

325 Ninth Avenue  
Seattle, Washington 98104  
(206) 731-3000

*Hypertonic Saline/Dextran Study*  
*Eileen M. Bulger, M.D.*  
*Primary Investigator*  
*Division of Surgery Box 359796*  
*Telephone 206-731-6448*  
*Fax 206-731-3656*



FDA  
Dockets Management Branch  
Docket Number 95s-0158  
IND 10292  
January 28th, 2004

*Claudette Cooper, R.N.*  
*Project Manager*  
*Office 206-341-4720*

Dear Sirs and Madams,

Enclosed you will find the working protocol (dated September 2003) and first amendment (dated 1-28-04) for the above-mentioned IND application for your files. At the time of our approval we only had the grant available. We hope that this further clarifies the study procedures.

Please feel free to contact us with any questions or concerns you may have.  
Sincerely,

Eileen M. Bulger, M.D.  
Sponsor/Primary Investigator  
IND 10292

95S-0158

RPT 16

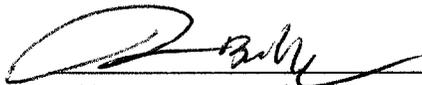
Amendment No: 1 dated 1/28/03

# The Effect of Hypertonic Resuscitation for Blunt Trauma

IND Number: 10292

Amendment No: 1 to  
Protocol Version I  
September 2003

Section 3.4 of the current protocol (dated September 2003) states that subjects must be enrolled prior to receiving more than 500cc of any other resuscitative fluid. A recent trial out of Toronto (S.B. Rizoli, "Immunomodulatory Effects of Hypertonic Saline Resuscitation of Traumatic Hemorrhagic Shock: A Pilot Randomized Controlled Trial. Abstract form the Resuscitation Symposium 2003)) demonstrates that this number can be increased to 2000cc without diminishing the effect of the Hypertonic Saline /Dextran. This amendment changes the inclusion criteria to reflect that Airlift flight nurses may enroll subjects into the HSD study if the subject has not received more than 2000cc prior to receiving study drug. This parameter will only be changed for the Flight nurses. The paramedics will be held to the 500cc limit at this time.



Eileen M. Bulger, M.D.

P.I. The Effect of Hypertonic Resuscitation  
for Blunt Trauma Study.

## New Science Abstracts

### Characteristics Associated with CPR and AED Skill Retention: Results of the Public Access Defibrillation (PAD) Trial.

Barbara J Riegel, Univ Pennsylvania, Philadelphia, PA; Robert Swor, William Beaumont Hosp, Royal Oak, MI; Tom P Aufderheide, Med College Wisconsin, Milwaukee, WI; Alice Birbaumer, Univ Washington, Seattle, WA; Mark C Henry, Stony Brook Univ, Stony Brook, NY; Lois Van Ottingham, Univ Washington, Seattle, WA; Heather Payne, St. Paul's Hosp, Vancouver, Canada; Henry C Thode, Jr, Stony Brook Univ, Stony Brook, NY

**Background:** Little is known about skill retention in lay volunteers trained in CPR and AED use. The purpose of this study was to identify characteristics associated with skill retention. **Methods:** Skill retention was tested 1-12 months after initial training (mean 5.5 months). Adequacy of performance was defined as completing at least 80% of essential CPR skills (assess responsiveness, access 911, ventilate adequately, place hands correctly, compress chest) and/or 75% of AED skills (bare chest, place pads correctly, clear self, clear area verbally). Data on 5907 laypersons trained in CPR (of whom, 3328 also received AED training) who volunteered at 993 locations (in 24 cities in the US and Canada) were available from the on-going PAD clinical trial. Logistic regression was used to evaluate characteristics of volunteers, training classes, and location types as predictors of adequate performance. **Results:** 72% of volunteers were adequate in CPR performance and 78% in AED performance. Variables of interest were entered into the model in stepwise fashion. Significant predictors of CPR and AED adequacy, controlling for site and for the number of months since initial training, are given in the table below. Hispanic origin, computer use, English as a first language, family history of sudden death, and location size and type were not associated with skill retention. **Conclusion:** Overall, volunteers retained AED skills better than they retained CPR skills. Trainees in certain groups may need more frequent retraining to maintain their skills.

