  mmHg or SBP 71 - 90 mmHg AND Heart Rate  $\geq 108$ . A 9% difference of survival rates was found only in the patients requiring at least 10 units of PRBC. This study's sample size calculation will be based on these conservative findings assuming a monotonic relationship between effect of treatment on survival rates and amount of blood transfused. Therefore the sample size calculation is determined by expecting a 10% difference in the participants that received at least 10 units of PRBC, a 5% difference in patients that received PRBCs, but less than 10 units, and 0% survival difference in patients that did not receive any PRBCs. This yields a 4.8% overall difference in survival rates assuming 35%, 35%, and 30% of the total study population being within each transfusion group.

This trial is a one-sided trial, involving 3 arms, and therefore the traditional significance level of 0.025 is divided by n-1. To detect a 4.8% overall difference in survival (from 64.6% to 69.4%) for the placebo and each treatment group in at least one of the two comparisons with a overall power of 80% (62.6% power for an individual agent) and 6 looks (5 interim looks), a total of 3,726 patients is required (Lan-DeMets  $\alpha$ -Spending Function with O'Brien-Fleming type Boundary for Superiority). The most efficient

randomization distribution is 1:1:1.414 (1092 in each hypertonic saline group and 1542 control patients). The anticipated length of this trial with this sample size will be approximately 3.5 years.

### **B. TBI Cohort**

#### *Primary Outcome:*

The primary outcome for TBI patients will be neurologic function at 6 months after injury based on the GOSE obtained by telephone survey. For the purpose of estimating the power to assess neurologic outcome, we dichotomized the GOSE into Good vs. Poor outcome. Good outcome corresponds to either moderate disability or good recovery (GOSE>4), while poor outcome corresponds to dead, vegetative state, or severe disability (GOSE ≤4). We consider a 15% relative reduction in the prevalence of poor outcome to be clinically relevant. Review of the literature suggests that 40-57% of this population will have a poor outcome.

If we estimate a 51% incidence of good outcome and assume that hypertonic fluids offer a relative 15% reduction (absolute reduction 7.5%) in the risk of poor outcome, then a total of 1,688 patients are required to detect this difference with an overall power of 80% (One-sided, study-wide  $\alpha=0.025$ , Lan-DeMets  $\alpha$ -Spending Function with O'Brien-Fleming type Boundary for Superiority, 62.6% power for an individual agent, and 3 looks (2 interim looks)). The most efficient randomization distribution is 1:1:1.414 (494 in each hypertonic saline group and 699 control patients).

However, based on a previous trial that utilized a GCS ≤8 as a pre-hospital enrollment criterion, we anticipate that approximately 10% of the patients enrolled in the TBI cohort will actually have a less severe injury and have other reasons for altered mental status such as alcohol or drug intoxication. These patients will be included in the intention to treat analysis but may be less likely to benefit from this therapy. To account for these patients in the analysis, the power calculations need to be adjusted to N=2122 patients. The anticipated length of this trial with this sample size will be approximately 1.5 years for study to collect primary outcome at six months of follow-up.

In addition to this dichotomized endpoint, a secondary analysis will examine incremental differences in the point scale for the GOSE & DRS to detect a potential for a greater impact of this resuscitation strategy on the more severely injured TBI patients.

4. For multi-center research, indicate the overall sample size for the entire project (across all sites).

Not applicable - This study is not a multi-center study.

These studies call for the enrollment of approximately 5000 patients who have sustained a traumatic injury and are either hypotensive or have evidence of a severe TBI in the prehospital environment without ongoing CPR.

### **B. Inclusion and Exclusion Criteria**

1. Describe the characteristics of the proposed subject population (age, gender, health status, language, etc.)

Male and Female over the age of 14 or greater than or equal to 50 kg and seriously injured enough to be categorized as a Major Trauma Victim.

2. Provide the inclusion and/or exclusion criteria for the proposed subject population, as applicable.

Not applicable – This is not a clinical investigation and/or characteristics of the population sufficiently describe the proposed subject population.

**Inclusion Criteria**

Hypovolemic Shock Cohort

1. Blunt or Penetrating Trauma
2. Pre-hospital SBP  $\leq 70$  mmHg; or  
Pre-hospital SBP 71-90 mmHg AND HR  $\geq 108$
3. Age  $\geq 15$  yrs or  $\geq 50$  kg

TBI Cohort

1. Blunt trauma
2. Pre-hospital GCS  $< 8$  and pre-hospital SBP  $> 90$  mmHg\*
3. Age  $\geq 15$  yrs or  $\geq 50$  kg

\* Patients with both a GCS  $\leq 8$  & who meet the criteria for the hypovolemic shock cohort will be considered part of the hypovolemic shock cohort but will have assessment of neurologic outcome for subsequent subset analysis.

**Exclusion criteria (both cohorts)**

1. Known or suspected pregnancy
2. Age  $< 15$  or  $< 50$  kg if age unknown
3. Ongoing pre-hospital Cardiopulmonary Resuscitation (CPR)
4. Administration of  $> 2000$  cc crystalloid or any colloid or blood products
5. Severe hypothermia (suspected T  $< 28$  C)
6. Drowning or asphyxia due to hanging,
7. Burns TBSA  $> 20\%$
8. Isolated penetrating injury to the head
9. Inability to obtain pre-hospital intravenous access

3. If inclusion/exclusion is based on age, gender, pregnancy/childbearing potential, or social/ethnic group, provide a scientific rationale.

Women who are either known or suspected to be pregnant will be excluded as the effects of hypertonicity on the fetus are unknown. No other subgroups will be excluded.

**SECTION 5: RECRUITMENT METHODS AND PROCESS**

**A. Recruitment Methods**

Please check **all** applicable recruitment methods that apply to the study. Place an "X" in the bracket  next to the recruitment method.

<p>[ ] This study involves no direct contact with subjects (i.e., use of existing records, charts, specimens)</p> <ul style="list-style-type: none"> <li>• Skip to Section 6.</li> </ul>
<p>[ ] UCI IRB approved advertisements, flyers, notices, and/or media will be used to recruit subjects. Submit advertisements for IRB approval.</p> <ul style="list-style-type: none"> <li>• Passive Recruitment - Potential subjects initiate contact with the study team.</li> <li>• Complete Question 5B - Explain where recruitment materials will be posted.</li> </ul>
<p>[ ] The study team will recruit potential subjects who are unknown to them (e.g., snowball sampling, use of social networks, direct approach in public situations, random digit dialing, etc.)</p> <ul style="list-style-type: none"> <li>• Active Recruitment – Researchers contact potential subjects.</li> <li>• Complete Question 5B.</li> </ul>
<p>[ ] The UCIMC Clinical Trials web page will be used. Submit the UCIMC Standard Research Recruitment Advertisement for IRB approval.</p> <ul style="list-style-type: none"> <li>• Passive Recruitment - Potential subjects initiate contact with the study team.</li> <li>• Skip to Section 6.</li> </ul>
<p>[ ] The UCI Social Sciences human subject pool will be used. Submit the Social Science Human Subject Pool Recruitment Advertisement for IRB approval.</p> <ul style="list-style-type: none"> <li>• Passive Recruitment - Potential subjects initiate contact with the study team.</li> <li>• Skip to Section 6.</li> </ul>
<p>[ ] Study team members will contact potential subjects who have provided permission to be contacted for participation in future research studies.</p> <ul style="list-style-type: none"> <li>• Active Recruitment – Researchers contact potential subjects.</li> <li>• Complete Question 5B – Explain when and how these individuals granted permission for future contact; provide the IRB protocol numbers, if applicable.</li> </ul>
<p>[ ] Study team members will approach their own patients, students, employees for participation in the study.</p> <ul style="list-style-type: none"> <li>• Active Recruitment – Researchers contact potential subjects.</li> <li>• Complete Question 5B.</li> </ul>
<p>[ ] Study team members will send UCI IRB approved recruitment materials (e.g., recruitment flyer, introductory letter) to colleagues asking for referral of eligible participants.*</p> <ul style="list-style-type: none"> <li>• Passive Recruitment - Potential subjects initiate contact with the study team <u>or</u></li> <li>• Active Recruitment – Colleagues get permission from interested individuals to release contact information to researchers. Researchers contact potential subjects.</li> <li>• For <u>Active Recruitment</u>, complete Question 5B.</li> </ul> <p><i>*Additional requirements for using this recruitment method are included in the Protocol Narrative instructions.</i></p>

- Study team members will provide their colleagues with a UCI IRB approved introductory letter. The letter will be signed by the treating physician and sent to his/her patients to inform them about how to contact study team members.
- Passive Recruitment - Potential subjects initiate contact with the study team.
  - The IRB approved letter must be sent by the treating physician.
  - The study team does not have access to patient names and addresses for mailing.
  - Skip to Section 6.

- UCI study team members will screen UCIMC medical records to determine subject eligibility and approach patients directly about study participation.\*
- Active Recruitment – Researchers contact potential subjects.
  - Complete Appendix T to request a partial waiver of HIPAA Authorization.
  - Complete Question 5B.

*\*Additional requirements for using this recruitment method are included in the Protocol Narrative instructions.*

**Other Methods:** All screening will be completed by trained EMS paramedics upon first recognition that the subject has potential to be enrolled. The paramedics will enroll all the patients that meet all inclusion/exclusion criteria.

- Complete Question 5B, as applicable.

## B. Recruitment Process

1. Based on the boxes checked above, describe and provide **details of the recruitment process** (i.e. when, where, by whom and how potential subjects will be approached).
2. If active recruitment methods will be used, explain how the individual's privacy will be protected.

All screening will be completed by trained EMS paramedics upon first recognition that the subject has potential to be enrolled. The training will include inclusion and exclusion criteria for the protocol and how to enroll the subject into the study. There is no active recruitment due to the severity of the injuries.

## SECTION 6: INFORMED CONSENT PROCESS

Describe the specific steps for obtaining informed consent.

1. Include information about **when and where** consent will take place and the **length of time** subjects are given to decide whether they wish to participate.
2. If study team members will approach their own patients, students, or employees for participation in the study, explain what precautions will be taken to **minimize potential undue influence** or coercion, and how compromised objectivity will be avoided.

**Check all that apply:**

- Written (signed) informed consent will be obtained from subjects. Explain how you will obtain signed consent (i.e., describe the process).
- Requesting a waiver of written (signed) informed consent. Explain how you will obtain consent (i.e., describe the process). **Be sure to complete Appendix P.**
- Requesting a waiver of informed consent (i.e., consent will not be obtained). **Complete Appendix O. Skip to Section 7.**

This study qualifies for the "Exception from informed consent required for emergency research" outlined in FDA regulation 21CFR50.24. The study fluid needs to be administered as the first resuscitation fluid following traumatic injury. In this uncontrolled setting the patient has an altered mental status secondary to hypotension, which limits cerebral perfusion, potential traumatic brain injury, and potential for intoxication with sedating drugs or alcohol. As a result, the patient is unable to provide consent for study enrollment. Legal next-of-kin are often not immediately available at the injury scene, nor is it practical for the pre-hospital provider to explain the study and receive consent while caring for the critically injured patient. Taken together, these issues provide sufficient support for an emergency medicine exception from consent in order to evaluate an intervention that may have significant outcome benefits to this patient population. We have outlined below, each criteria stipulated in the regulations for this exception and how our study design applies to these criteria.

Sec. 50.24 Exception from informed consent requirements for emergency research

(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.

The proposed trial is a prospective, randomized trial of hypertonic saline/ dextran (HSD) or hypertonic saline (HS) alone to be administered as the first resuscitation fluid given to victims of blunt or penetrating traumatic injury with hypotension (systolic blood pressure <90) or severe traumatic brain injury (GCS < 8). These patients are in an immediate life threatening situation with a mortality approaching 30%. Standard of care for pre-hospital management of these patients includes the rapid infusion of crystalloid solutions. As reviewed in this proposal, previous studies of HSD resuscitation have suggested a survival advantage with this fluid but have not been definitive. These studies attest to the safety of HSD in the hypotensive trauma population and to the practicality of using this fluid in the pre-hospital environment. They also suggest that certain subgroups of patients are most likely to benefit from this intervention, including those at-risk for inflammatory organ dysfunction and those with traumatic brain injury. The major limitations of previous studies have been either the insufficient patient number to detect significant clinical differences in outcome or the lack of focus on the specific patient population most likely to benefit. These studies were also conducted prior to the evolution of the basic science literature demonstrating the effects of hypertonicity on the immuno-inflammatory response. Thus, critical evaluation of these effects in humans has not been undertaken. We propose the definitive clinical trial, focusing on the multisystem trauma population, which will maximize the statistical power to detect changes in outcome and provide a detailed analysis of the immuno-inflammatory effects of HSD and HS resuscitation. Furthermore, an emphasis on the functional outcome of brain-injured patients will define the clinical utility of this resuscitation approach for these patients.

(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.

The test fluids, HSD or HS, need to be administered as the first resuscitation fluid following traumatic injury (see discussion of therapeutic window below). In this uncontrolled setting the patient has an altered mental status secondary to hypotension, which limits cerebral perfusion, potential traumatic brain injury, and potential for intoxication with sedating drugs or alcohol. As a result, the patient is unable to provide consent for study enrollment. Legal next-of-kin are often not immediately available at the injury scene, nor is it practical for the pre-hospital provider to explain the full study and receive consent while caring for the critically injured patient. Because we are studying traumatic injury, which is unpredictable, there is no way to prospectively identify individuals who are likely to become eligible for this trial.

- (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.

As defined, these patients with hypovolemic shock or severe TBI are facing a life threatening situation which requires immediate intervention.

Previous trials have been conducted in the trauma population and suggest a survival advantage overall and significant direct benefit to patients with traumatic brain injury. A recent meta-analysis of studies involving the pre-hospital administration of HSD concludes that patients with traumatic brain injury in the presence of hypotension who receive HSD are twice as likely to survive as those who receive standard resuscitation<sup>66</sup>. Sub-group analysis of the individual trials also suggested that patients with traumatic brain injury (Glasgow coma score (GCS) < 8) who received HSD had a significant survival advantage. Vassar et al. reported a survival to discharge for patients with severe brain injury of 34% for those receiving HSD vs. 12% for those receiving conventional resuscitation<sup>94</sup>.

The mechanism of action of HSD in these patients is likely multifactorial. Hypertonic saline administration in animals and humans with hypovolemic shock results in rapid improvement in the mean arterial pressure<sup>68-73, 133</sup>. This effect is due to plasma volume expansion due to the increased osmotic load, along with centrally mediated effects on cardiac output. Rapid restoration of mean arterial pressure results in improved cerebral perfusion pressure, which supports the injured brain. Furthermore, hypertonic resuscitation has been shown to restore tissue perfusion and preclinical trials suggest that hypertonicity may have immunomodulatory effects that may reduce the incidence of post-injury organ failure.

HSD administration has been tested in eight previous clinical trials with no adverse effects reported. As discussed above, there are potential risks to subjects that may have not been observed in previous trials. We contend that these risks are reasonable in light of the potential benefits outlined in this proposal.

- (4) The clinical investigation could not be conducted without the exemption of consent due to the need to administer the study fluid as the first resuscitation fluid given by the pre-hospital provider to these critically injured patients.
- (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.

There have been eight clinical trials of HSD for the acute resuscitation of hypovolemic patients<sup>11-15, 74, 94, 135</sup>. In six of the trials HSD was administered in the pre-hospital environment, while in two it was administered upon arrival to the hospital. The six pre-hospital trials all demonstrated a survival benefit for patients treated with HSD vs. conventional isotonic resuscitation. The two emergency room trials showed no difference in survival, suggesting that the administration of this fluid at the time of initial reperfusion may be critical. Preclinical trials support that a key potential mechanism by which HSD resuscitation may be beneficial involves modulation of the systemic inflammatory response at the time reperfusion following whole body ischemia. Reperfusion injury results in the upregulation of inflammatory cells and the activation of endothelial adhesion cascades that result in activation and migration of circulating monocytes and neutrophils into the tissues. This process has been linked to the development of a subsequent capillary leak and inflammatory organ injury such as ARDS. Intervention at the time of reperfusion, which begins the moment intravenous fluid is begun, appears critical to halting the onset of these deleterious inflammatory cascades.

Several studies suggest that hypertonicity can have profound effects on neutrophil function. In vitro studies have shown that hypertonic saline prevents up-regulation of the important adhesion molecule CD11b on the surface of neutrophils and induces the shedding of L-selectin adhesion link from the surface of the neutrophil<sup>30-32</sup>. These adhesion molecules are critical to the adherence of neutrophils to the endothelium resulting in extra vascular migration and activation of these cells during reperfusion injury. Furthermore, this effect appears to be transient and reversible, suggesting that the acute reperfusion injury could be attenuated without increasing the risk of subsequent infection from neutrophil dysfunction<sup>33</sup>. HS resuscitation has also been shown to significantly attenuate inflammatory lung injury in a two-hit animal model consisting of an initial hemorrhagic shock with reperfusion followed by and intratracheal endotoxin challenge<sup>1</sup>. Lung injury was also attenuated by HS resuscitation in a hemorrhagic shock model secondary to suppression of the hemorrhage-induced neutrophil oxidative burst<sup>34</sup>. Finally, the timing of HS administration appears critical, as lung injury is attenuated by administration at the time of reperfusion but was enhanced in animals given HS after partial resuscitation with crystalloid<sup>35</sup>.

Based on these data, coupled with the previous clinical trials, the therapeutic window for this agent is at the time of initial fluid resuscitation, which occurs when intravenous fluids are administered by pre-hospital care providers. Because this is an immediate life threatening situation, it will not be possible to contact legal representatives at the time of study entry.

However, EMS personnel will be trained to read a prepared script prior to patient enrollment if there is an available LAR or family member at the scene. The prepared script option is part of the FDA approved protocol and thus it is a required process for this study. The script reading option is only done on an "if feasible basis," that is to say that reading this script will not happen if it will interfere with pre-hospital care. As stated in the protocol, page 42:

We intend to train the EMS personnel to read a prepared short script prior to patient enrollment if a conscious, alert, uninjured, and clearly identifiable legally authorized representative (LAR) is available at the accident scene. If there is objection to enrollment, the patient would not be enrolled. We will also prepare laminated cards that could be given to the LAR containing this information along with contact information for the local investigators. The EMS providers will determine the feasibility of obtaining this pre-enrollment disclosure based on a standard set of guidelines including appropriate LAR present and sufficient time and adequate numbers of EMS personnel available to avoid any disruption of patient care. If the EMS providers determine any of these conditions do not exist, then pre-enrollment disclosure will not be performed. We believe that it would be detrimental to patient care to require the pre-hospital provider to conduct a lengthy full informed consent while they are focused on caring for the critically ill patient. Thus the LAR would subsequently be approached by the research coordinator after arrival at the hospital to

review the full written consent forms in a more controlled setting. If a subject is entered into the clinical investigation and the subject dies before an LAR or family member can be contacted, information about the clinical investigation will be provided to the subject's legally authorized representative or family member, if feasible.

We will make every effort to contact legal representatives upon admission to the hospital to obtain informed consent to continue with the study procedures including blood sampling and data collection. If legal representatives are not immediately available, the research coordinator will attempt to contact the subject's legal representative as soon as feasible and a summary of these efforts will be documented in the patient's chart. If the subject becomes competent to provide consent during the study period, then he/she will be approached by the research coordinator for consent.

When approached for consent following enrollment, the patient or their legal representative will have the option of refusing to continue the study. In this circumstance, we will be limited to a description of baseline data and survival to ensure that subjects who drop out are comparable among the groups. Our previous experience suggests that refusals of this nature are rare. 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.

- (6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sec. 50.25. 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.
- (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

We expect that the majority of patients who meet the enrollment criteria will either be unconscious or have an altered mental status secondary to hypotension and the potential for traumatic brain injury or intoxicating substances. In the event that a patient meets the entry criteria and is awake and alert, the patient is still under considerable duress due to the acute life threatening injury and thus not in a position to provide informed consent in the pre-hospital setting. In addition, any delay in medical care that would be required for the paramedic to attempt to explain and obtain consent would be life threatening. Thus it will not be feasible to attempt to obtain informed consent during the therapeutic window and to give the short script if deemed not feasible by the EMS personnel.

Community consultation will be undertaken prior to IRB approval. Because the population eligible for

enrollment includes all citizens in the study regions it will not be possible to target any particular small group. The community consultation plan for each study site will have to be individualized to fit the IRB/REB requirements. The following is a proposed plan for community consultation for this site, which has been used in a prior hypertonic resuscitation trial.

### **Meeting with Elected Officials**

Dr. David Hoyt, the Lead Researcher of this study, has met with the Orange County Health Care Agency Medical Director, Dr. Sam Stratton, and the Orange County Fire Authority Medical Director, Dr. Ken Miller. Dr. Hoyt and Dr. Stratton presented the HS trial to the Orange County Emergency Medical Care Committee which acts as an advisory committee to the County Board of Supervisors and the Orange County Emergency Medical Services on all matters relating to emergency medical care within the County. Letters of cooperation from the EMS agencies are currently being collected with the help of Dr. Stratton's office and will be submitted to the IRB once they are obtained.

The plan for community consultation has 4 elements:

1. Random Digit Dialing
2. Community Meetings
3. Press Releases
4. Website

#### **(1) Random Digit Dialing**

Random Digit Dialing will be used to assess objectively a population sample for community consent. This process has been used in other ROC centers throughout the United States and uniformly, about 70-75% of people contacted through this process agreed to the study. This has been recognized by the FDA and the Patient Safety Monitoring Committee of the study as an appropriate threshold. Our plans are to use the vendor, Hebert Research (a survey company hired and very experienced about this study), which was used in the San Diego County, to pull all zip codes in Orange County through this process. The company will send out a telephone survey with questions that will appropriately address the program on a 6<sup>th</sup> grade level. The survey will contain a description of the trial and ask 5-7 questions about the trial. These questions will be submitted to the IRB for approval first before disbursement. The survey will record demographic information about the person filling out the survey (i.e., zip code). The standard number of surveys collected at the other sites is 500. Results of the program for this site will be made available to the IRB in making their assessment of the adequacy of community consent.

#### **(2) Community Meetings**

The plan for community meetings will be public presentations of the trial which will be held around Orange County within the different major ethnic groups. John Gilwee, Senior Director of Government Healthcare Programs, will be coordinating the sites to include the following contacts:

1. Latino Health Access will determine the site for the Spanish speaking community. TBD
2. Assemblyman Van Tran will be contacted to obtain a site for the Vietnamese Community. TBD
3. Korean First Presbyterian Church  
8500 Bolsa Ave, Westminster CA 92683  
- Wednesday evenings 100 members, Sunday afternoon 500 members  
(Contact via Jon Gilwee is Kyu Kim, RN, Clinical Nurse III Supervisor)
4. Assembly Member Mimi Walters as contact for a community source in South Orange County. TBD
5. Orange County Healthcare Safety Net Coalition meets at Beckman Center on December 5, 2007.
6. Meeting with local AARP group, site to be determined.

**\*\*Date and time of these meetings are subject to timeline of IRB approval and will be set once IRB approval is obtained.**

A PowerPoint presentation with handouts and questionnaires will be distributed at the community consultation meetings. There will be time allocated at the end of the presentation for Questions and Answers. The PowerPoint presentation slides and handouts will be submitted to the IRB for review prior to disbursement.

The "opt out bracelet" is a silicon stretchy wrist band (white embossed with ROC) with the name of the study written on it. UCSD has 600 of these and will send them to UCI. The bracelet will be explained at the community consultation meetings. The community will be advised that they must wear the bracelet if they do not wish to participate in this study as this is where the EMS personnel will look for it. The opt out bracelet will also be described on the study's website as to the process of obtaining the opt out bracelet. The website will also have the contact information of the Lead Researcher and the Research Personnel for this study.

### **(3) Press Releases**

The study will be advertised in the following newspapers:

Orange County Register	Circulation: 302,864
LA Times Orange County	Circulation: 200,000
Orange County Post	Circulation: 104,000
L'Opinion (Spanish Speaking)	Circulation: 114,000
Nguoi Viet Daily News (Vietnamese)	Circulation: 18,000
Suc Song News (Vietnamese)	Circulation: 20,000

These will be coordinated by Tom Vasich, Assistant Director for Health Science Communications and Susan Mancia, Senior Public Information officer.

### **(4) Website**

A website will be created for this study at this site containing information on this study with contact information. The website will be linked to the \_\_\_ website.

Public disclosures will be performed both prior to study enrollment and at the completion of the study in the form of multimedia press releases organized by the Resuscitation Outcomes Consortium. These will include plans for the study including potential risks and benefits and a summary of the results of the study upon completion. In the event that the press releases are not widely circulated, advertisements will also be placed in local papers describing the study.

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**3. Non-English Speaking Participants:** In order to consent subjects who are unable to read and speak English, the English version of the consent form must be translated into appropriate languages once IRB approval is granted.

**Check all that apply:**

Not applicable - Only individuals who can read and speak English are eligible for this study.

The English version of the consent form will be translated into appropriate languages for non-English speaking subjects once IRB approval is granted. **Note:** The IRB must stamp the translated consent forms before they are used. An interpreter will be involved in the consenting process.

Requesting a short form consent process. Complete Appendix Q.

## **SECTION 7: RISK ASSESSMENT AND POSSIBLE BENEFITS**

*Review of the instructions for this section is strongly recommended.*

### **A. Risk Assessment**

Place an "X" in the bracket  next to the level of review (based upon the investigator's risk assessment).

This study requires **full committee** review.

This study qualifies as **Exempt or Expedited research**. Below provide justification for the level of review and for the applicable **Exempt or Expedited** category(ies) that you have chosen:

<Type here>

### **B. Risks and Discomforts**

1. Describe the **risks/potential discomforts** (e.g., physical, psychological, social, economic) associated with **each** intervention or research procedure.
2. Estimate the probability (e.g., chance or likelihood of occurrence) that a given harm may occur and its severity (e.g., mild, moderate, severe).

#### **Serious Adverse Events**

- Any evidence of anaphylactic reaction to HSD (Shock: 0%, TBI only: 0%)
- Seizure activity associated with hypernatremia (Shock: 0%, TBI only: 0%)
- Hypernatremia (Na<sup>></sup> 160 mEq/L) requiring therapeutic intervention (Shock: 0.9%, TBI only: 3.5%)
- Evidence of increased intracranial hemorrhage on Head CT scan (Shock: 3.3%, TBI only: 17%)
- Unexplained coagulopathy
- Any death not explained by the injury severity (Shock: 0%, TBI only, 0%)

#### **Other Adverse Events**

- Irritation at the site of infusion (Shock: 0%, TBI only: 0%)
- Minor allergic reaction, skin rash with no hemodynamic effects (Shock: 0.3%, TBI only: 0%)
- Evidence of increased bleeding based on blood & fluid requirements in the first 24 hours (evaluated at interim analyses) (Shock: 0.6%, TBI only: 0.3%)

\*\*Adverse events percentages based on first ~700 subjects, 332 subjects for the Shock arm and 370 for the TBI only arm)

An additional risk to subjects in this proposal pertains to the potential for a breach in patient confidentiality.

There is a possibility that contact with subjects in the post-discharge period will serve as a reminder of the events surrounding the injury and may contribute to feelings of anxiety. In addition, follow-up questions regarding neurologic impairment following traumatic brain injury may lead to frustration on the part of the subject who may become more aware of his/her deficits.

**3. Discuss what measures have been taken and/or will be taken to prevent and minimize any risks/ potential discomforts.**

**Protection Against Risks**

In accordance with the FDA, we will develop an adverse event reporting system to identify and treat any potential adverse events. We intend to closely monitor the clinical course of all patients enrolled in this trial to identify any expected or unexpected adverse events. Data regarding adverse events will be collected in both a structured (standard form) and open (describing any difficulties encountered) format. In accordance with the regulations 21 CFR 312.32, we have outlined below the expected serious and non-serious adverse events, our plans to identify these and the timeline for reporting to the FDA, IRB and DSMB.

All members of the trauma team will be instructed as to the possible adverse events prior to the start of the trial and will be given an emergency contact number to immediately report any suspected adverse event to the investigators. In addition, all pre-hospital providers will be advised as to the clinical signs and symptoms suggestive of a potential anaphylactic reaction. Should this occur they will be advised to immediately discontinue the infusion, treat the reaction appropriately, and report the event to the trauma team and the investigators. Any serious and life threatening adverse event (either expected or unexpected) will be reported by telephone to the FDA, IRB and chairperson of the DSMB within 72 hours and in writing within 7 days. All non-life-threatening unexpected serious adverse events will be reported in writing within 15 days. All other potential adverse events will be reported to the chair of the DSMB and reviewed at the interim analyses and included in a safety report to the FDA at that time. At the interim analyses, all adverse events will be reviewed and mortality and 24 hour fluid and blood product requirements will be compared between the groups. The chair of the DSMB can convene additional meetings as necessary to investigate adverse events.

In addition to the outcome parameters & baseline data, the research coordinator will collect the following data, which will aid in the identification of any potential adverse events:

**For all patients:**

- Total fluid and blood products required in the first 12 and 24 hours
- Coagulation parameters on admission
- Amount of blood loss reported in the operating room
- Potassium level on admission and presence of any cardiac arrhythmias
- All operative procedures performed during the hospital stay

**For patients with Traumatic Brain Injury**

- Results of the first 3 Head CT scans obtained within the first week after injury
- Intracranial pressure (ICP) and cerebral perfusion pressure (CPP) at the time of ICP monitor placement.
- Highest ICP and lowest CPP recorded for every 12 hour period in the first 48 hours after injury
- Total amount of Mannitol administered every 12 hours for the first 48 hrs after injury
- All reports of seizure activity and anti-convulsant medications administered

To safeguard patient confidentiality, all study personnel involved in data collection and analysis will be required to sign a confidentiality agreement as required by the institutional review board. In addition,

subjects will be identified in the database by a study number and links to specific identifiers will be kept in a separate secure location. Database files will be maintained on a password protected computer in a secure location.

To minimize feelings of anxiety in post discharge contact,, questions will be limited to events in the post-discharge period and telephone interviewers will receive training concerning sensitivity to patient concerns.

The interviewers will also provide subjects referrals for counseling if it appears that they are distressed by the interviews.

4. For **Full Committee protocols**, state whether any study procedures may involve risks to the subject (or embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable.

Not applicable - This study qualifies as **Exempt or Expedited research**.

The risks to a fetus or to a pregnant or nursing woman are not fully known at this time. Subjects cannot participate in this study if they are pregnant or are currently a nursing mother if known at the moment of enrollment.

### C. Potential Benefits

1. Discuss the benefits that may accrue **directly to the subjects**. *Note: Compensation is not a benefit. Do not include it in this section.*

There is no direct benefit anticipated for the subjects.

**OR**

There are several potential benefits to subjects in the hypertonic arms of the protocol. These include: improved tissue perfusion following hemorrhagic shock; reduced activity of inflammatory cells resulting in a reduced incidence of organ dysfunction such as ARDS; enhanced T cell function resulting in reduction in the risk of nosocomial infection; and reduction in secondary brain injury for head injured patients.

2. Describe the **potential societal/scientific benefit(s)** that may be expected from this study.

The potential benefit to society involves a critical evaluation of this therapy in a patient population that is most likely to benefit from this intervention. This could result in a significant change in the resuscitation strategy for these patients in the future.

### D. Risk/Benefit Assessment

**For Expedited and Full Committee protocols, explain why the study risks are reasonable in relation to the potential benefits to subjects and society.**

Not applicable - This study qualifies as **Exempt research**; there is virtually no risk/potential discomfort to the subjects.

**OR**

Trauma is the leading cause of death among North Americans between the ages of 1 and 44 years. The majority of these deaths result from hypovolemic shock or severe brain injury. Patients in hypovolemic shock develop a state of systemic tissue ischemia with a subsequent reperfusion injury at the time of fluid resuscitation. Conventional resuscitation involves the intravenous (IV) administration of a large volume of isotonic (normal saline) or slightly hypotonic (lactated ringers, LR) solutions beginning in the pre-hospital setting. Although not conclusive, prior animal and human studies have suggested that alternative resuscitation with hypertonic saline (7.5%) solutions may reduce mortality in these patients. Furthermore, hypertonic fluids may have specific advantages in the brain-injured patient, as they may aid in the rapid restoration of cerebral perfusion and prevent extravascular fluid sequestration, thereby limiting secondary brain injury. In addition, recent studies have demonstrated that hypertonicity significantly alters the activation of inflammatory cells, an effect that may reduce subsequent organ injury from ischemia-reperfusion and decrease nosocomial infection.

This study seeks to address the impact of hypertonic resuscitation on two injured patient populations, those with hypovolemic shock (either prehospital SBP  $\leq 70$ ; or prehospital SBP 71-90 AND HR  $\geq 108$ ) and those with severe traumatic brain injury (prehospital GCS  $\leq 8$ ). The possible benefits of increased survival rates on these two patient populations outweigh the possible risks involved.

## **SECTION 8: ALTERNATIVES TO PARTICIPATION**

Describe appropriate **alternative procedures or courses of treatment**, if any, which might be advantageous to the subject or indicate that the only alternative is non-participation.

No alternatives exist. The only alternative to subjects is not to participate in the study.

**OR**

The alternative is to provide the standard of care with the administration of crystalloid fluids according to the patient specific need related to the traumatic injury. Subjects will receive standard of care if they verbally state not to participate, do not meet criteria for enrollment, or is wearing the "opt out bracelet."

## **SECTION 9: ADVERSE EVENT REPORTING/MANAGEMENT AND COMPENSATION FOR INJURY**

### **A. Adverse Events and Unanticipated Problems**

1. Indicate that you are familiar with UCI's Adverse Events/Unanticipated Problems reporting policy and procedures. See <http://www.rgs.uci.edu/ora/rp/hrpp/adverseexperiences.htm> for details.

Not applicable - This study involves no subject contact (i.e., use of existing records, charts, specimens).

The researchers will comply with UCI's Adverse Events/Unanticipated Problems reporting policy and procedures.

2. Explain how the research team will **respond to adverse events and unanticipated problems** that may occur during the study or after completion of the study (i.e., how will you manage the event/problem; provide a plan).

Not applicable - This study involves no subject contact (i.e., use of existing records, charts, specimens).

Not applicable - This study qualifies as **Exempt research**; there is virtually no risk to the subjects.

#### **Data safety and monitoring plan**

This study will be monitored by an independent Data Safety & Monitoring Board (DSMB) established by the National Heart, Lung and Blood Institute (NHLBI). All adverse events will be reported to the DSMB as described.

#### **Procedures for Reporting Adverse Events**

##### ***Reporting from the EMS Paramedics***

Adverse Event data will be recorded by the EMS team and will be relayed to the clinical site once patient has been hospitalized via telephone and fax. The study team will then log in the event and report it to the ROC Data Coordinating Center.

Assuring patient safety is an essential component of this protocol. The Principal investigator has primary responsibility for the safety of the individual participants under his care. All adverse events will be evaluated by the Principal Investigator. The study coordinator must view patient records for possible adverse events throughout the study period. All adverse events occurring within the study period must be reported in the participant's case report forms. Data regarding adverse events will be collected in both a structured (standard form) and open (describing any difficulties encountered) format.

Any serious and life threatening adverse event (either expected or unexpected) will be reported by telephone to the FDA, IRB and chairperson of the DSMB within 72 hours and in writing within 7 days. All non-life-threatening unexpected serious adverse events will be reported in writing within 15 days. All other potential adverse events will be reported to the chair of the DSMB and reviewed at the interim analyses and included in a safety report to the FDA at that time. The Institutional Review Board must all also be informed in a timely manner. . All adverse events should be reported promptly to the CTC. These reports must include a **blinded** copy of the AE report sent to the local IRB/REB with the PI's signature and a clinical summary of the incident. The CTC will notify the DSMB, the FDA and the NIH as required by the protocol.

All SAEs are monitored closely by the participating clinical centers, who report the SAEs to the ROC Data Coordinating Center in Seattle Washington. The Data Coordinating Center monitors the participating clinical centers with respect to completeness and timeliness of all such reports. As they arrive, the reports are reviewed by the Data Coordinating Center Medical Director (Dr. G. Nichol) and then forwarded to the FDA and the Chair of the DSMB. The Chair of the DSMB may refer specific SAEs to the entire DSMB whenever he feels such an immediate review by the entire board is indicated. In any case, the cumulative incidence of all SAEs is reviewed by the entire DSMB during their regularly scheduled meetings. The DSMB meets twice a year. However, they do conduct telephone-conference intermittently in-between the meetings. The last face to face meeting was October 2, 2007. The next face to face conference is in Bethesda, MD in March 2008. To date, the trial has enrolled 1000 subjects. No safety issues were raised by the DSMB.

All adverse events related to the risks described in this study and any unanticipated risk will be treated on a case by case basis by the study team on this study according to good clinical practice.

## B. Compensation for Injury

For **Full Committee protocols**, explain how costs of treatment for research related injury will be covered.

Not applicable - This study qualifies as **Exempt or Expedited research**.

Subjects who are injured as a direct result of their participation in this study will be provided reasonable and necessary medical care to treat the injury at no cost to them or their insurer/third party payer. The University of California does not routinely provide any other form of compensation for injury.

Other: <Type here>

## SECTION 10: PARTICIPANT COSTS

**Identify and estimate** those costs to be borne by subjects or their insurers, including costs of standard medical interventions or procedures.

Not applicable - This study involves no subject contact (i.e., use of existing records, charts, specimens).

There are no costs to subjects/insurers.

**OR**

<Type here>

## **SECTION 11: PARTICIPANT COMPENSATION AND REIMBURSEMENT**

If subjects will be compensated for their participation, provide detailed information about the amount and the method/terms of payment (e.g., money; check; extra credit; gift certificate). In addition:

1. Describe the schedule of compensation (e.g., at end of study; after each session/visit).
2. Compensation should be offered on a prorated basis.
3. Specify whether subjects will be reimbursed for out-of-pocket expenses. If so, describe any requirements for reimbursement (e.g., receipt).

Not applicable - This study involves no subject contact (i.e., use of existing records, charts, specimens).

No compensation will be provided to subjects.

No reimbursement will be provided to subjects.

**OR**

There will be no compensation to the subjects screened or enrolled who are enrolled as hypotensive only. A nominal sum will be provided upon completion of the 6 month interview by phone to the TBI group. This would be broken out to \$20.00 at discharge, \$10.00 at a 3 month follow up call to reconfirm contact information and \$20.00 after completing the 6 month phone follow up.

## **SECTION 12: CONFIDENTIALITY OF RESEARCH DATA**

1. Explain how data will be **collected and recorded**.

**Data Collection/Method of Recording (check all that apply):**

- Paper documents/records
- Computer files/database
- Audio recording
- Video recording
- Photographs
- Biological specimens
- Other(s) (specify): <Type here>

2. Indicate whether **subject identifiers** will be linked (directly or indirectly via a code) to the research data.

**No Subject Identifiers will be collected**  
(i.e., the data are anonymous; no one will collect information that can link the subjects to their data)

**Indirect link to Subject Identifiers**

(i.e., a code will be assigned to the data and a key linking the code to the identity of the subjects exists)

**Direct link - Subject Identifiers will be maintained with data**

(i.e., personal or private information about the subjects are associated with the data)

List the direct identifiers to be collected here: <Type here>

**Other (explain here):** <Type here>

**3. Indicate how data will be stored, secured** including paper records, electronic files, audio/video tapes, specimens, etc.

**Note:** *The more sensitive the study data, the more sophisticated the methods should be to maintain confidentiality.*

**Electronic Data (check all that apply):**

Anonymous or de-identified data only (i.e., no code key or key destroyed)

Coded data with the code key kept in separate location

Encryption or password protection software will be used

Secure network server will store data

Stand alone desktop computer will house data (not connected to server/internet)

Other (specify here): <Type here>

**Hardcopy Data, Recordings and Specimens (check all that apply):**

Anonymous or de-identified only (i.e., no code key or key destroyed)

Locked file cabinet or locked room at UCI/UCIMC will house data

Locked lab/refrigerator/freezer at UCI/UCIMC will be used to store data

Other (specify here): <Type here>

**4. Data on portable devices:**

- Describe the portable device(s) to be used (e.g. laptop, PDA, iPod, portable hard drive).
- Specify whether subject identifiable data will be stored on the device. If so, **justify why it is necessary** to store subject identifiers on the device.

**Note:** only the "minimum data necessary" should be stored on portable devices.

**Not applicable** – No study data will be maintained on portable devices.

**OR**

<Type here>

**5. Specify who will have access to subject identifiable data and records.**

Not applicable – No subject identifiers will be collected.

The research team, authorized UCI personnel, the study sponsor (if applicable), and regulatory entities such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP), may have access to study records to protect subject safety and welfare. Any study data that identifies the subjects will not be voluntarily released or disclosed without the subjects' separate consent, except as specifically required by law. Publications and/or presentations that result from this study will not include subject identifiable information.

Other: <Type here>

6. Explain how long subject identifiable research data (hard copy documents, computer files, recordings, specimens) will be retained (e.g., key code destroyed upon study completion; identifiers stored for future research; identifiers retained for...specify timeframe, anonymized/de-identified data retained indefinitely, etc.)

**Note:** If your study involves the creation of a research database, specimen repository, or you plan to share data or specimens for secondary uses or analyses, Appendix M is required.

Not applicable – No subject identifiers will be collected.

**OR**

Data will be retained for at least 6 years since the study involves HIPAA.

Data on the minor population of this study will be retained for 7 years after all minors enrolled in the study reach the age of majority [age 18 in California].

Data collected from the subjects will be stored in a secure area of the principal investigator office (City Blvd. West Suite 700 Orange, CA 92868) with limited access to the study team.

**7. Certificates of Confidentiality:**

- Specify whether a Certificate of Confidentiality (COC) has been requested from the NIH.
- If yes, explain in what situations personally identifiable information protected by a COC will be disclosed by the UCI study team.

**Note:** A copy of the COC should accompany the IRB application or be provided to the IRB upon receipt.

Not applicable – No COC has been requested for this study.

**OR**

<Type here>

**Appendix S**  
**DESCRIPTION OF DATA SAFETY MONITORING PLAN (DSMP)**

University of California, Irvine  
Institutional Review Board

Please read the HRPP webpage at <http://www.rgs.uci.edu/ora/rp/hrpp/dataandsafetymonitoring.htm> for information about the data and safety monitoring plans.

**All clinical investigations, including Phase I, II and III clinical studies, involving greater than minimal risk to participants are, at a minimum, required to develop a plan to assure the safety and welfare of the research participants.**

For **NIH-sponsored clinical trials**, the DSMP should be part of the grant application. Submit the DHHS grant application in lieu of completing this appendix.

For **“for-profit” sponsor-initiated clinical trials**, a FDA-approved DSMP may be submitted in lieu of completing this appendix.

For **studies conducted at the General Clinical Research Center (GCRC) or Cancer Center (CTPRMC)**, a DSMP approved by one of these committees may be submitted in lieu of completing this appendix.

**All other researchers please answer all of the following:**

1. List who will conduct the safety review. Include the name, title and experience of the individual(s). The safety reviews will be conducted by the Data Safety Management Board (DSMB) Members for this trial. The DSMB is composed of 10 members appointed by the NHLBI:

**Jay Mason, MD (Chair):** Medical Director at Covance Cardiac Safety Services, University of Arizona.

**Lance Becker, MD:** Director, Center for Resuscitation Science, Dept. of Emergency Medicine Hospital of the University of Pennsylvania.

**David Gordon, MD, PhD (NHLBI):** Special Assistant for Clinical Studies, Division of Cardiovascular Diseases, NHLBI

**Karl Kern, MD:** Chief of Staff at University of Arizona Medical Center. Specialty: Interventional Cardiology

**David Lathrop, PhD:** joined NHLBI in 1997. Since 2003, he has been the Leader of the Arrhythmias, Ischemia, and Sudden Cardiac Death Science Research Group in the Institute's Division of Cardiovascular Diseases.

**Laurence McCullough, PhD:** Professor of Medicine and Medical Ethics, Baylor College of Medicine

**Ralph d'Agostino, PhD:** Professor Section on Biostatistics ... Data Safety and Monitoring boards (DSMBs) for NIH and industry funded clinical trials.

**Peter Rhee, MD:** Professor of Surgery, Chief, Section of Trauma, Critical care and Emergency Surgery; Arizona Health Sciences Center

**Claudia Robertosn, MD:** Professor, Medical Director, The Center for Neurosurgical Intensive Care, Ben Taub General Hospital, Baylor College of Medicine

**Herbert Wiedemann, MD:** Institute Chair Pulmonary Medicine, The Cleveland Clinic, Ohio

**Robert Zalenski, MD:** Professor of Emergency Medicine, Wayne State University School of Medicine, Detroit

2. Indicate how frequently the monitor will review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy.  
All SAEs are monitored closely by the participating clinical centers, who report the SAEs to the ROC Data Coordinating Center in Seattle Washington. The Data Coordinating Center monitors the participating clinical centers with respect to completeness and timeliness of all such reports. As they arrive, the reports are reviewed by the Data Coordinating Center Medical Director (Dr. G. Nichol) and then forwarded to the FDA and the Chair of the DSMB. The Chair of the DSMB may refer specific SAEs to the entire DSMB whenever he feels such an immediate review by the entire board is indicated. In any case, the cumulative incidence of all SAEs is reviewed by the entire DSMB during their regularly scheduled meetings. The DSMB meets twice a year. However, they do conduct telephone-conference intermittently in-between the meetings. The last face to face meeting was October 2, 2007. The next face to face conference is in Bethesda, MD in March 2008. To date, the trial has enrolled 1000 subjects. No safety issues were raised by the DSMB.
  
3. Explain the process by which the monitor will make recommendations concerning the continuation, modification, or termination of the trial.  
General Stopping Rules: The two trials will be conducted simultaneously utilizing the same infrastructure. This has implications for what actions can be taken since actions on one study can seriously affect the ability to continue the other (particularly with regard to drug distribution and blinding and training). If the DMC stops one fluid in one cohort for concerns of harm the fluid would likely be stopped in the other cohort as well. If a therapy crosses the futility bound in one study, but not the other, and the DMC is not concerned about harm, it would not be dropped from either study. If the study specific boundary for futility were crossed in both studies, the agent would be discontinued and the studies continued with the other agent Non-inferior is defined as the lower 90% CI for the observed difference between treatment and control rates is  $\geq$ negative 3%. At looks after look 1 increasing the sample size will be considered if the conditional power for efficacy "under the observed to date difference" and the original planned sample size is between 50% and 80%. The sample size will be increased based on agreement among investigators and the DMC and availability of resources.
  - 1) Efficacy Boundary of O'Brien-Fleming Type
  - 2) Modification of sample size if Conditional Power under observed for efficacy between 50% and 80%

Characteristics of the Monitoring Plan:

A simulation was conducted to first determine the superiority boundary and then explore what occurs for a given study under the superiority, futility, and harm boundaries. Details of the simulation are presented in Appendix I. A harm boundary was formulated to be similarly conservative in stopping the study for superiority or harm in the early looks when there is in fact no difference between a given treatment and saline, but to stop the study more conservatively later on in the trial for harm compared to efficacy. Note that the harm boundary is needed for the simulation, but that the DMC has indicated that they will not entertain a formal boundary for harm. The results of the simulations are summarized in Tables 5 and 6 below taken from the Master Protocol.

**Table 5: % of 50,000 simulated trials in which at least one agent is classified as Efficacious and as Non-Inferior for the TBI cohort for different treatment survival probabilities.**

		Difference: $\theta_T - \theta_C$	-0.050	-0.030	-0.010	0.000	0.034	0.067
Final	% Efficacy		0.01	0.09	0.87	2.39	27.65	79.83
	% Non-Inferior		4.11	18.98	50.88	66.95	70.79	20.16

**Table 6: % of 50,000 simulated trials in which at least one agent is classified as Efficacious and as Non-Inferior for the SHOCK cohort for different treatment survival probabilities.**

		Difference: $\theta_T - \theta_C$	-0.050	-0.030	-0.010	0.000	0.024	0.048
Final	% Efficacy		0.01	0.09	0.87	2.39	27.65	79.83
	% Non-Inferior		2.06	18.10	62.03	81.32	71.92	20.17

4. Describe the event(s) that would trigger an unscheduled review. Also include stopping guidelines and un-blinding rules, if applicable.

The event that would trigger an unscheduled review is the Data Coordinating Center receiving unexpected SAEs or there is evidence from the data submitted of protocol deviations by the site.

#### UNBLINDING

If a physician caring for the patient feels it is imperative to learn which type of study fluid the patient received in order to safely continue treatment, an unblinding service is available 24 hours a day. *The study fluid bag number **must** be provided for unblinding to occur.*

##### Procedure for Unblinding

- a) Between 8 am and 5pm PST:
  - The site will contact the UW Clinical Trial Center call center at 1-800-332-0586 and request a patient be unblinded.

At all other times and on holidays and weekends

  - The site will contact the Almac Hotline at 1-800-923-3209
- b) The call center will record the following information on the unblinding worksheet:
  - Name of individual requesting unblinding
  - Complete site information (address, phone and fax)
  - Study Fluid Bag number given to patient
  - Reason for request
- c) If applicable, the call center will access the study kit list and will obtain the corresponding treatment to the bag administered. This will be recorded on the Unblinding Worksheet and verbally conveyed to the authorized caller.
- d) The call center will record the disposition of the call and forward this information to the CTC.

The site coordinator will participate in this process. If the patient is to be unblinded, it will be best if the coordinator turns the call over to the interested physician and remains blinded. *If site personnel are unblinded to the treatment arm received by a patient, bias may occur in collection and interpretation of clinical data and such bias is to be avoided at all costs. If the coordinator is inadvertently unblinded the unblinding information will not be shared with other site personnel.*

An "Alert CTC Form" will be completed for all unblinding requests by the site coordinator. Additionally, a brief summary about all unblinding events will be sent to the CTC which will include: Episode ID; the date/time of episode; the date/time of the unblinding request; a brief patient summary including age and gender of patient, mechanism of injury, inclusion criteria met for HS study; list of injuries; and a description of the events leading up to the unblinding.

#### Potential Unblinding Scenarios

Based on this trial design in which providers are not blinded to serum sodium levels, there should be very little reason to consider unblinding a patient for clinical care. Below are listed possible

reasons that a care provider may propose to unblind a patient and the suggested response to these inquiries:

**1. Concern about impact of hypernatremia on further treatment:**

A care provider may request to unblind whether or not the patient has received one of the two hypertonic solutions to guide further treatment such as the administration of 3% saline to control ICP. In this circumstance you should remind the provider that it is OK to send a serum sodium to guide this therapy and thus formal unblinding is not necessary.

Previous studies of the prehospital administration of 7.5% saline solutions have demonstrated that the mean serum sodium on admission is 155mEq/L. This level should not prompt alterations in care by the trauma team. Care providers should be encouraged NOT to try to lower the serum sodium with hypotonic fluids as this will defeat the purpose of this therapy. Serum sodium can be expected to normalize within 12 hours of administration of study fluid. A subsequent change in serum sodium should not be assumed to be related to study drug administration. Other causes of hypernatremia should be considered, for example, central diabetes insipidus following severe head injury.

**2. Concern for anaphylactic reaction:**

If a patient is manifesting signs of a severe allergic reaction, the care provider may want to unblind the patient to determine if he/she received the dextran containing solution. Anaphylaxis to dextran has been reported and although this is exceedingly rare it is OK to unblind in this circumstance as you will want to report this as an SAE and it is possible that the patient is reacting to some other therapy such as a transfusion reaction and thus it will be important for the care provider to consider these options.

**3. Concern about effect of dextran on coagulopathy:**

Most severely injured patients are coagulopathic due to their injuries and severe blood loss. The dose of dextran given with HSD should not exacerbate this coagulopathy. If a care provider wishes to unblind for this reason, you should remind them that the correction of coagulopathy will not be altered by knowing which fluid was given and thus unblinding will not change therapy in this circumstance.

**5. List who will be monitoring and collecting information on adverse events and/or unanticipated problems (e.g., Lead Researcher, Research Coordinator, etc.). Include the name, title and experience of the individual(s).**

Dr. Hoyt, the Lead Researcher, will be monitoring and collecting information on adverse events and/or unanticipated problems for this study. Dr. David B. Hoyt is the Chair of the Department of Surgery at UCI Medical Center and co principal investigator. Dr. Hoyt will be the Principal Investigator of the study and will coordinate all aspects of this project. Dr. Hoyt has a long-term interest in surgical aspects of trauma, and immunosuppression in trauma patients. He has been involved in extramurally funded basic research and mechanisms of immunosuppression throughout his career. He has 30 years of experience in his field. He has extensive experience performing clinical trials and multi-center clinical trials. He also has been very involved in the development of large databases and overseeing the quality of data used in the care of trauma patients.

**6. Describe procedures to assure compliance with reporting of adverse events and/or unanticipated problems involving risk to participants or others.**

If a Serious Adverse Event is noted by the study team on this trial, Dr. Hoyt will be notified of this information and the Adverse Event Form will be completed within 24 hours of learning of the event. This paperwork will then be filed in the patient's binder. The study team understands that if there is a significant adverse event that is brought to their attention, they know to notify Dr. Hoyt as soon as possible so that the event can be sent to the IRB and the Data Coordinating Center. Dr. Hoyt will also be notified of the Serious Adverse Events once those events occur. These events will be monitored by both the Data Coordinating center and by the Chair of the DSMB.

7. Explain the process for detecting and reporting adverse events and/or unanticipated problems involving risk to participants or others and specify of who will be notified of such events (e.g., IRB, NIH, FDA).

#### **Procedures for Reporting Adverse Events**

Assuring patient safety is an essential component of this protocol. The Principal investigator has primary responsibility for the safety of the individual participants under his care. All adverse events will be evaluated by the Principal Investigator. The study coordinator must view patient records for possible adverse events throughout the study period. All adverse events occurring within the study period must be reported in the participant's case report forms. Data regarding adverse events will be collected in both a structured (standard form) and open (describing any difficulties encountered) format.

Any serious and life threatening adverse event (either expected or unexpected) will be reported by telephone to the FDA, IRB and chairperson of the DSMB within 72 hours and in writing within 7 days. All non-life-threatening unexpected serious adverse events will be reported in writing within 15 days. All other potential adverse events will be reported to the chair of the DSMB and reviewed at the interim analyses and included in a safety report to the FDA at that time. The Institutional Review Board must all also be informed in a timely manner. . All adverse events should be reported promptly to the CTC. These reports must include a **blinded** copy of the AE report sent to the local IRB/REB with the PI's signature and a clinical summary of the incident. The CTC will notify the DSMB, the FDA and the NIH as required by the protocol.

8. Describe the plan for annual reporting of the participants' safety, and the study's conduct, progress, and efficacy, when appropriate. *Note: DSM reports are required to be submitted to the IRB at Continuing Review.*  
Once the research team receives word from the IRB that the annual continuing renewal needs to be filed, the study team will fill out the Continuing Review Renewal Application and submit before the deadline to the IRB. The research coordinator, Bernardine Donato, will collect the necessary information to complete the CR application. This information will include patient's safety data, the progress of the study (i.e. number of patient consented, randomized, adverse events, as well as treatment failures and withdrawals). Once this information is accumulated, this will be sent to Dr. Hoyt and he will fill out the necessary IRB e-form for submission. Once submitted to the IRB, the continuing review report will be sent to the Data Coordinating Center and filed in the regulatory binder.
9. Explain how you will assure data accuracy and protocol compliance.  
The principal investigator will ensure that appropriate training relevant to the study is given to all of his study team members and that any new information of relevance to the performance of this study is forwarded to the staff involved. The investigational staff will be trained on the research protocol involving data collection to be submitted to the Data Coordinating Center. Any protocol violations will be documented on the case report form, as will potential safety issues related to the protocol and any other unusual circumstances and will be submitted to the Data Coordinating Center in a timely manner.

Accuracy of data and protocol compliance will be monitored by the Data Coordinating Center as the reports are submitted to the Coordinating Center. Oversight of data accuracy will also be monitored with an online database by the Data Coordinating Center and every other weekly phone call to the site.



- b) Would the granting of the waiver adversely affect privacy rights and welfare of the individuals whose records will be used or disclosed?

Yes             No

Explain (justify) the answer: Subjects' data will be de-identified and assigned unique study numbers. Only the study numbers will be referenced in correspondences for this trial. Data will only be submitted to the Data Coordinating Center and not to other participating centers in this study from this site.

- c) Could the research practicably be conducted without a waiver of HIPAA authorization?

Yes             No

Explain the answer: Since this study involves emergency medical intervention for a life-threatening medical condition and is approved for exception from informed consent, this study cannot be conducted without a waiver of HIPAA authorization. Subjects enrolled in this study will not have the capacity to provide HIPAA authorization at the time of the accident. Subjects must be enrolled immediately to treat their life-threatening condition.

- d) Could the research practicably be conducted without access to, use or disclosure of the personal identifiers listed in #1?

Yes             No

Explain the answer: The research cannot be conducted without access to personal identifiers since treatment is needed immediately to save subject's life. The medical team would need access to subject's information to help treat subject accordingly.

- e) Are the privacy risks reasonable relative to the anticipated benefits of the research?

Yes             No

Describe the risk/benefit analysis performed to explain the answer above: Trauma is the leading cause of death among North Americans between the ages of 1 and 44 years. The majority of these deaths result from hypovolemic shock or severe brain injury. Patients in hypovolemic shock develop a state of systemic tissue ischemia with a subsequent reperfusion injury at the time of fluid resuscitation. Conventional resuscitation involves the intravenous (IV) administration of a large volume of isotonic (normal saline) or slightly hypotonic (lactated ringers, LR) solutions beginning in the pre-hospital setting. Although not conclusive, prior animal and human studies have suggested that alternative resuscitation with hypertonic saline (7.5%) solutions may reduce mortality in these patients. Furthermore, hypertonic fluids may have specific advantages in the brain-injured patient, as they may aid in the rapid restoration of cerebral perfusion and prevent extravascular fluid sequestration, thereby limiting secondary brain injury. In addition, recent studies have demonstrated that hypertonicity significantly alters the activation of inflammatory cells, an effect that may reduce subsequent organ injury from ischemia-reperfusion and decrease nosocomial infection.

This study seeks to address the impact of hypertonic resuscitation on two injured patient populations, those with hypovolemic shock (either prehospital SBP  $\leq 70$ ; or prehospital SBP 71-90 AND HR  $\geq 108$ ) and those with severe traumatic brain injury (prehospital GCS  $\leq 8$ ). The possible benefits of increased survival rates on these two patient populations outweigh the possible study risks and privacy risks involved.

- f) Describe the plan to protect the personal identifiers from improper use and disclosure (i.e., describe data security methods):

Study data will be de-identified and assigned a unique study number. Only the Lead Researcher will have access to the key code. Data will be stored at a secure location and on a secure server with password encryption. Data will only be transferred to the Data Coordinating Center for this study which will be de-identified (please see below).

#### **Confidentiality and Privacy**

Clinical data about human subjects is collected under IRB -approved protocols. Each site must provide a copy of its IRB approval prior to collecting and entering data into the ROC web-based

data collection system. All study personnel involved in data collection and analysis will be required to sign a confidentiality agreement.

When a research subject is enrolled at an RCC and the event is entered into the ROC data collection system, a unique identifying number is assigned to that subject. This number will allow tracking of all data forms related to a particular subject. The local hospital medical record number and any local study I.D. number generated by the local site will remain unknown to all participating investigators except the local investigators who enrolled that subject in the study. The enrolling site will be the only holder of a code that links to an identifiable subject name or number. The privacy of that information at the clinical site should be protected according to both good clinical practice guidelines and guidelines from each local IRB.

- g) Describe the plan to destroy the personal identifiers at the earliest opportunity, or provide a health or research justification for retaining the identifiers:  
Data collected from the subjects will be stored in a secure area of the principal investigator office (City Blvd. West Suite 700 Orange, CA 92868) with limited access to the study team for at least 2 years after the FDA approval for the proposed study treatment.
- h) If the Lead Researcher is applying for a *partial waiver* for subject identification, describe how potential subjects will be identified:  
No potential subject will be identified for this study since there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation. Subjects who are involved in a traumatic injury will be treated at the scene. Once entered into the trial, subject data will be de-identified and assigned a study number.

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## EMS Online Training

Instructions for completing web-based modules for:

ROC 101 Research  
ROC 102 Hypertonic Saline

- Go to [www.emsonline.net](http://www.emsonline.net)
- Enter password: **Orangecounty01**
- Enter username: **Orangecounty01**
- Under purple heading "Resuscitation Outcomes Consortium"  
Select and complete Module(s) 101 and 102
- Complete the quiz at the end of each Module.
- Enter the following information in the single space provided for the  
Name: **Name, certification number, and agency**  
\*We can't find you if we don't know the agency\*
- Email confirmation to Bernardine (Bernie) Donato at UC Irvine  
(as prompted to do so)



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## ROC 101 – Research for EMS Providers

### Intro

This course explains how you, as an EMS provider, can collaborate in important research being conducted by the Resuscitation Outcomes Consortium

You will learn the standards for clinical research and be able to apply them to your ROC study. These standards protect study patients and help ensure the integrity of the study.

The ROC is your opportunity to shape the future of EMS. Future patients and you and the ROC sites are doing today. Your full participation is vital.

[Click here](#) to view a video clip explaining the importance of ROC (Flash Player required). [View a transcript of the video clip.](#)



### Course Objectives

ROC 101 Research is an online EMS continuing education module for EMS Canada including first responder, emergency medical technician (EMT), Paramedic (ACP (advanced care paramedic) and paramedics. After completing this course, you will be able to:

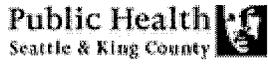
1. Identify the goals of the ROC and the makeup of the ROC sites.
2. Identify the three elements required of an EMS provider to participate in research.
3. Identify the criteria for an emergency exception from consent and when it is appropriate.
4. Identify the reasons why patients need to meet enrollment criteria.
5. Identify reasons why it is important to correctly record data.
6. Identify the reasons for restricting use of investigational therapy to research.

[+ View elaboration](#) — [Tips for Completing this Course](#)

### DISCLAIMER

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**study coordinator** - an individual who facilitates the running of a study, for example, helps teach study criteria, answers questions, follows up on patient data, or makes sure there is inventory of the study drug or device.

[Click here](#) to test your knowledge of these terms with EMS Online Flash Cards.

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## ROC 101 – Research for EMS Providers

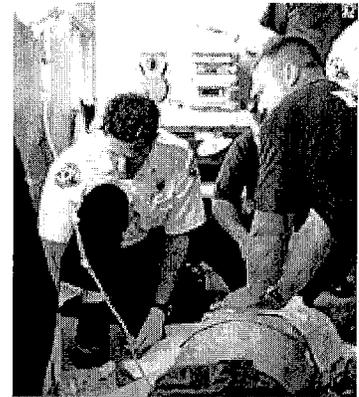
### Why Do EMS Research?

Each year, thousands of people die from cardiac arrest and trauma--enough to fill more than 1,000 jumbo jets. Scientific research will play a crucial role in improving outcomes for these patients. EMS researchers will have many challenges due to the difficulties of doing research in the field, the differences between communities and EMS, and the sheer number of patients needed to draw meaningful conclusions.



**Trauma**

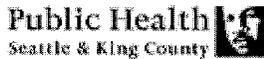
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**Cardiac arrest**

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## ROC 101 – Research for EMS Providers

### What is ROC?

The **Resuscitation Outcomes Consortium** (the ROC) is the first-ever peer network of its size and purpose. It aims to learn, over a relatively short period, which resuscitation techniques work best for cardiac arrest and severe trauma.

The ROC strives to conduct research that is free of scientific and personal bias to study results that are meaningful. By working together as a group, all members within the ROC hope to promote evidence-based changes to prehospital care to improve patient survival.

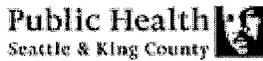
#### Question

What are the three goals of the ROC? (Select all that apply)

- A. learn about resuscitation techniques
- B. conduct meaningful research
- C. promote evidence-based changes
- D. promote healthy lifestyles in the general population

[Check My Answer](#)

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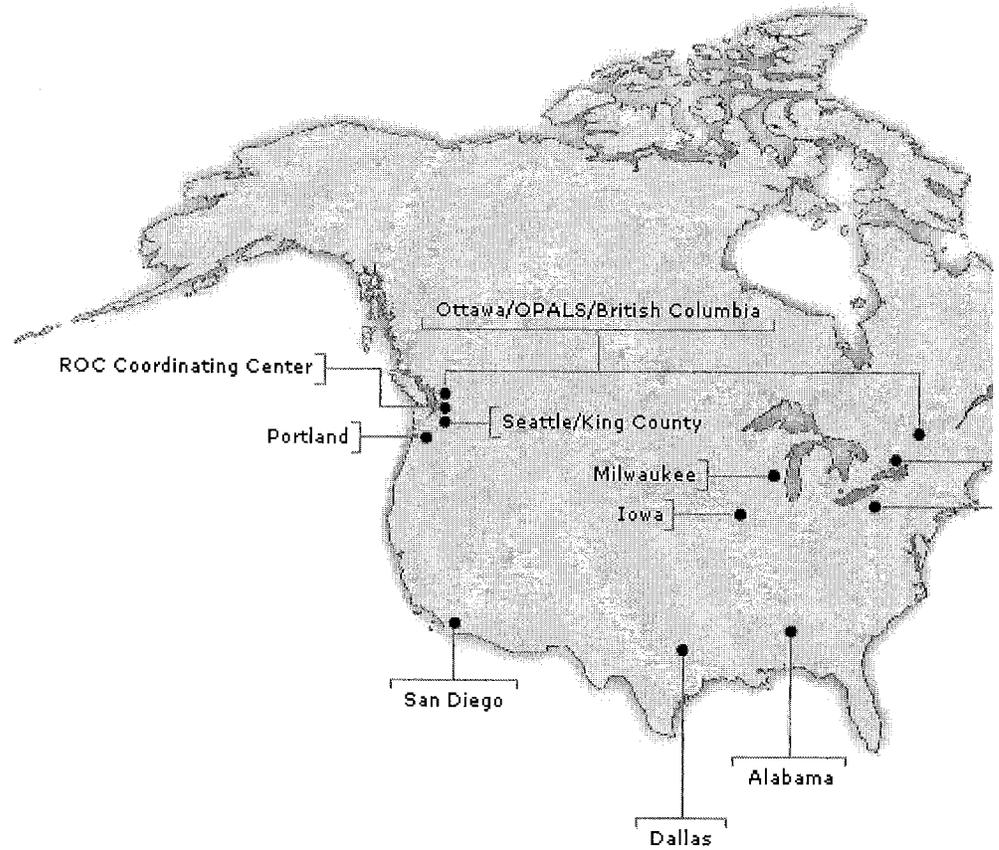
## ROC 101 – Research for EMS Providers

### You are the ROC

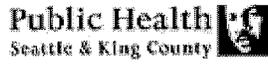
Your EMS agency has joined the Resuscitation Outcomes Consortium (ROC) how to improve patient survival. Ten sites within the US and Canada were competitive process to be in the ROC. Together they serve over 26,000,000 employ nearly 20,000 EMS providers.

The research studies that the ROC is conducting could change the future c for cardiac and trauma patients. You are part of a team that is improving will benefit your patients.

Place your cursor over each ROC site to view site-specific information.



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## ROC 101 – Research for EMS Providers EMS Evolves

EMS has changed greatly over the years. Some therapies have fallen out of use and others have taken their place, many times with little research to back up. The ROC could speed the rate at which EMS knowledge is acquired and new therapies adopted.

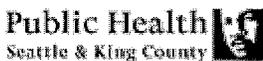
Test your knowledge of important EMS events and therapies.  
Drag and drop the event to its place on the timeline.

1947	Event	Mobile intensive care
1956	Event	Chest compressions
1960	Event	External defibrillator
1966	Event	Paramedic programs
1969	Event	EMT defibrillation
1972	Event	Squad 51 – "Emergency" TV
1980	Event	Mouth-to-mouth resuscitation
1987	Event	ROC (largest EMS research effort)
1994	Event	Chain of Survival
Now	Event	Lay defibrillation

[Show Answers](#)

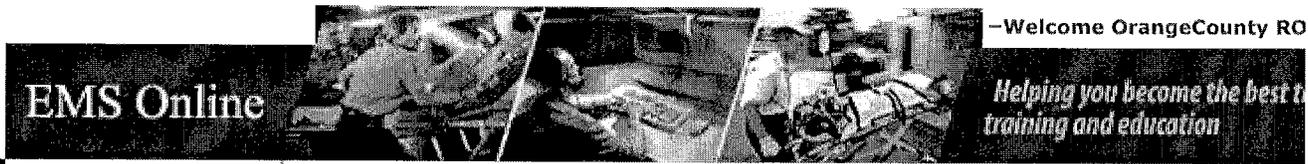
[+ View elaboration](#) — References for the EMS History Buff

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## ROC 101 – Research for EMS Providers

### The Road to Improved Survival

A clinical research study can be thought of as a journey on the road to survival. The road has a series of checkpoints, wrong turns and dead ends. There are signs and guardrails to help keep you on the road.

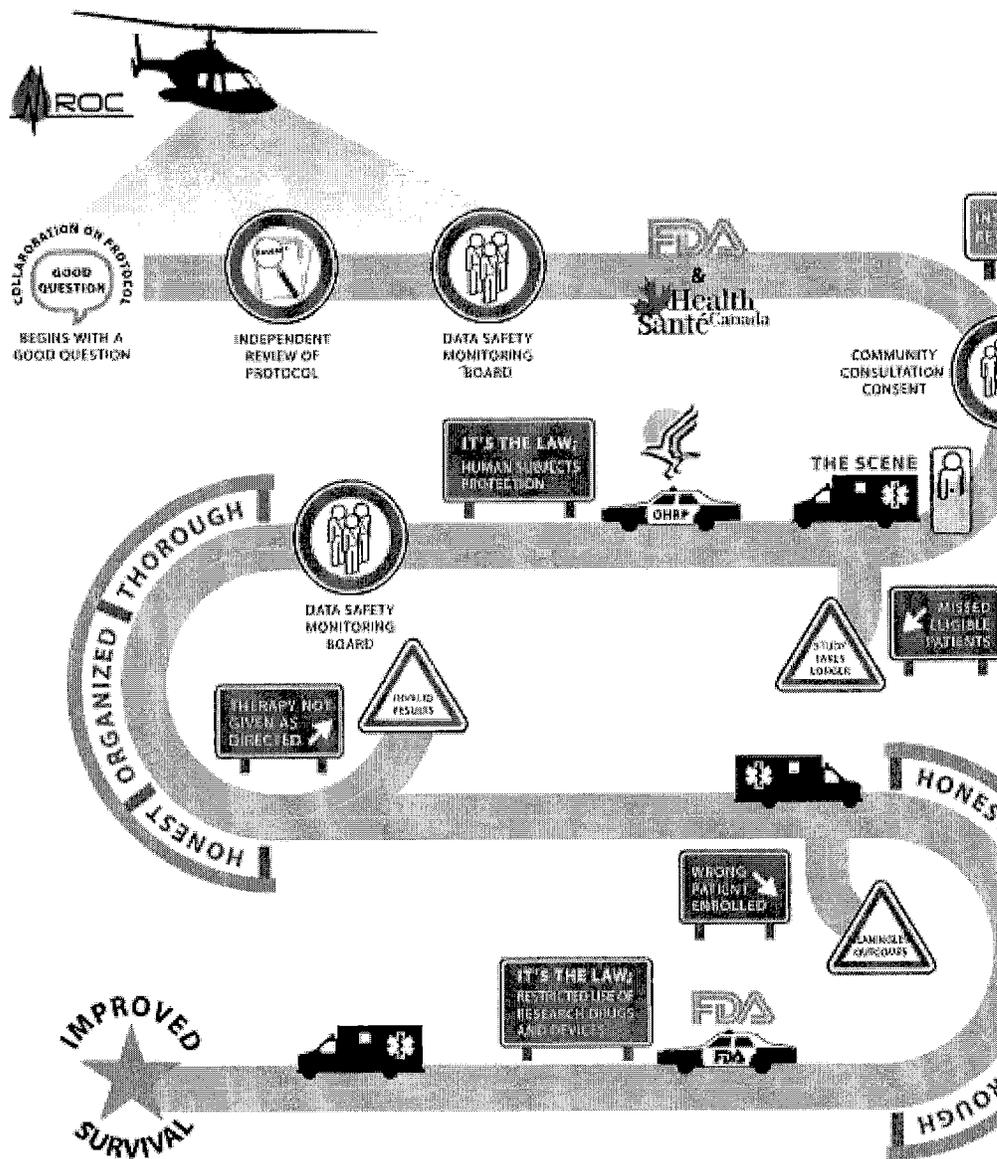
### Tour of The Road to Improved Survival

Start Guided Tour



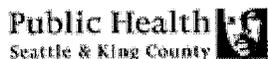
Stop Guided Tour

Click the Start Guided Tour button to begin an audio tour of The Road to Improved Survival.



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Helping you become the best in training and education

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## ROC 101 – Research for EMS Providers Study Protocols

A **protocol** is the master plan for all aspects of a research study. It is a le document that specifies the population to be enrolled and how the therapy randomly assigned to patients. Also, the protocol addresses what data is t collected and the measures for success.

Before EMS gets the green light to enroll patients in a ROC study, the stud protocol is rigorously reviewed and must be approved by at least four independent groups responsible for safeguarding the health and welfare o patients:

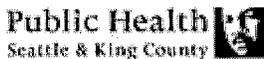
- Independent Review of Protocol (Protocol Review Committee)
- Data Safety and Monitoring Board
- FDA and Health Canada
- Institutional Review Board



Groups that review study protocols

Any changes to how a study is conducted in the field-patient criteria, cons process, data collection, administration of study therapy-must be approve your community's institutional review board before it is implemented.

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## ROC 101 - Research for EMS Providers Consent

**Informed consent** is voluntary approval given by a person for participation in a study after being informed of the purpose, methods, procedures, benefits and risks. It is an ongoing process that allows the patient to decide whether to enter, continue, or withdraw from a research study.

In the prehospital setting, it is often impractical for patients to give consent. Therefore, under *very special* circumstances, provisions are made for emergency medical research to be conducted without voluntary informed consent. This is called an **emergency exception from consent**.

An emergency exception is allowed ONLY when the Institutional Review Board or Research Ethics Board has determined that a research study meets ALL seven of the following criteria:

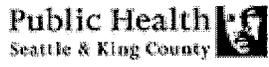
1. Situation is life-threatening
2. Available treatments are unproven or unsatisfactory
3. The research is necessary to determine best intervention
4. Informed consent not feasible
5. Patient may directly benefit
6. Study could not otherwise be done
7. Community consultation fulfilled

Your medical director or study coordinator will tell you if a research study has been approved to use an emergency exception from consent. In most cases where an emergency exception is used, the patient or family must later be notified and consent given to continue in the study. The study coordinator is responsible for follow-up with the patient or family.

[+ View elaboration](#) — More on Informed Consent

[+ View elaboration](#) — Believe It or Not: Lapses in Research Integrity

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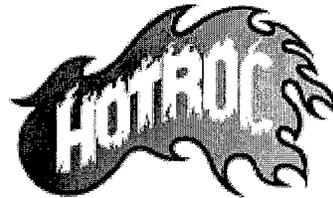
## ROC 101 – Research for EMS Providers

### H-O-T – The Three Elements of Good Research

ROC research is a landmark effort, made possible only through the cooperation of many different people and organizations. It includes doctors and coordinators at sites, ethics and research boards at participating universities and hospitals, statisticians, government agencies, EMS agencies and YOU-the EMS provider.

Each EMS provider involved in a ROC study needs to apply the three basic elements of good clinical research. They can be summed up using the mnemonic **H-O-T** that stands for:

- **Honest**
- **Organized**
- **Thorough**



Being **honest** means that you should record factual data and record only what you observe--never make up data. Also, it means you should give the assigned study therapy only to patients who are eligible for the study.

Being **organized** means you know and regularly review the protocol (the interventions, patient criteria, and required information) and have a systematic way to accurately record the data. It also means that you protect patient privacy and maintain confidentiality.

Finally, being **thorough** means that you give the assigned therapy to all eligible patients, observe them for potential adverse effects, and make sure the study coordinator receives all data and any materials that must be returned.

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### ROC 101 – Research for EMS Providers Honest

It's been said that success is simple. "Do what's right, the right way, at the right time." Not too tall an order for EMS where honesty has been ranked a top attribute by our members.

As an EMS provider involved in ROC research in order to safeguard the welfare of our patients and to ensure valid study results, you must:

- Comply with patient consent regulations
- Give assigned therapy
- Do not give study therapy to non-eligible patients
- Never make up data
- Ask questions if you do not understand

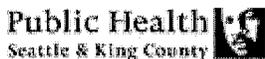
Question

What should you do if you realize that you forgot to record a piece of data? (Select all that apply)

- A. record nothing
- B. make up something that would fit patient condition
- C. tell the site coordinator and communicate the data
- D. follow local procedures for documenting additional data

Check My Answer

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## ROC 101 – Research for EMS Providers Organized

Being organized is an important part of collecting data in the field. To help research study leads to meaningful results you must:

- Know how to use the inclusion and exclusion criteria
- Notify study staff of patient enrollment
- Record all required data and/or send the electronic ECG
- Maintain patient privacy/confidentiality
- Restock your rig with the investigational product

+ [View elaboration](#) — Inclusion and Exclusion Criteria

### Question

The purpose of inclusion and exclusion criteria is to identify who can be enrolled

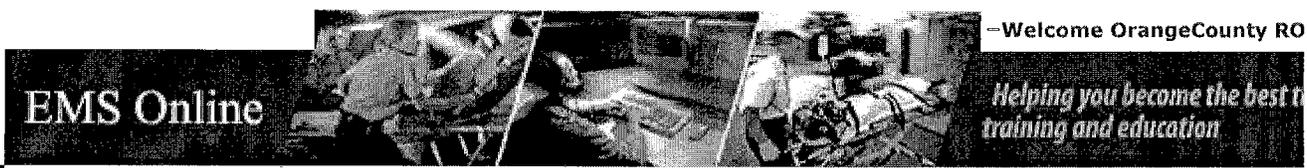
- A. true
- B. false

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## ROC 101 – Research for EMS Providers Thorough

Thoroughness is the third element of HOT. Being thorough means that you

- Screen all patients for eligibility
- Observe rules for special handling of investigational products
- Observe patient for potential adverse effects
- Document all adverse effects
- Communicate unusual or unsafe situations to the study coordinator

### 🔍 Question

You know that hiccups are a potential adverse effect of a study drug. Your patient has a mild case of hiccups 15 minutes after you administer the study drug. What do you do? (Select the best answer)

- A. record mild hiccups, including time they began and ended
- B. nothing, because hiccups are not very serious
- C. nothing, because the hiccups began long after you gave the study drug
- D. nothing, because you have observed this in patients who did not get the study drug

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## ROC 101 – Research for EMS Providers Enrolling Patients

Even the most compelling research question cannot be answered without cooperation and attention to detail. These are necessary for researchers to definitive answers about the benefits and safety of selected therapies.

If you do not enroll all eligible patients you can cause the study to take longer anticipated. Even worse, it may create problems when interpreting study results understanding the implications for all patients.

[+ View elaboration](#) — Longer Study

If you enroll patients who are not eligible, it can lead to study results that are not meaningful. This is because a study is designed to measure an effect on a specific patient group. When the wrong patients are enrolled, the study results can be misleading.



**Wrong turns on the Road to Improved Survival**

It is important that you enroll patients according to the inclusion and exclusion criteria. Small deviations made by a few EMS providers can greatly affect the results. Also, giving a therapy to the wrong patient can be harmful.

We are asking you to put your own bias on the shelf for the ROC study and to follow the protocol to reach meaningful results in a timely way.

**! Know and apply the inclusion and exclusion criteria**

IN or OUT of the Study?

Enroll as many patients as you can based on the study inclusion and exclusion criteria.

<b>Study 1 Criteria</b>	
<u>Inclusion</u>	<u>Exclusion</u>
undefined	undefined

<b>Patient 1 Information</b>	
undefined	<div style="border: 1px solid black; border-radius: 50%; width: 30px; height: 30px; margin: 5px auto; display: flex; align-items: center; justify-content: center;">IN</div> <div style="border: 1px solid black; border-radius: 50%; width: 30px; height: 30px; margin: 5px auto; display: flex; align-items: center; justify-content: center;">OUT</div>

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**Question**

The study inclusion criteria calls for children less than 15 years and > 50 kg. The patient meets the criteria and is eligible to be enrolled; however, you believe that the assigned therapy is an inferior choice. What should you do? (Select the best answer)

- A. ignore assignment and give other treatment
- B. follow protocol and give assigned treatment
- C. give other treatment and record study data elements
- D. ask patient's family which they prefer

Check My Answer

**Question**

What should you do if you accidentally enroll an ineligible patient? (Select all th.

- A. tell the study coordinator
- B. remove the patient from the study
- C. adjust the count by not enrolling the next eligible patient
- D. record all study data and observe for adverse effects

[Check My Answer](#)

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**Question**

You have enrolled a patient in a study that requires a Glasgow Coma Score (GCS) and a systolic BP less than 90. You've transported the patient to the ER, cleaned, restocked the rig and begin charting. You recall the GCS (which was 12 at the start during transport), but do not have notes for blood pressure. What do you chart that apply)

- A. initial GCS of 12, quickly deteriorated
- B. initial GCS of 12, deteriorated to an 8
- C. blood pressure less than 90 systolic
- D. BP not recorded

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## ROC 101 – Research for EMS Providers Giving the Therapy

An *investigational product* is a drug or device being tested through research or gain further information about its safety and benefit. Rules and regulations govern the use of investigational products.

Do not use an investigational product on someone who is not eligible for study enrollment.

On the other hand, if you fail to provide the research therapy to someone eligible this can lead to *invalid study results*. The bottom line is, know the inclusion and exclusion criteria and give the research therapy to all the right



Wrong turn on the Road to Improved Survival

Every investigational product has a unique tracking number. Be sure to write the number down on the patient care record to indicate it was given.

 **Give research therapy to all eligible patients.**  
**Don't give to anyone else.**

[+ View elaboration](#) — Invalid Results

[+ View elaboration](#) — More on the Use of Investigational Products

**2 Question**

You determine that a patient meets criteria for a research study. You open the containing the research device and see that it is damaged. What should you do (that apply)

- A. throw it away
- B. set it aside and later return to the study coordinator
- C. revert to conventional therapy
- D. open a new kit

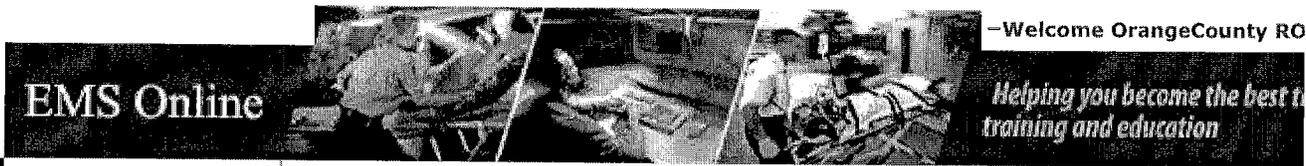
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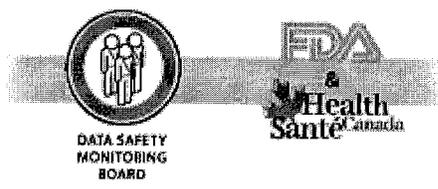
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## ROC 101 – Research for EMS Providers Reporting Potential Adverse Events

Your observations in the field may shed light on the safety of an investiga product. Document the sequence and timing of any unusual events wheth believe they are related to the study therapy.

Remember, the safety of future patients is at stake. Not all medical device work as expected out in the field. Potential adverse events can be minor c are important to report. Study protocols may direct you to contact the stu coordinator in certain circumstances.



**Safety is important in the Road to Improved Survival**

ROC researchers will compile your reports of unusual and potential advers those made by others and analyze for trends. In some cases, the FDA, He and the Data Safety Monitoring Board will be notified of a potential safety

**! Report all unusual and potential adverse events.**

**Question**

Which of the following potential adverse reactions are worthy of documentation that apply)

- A. irritation at site of intravenous infusion, skin rash
- B. drop in blood pressure
- C. device not working properly
- D. seizures
- E. pulmonary edema
- F. decreased level of consciousness
- G. vomiting, aspiration

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**ROC 101 – Research for EMS Providers Summary**

The following key points were covered in this module:

**1. The goals of ROC are to:**

- Learn about resuscitation therapies
- Conduct meaningful research
- Promote evidence-based changes

**2. EMS providers should be **H-O-T** when participating in research:**

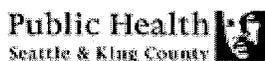
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- Organized
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**3. An emergency exception from consent** is a special circumstance and allows a patient to be enrolled in a study before he or she is able to give consent.

**4. The ROC expects you to do the following when participating in a study:**

- **Enroll patients correctly** — know and apply the inclusion and exclusion criteria
- **Record data carefully** — never make up data
- **Administer assigned study therapy** — give investigational drugs or devices to all eligible patients
- **Report potential adverse events**

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# EMS Online



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## ROC 101 – Research for EMS Providers Practice Exam

1. The goal of the ROC is to conduct research in... (Select the best answer)

- A. ways to reduce transport time for trauma patients
- B. costs associated with medical interventions by EMS personnel
- C. prehospital interventions for cardiac arrest and trauma
- D. methods of improving cardiac defibrillation

Check My Answer

2. Which of the following attributes best characterizes ROC sites? (Select all the

- A. 5 sites
- B. 10 sites
- C. 5,000 EMS providers
- D. 20,000 EMS providers
- E. all EMS providers in the US and Canada
- F. none of the above

Check My Answer

3. Which criteria must a research study meet to allow an emergency exception 1  
(Select all that apply)

- A. situation is life-threatening
- B. available treatments are unproven or unsatisfactory
- C. informed consent not feasible
- D. patient may directly benefit
- E. study could not otherwise be done

Check My Answer

4. What are the three attributes required of EMS providers who participate in re  
(Select all that apply)

- A. honest
- B. open
- C. organized
- D. thorough
- E. therapeutic

Check My Answer

5. What are the consequences of incorrectly enrolling a patient in a study? (Sel  
apply)

- A. study takes longer
- B. invalid results
- C. meaningless outcomes
- D. nothing

Check My Answer

6. You should document all potential adverse events related to a study therapy are...(Select all that apply)

- A. expected
- B. mild
- C. serious
- D. unexpected
- E. minor

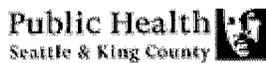
[Check My Answer](#)

7. Why should you limit investigational therapies to enrolled patients only? (Select all that apply)

- A. it would increase the cost of the study
- B. you risk fines or a jail sentence
- C. you could be expelled from the study
- D. potential for invalid study results
- E. in some instances it is okay to withhold a therapy from an eligible patient

[Check My Answer](#)

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## ROC 101 – Research for EMS Providers Resources

[Resuscitation Outcomes Consortium \(The ROC\) Public Page](#)

[International Commission on Harmonization Good Clinical Practice Guidelines](#)

[Department of Health and Human Services Code of Federal Regulations, Title 45, Part 46 \(45 CFR 46\) Protection of Human Subjects](#)

[U.S. Food and Drug Administration Code of Federal Regulations, Title 21, Part 50 \(21 CFR 50\) Protection of Human Subjects](#)

[Canada Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans](#)

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