Variable	CPR Adequacy (N=5607)		AED Adequacy (N=3328)	
	Odds Ratio	p	Odds Ratio	p
Younger Age (per 10-year decrement)	1.213	.001	1.189	.001
Gender = Male	1.173	.017		NS
Race = White	1.576	.001	1.618	.001
Education (at least some college)	1.161	.048	1.356	.007
Possession of driver's license	1.990	.001		NS
Experience in emergency situation	1.306	.001	1.219	.002
Prior training in CPR	1.363	.001	1.141	.016
Fewer than 1 manikin per 2 students provided in initial training class		NS	0.5781.422	.011

### Hyperventilation: A Common and Potentially Life-Threatening Problem During Cardiopulmonary Resuscitation.

Tom P Aufderheide, Ronald G Pirralo, Med College of Wisconsin, Milwaukee, WI; Gardar Sigurdsson, Demetris Yannopoulos, Univ of Minnesota, Minneapolis, MN; Chris von Brjesen, Self-employed, Thiensville, WI; Christopher Sparks, Self-employed, South Milwaukee, WI; Craig Cohrad, Med College of Wisconsin, Milwaukee, WI; Terry A Provo, Advanced Circulatory Systems, Inc., Eden Prairie, MN; Keith G Lurie, Univ of Minnesota, Minneapolis, MN

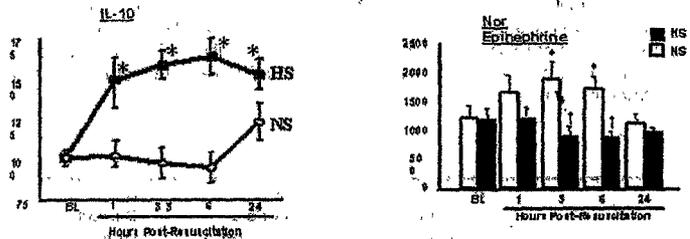
**Objective:** AHA recommends 12 - 15 breaths per minute in patients with secured airways during the performance of CPR by professional rescuers. Recent hemodynamic and survival studies during CPR in pigs demonstrate that excessive ventilation rates significantly inhibit venous blood flow back to the heart, blunt the development of negative intrathoracic pressure during the chest wall decompression phase, and thereby decrease coronary perfusion pressures and survival rates. The objective of this prospective, observational, case series was to determine actual ventilation frequency and duration during CPR by trained and certified professional emergency medical services (EMS) personnel in patients at the scene of cardiac arrests. **Methods:** Airway pressures were recorded continuously with a non-invasive airway pressure transducer in intubated adults with out-of-hospital cardiac arrest of presumed cardiac etiology during standard, two-rescuer CPR. **Results:** In 13 consecutive adults (63 ± 5.8 years) receiving CPR (7 males) the average ventilation rate was 30 ± 3.2 per minute (range 15 - 49) and the average duration of each breath was 1.0 ± 0.1 second. The average percent of time in which a positive pressure was recorded in the lungs was 47 ± 4.3%. No patient survived. **Conclusions:** To our knowledge, this represents the first time that ventilation frequency and duration have been objectively and electronically recorded at the scene of out-of-hospital cardiac arrests. Despite seemingly adequate training, professional rescuers consistently hyperventilated patients. The marked increase in ventilation rate (twice that recommended) and prolonged duration of positive intrathoracic pressure are associated with significantly decreased survival in an animal model. Given the potentially lethal consequences of hyperventilation during CPR, additional study in other EMS systems and education of CPR providers appears urgently needed.

### Immunomodulatory Effects of Hypertonic Saline Resuscitation of Traumatic Hemorrhagic Shock: A Pilot Randomized Controlled Trial.

Sandro B Rizoli, Shawn G Riland, Pang N Shek, Kenji Inaba, Dennis Filipis, Homer Tien, Fred Brenneman, Ori D Rotstein; Univ of Toronto, Toronto, Canada

**Rationale:** The ideal fluid for trauma resuscitation remains controversial. Recent animal studies demonstrated that hypertonic saline (HS) is an effective resuscitation fluid with immunological and anti-inflammatory properties that may reduce multi organ dysfunction and sepsis. It remains unclear whether HS has similar effects in humans. **Objective:** To determine whether a single bolus of HS modulate the immunological and anti-inflammatory response in trauma patients with hemorrhagic shock. To assess the feasibility of a large simple randomized trial to compare HS versus NS in such

patients. **Methods:** Design- Single-center randomized double-blinded trial comparing 250 ml of either HS (7.5% NaCl in 6% dextran 70) or normal saline (NS). **Population:** Adult blunt trauma patients in hemorrhagic shock (systolic BP < 90 mmHg) who were brought to Sunnybrook Trauma Center. **Outcomes:** Evaluated were fluid and blood volumes in hospital, days of ventilation, organ dysfunction and survival to discharge. Neutrophil activation was measured by changes in key adhesion molecules. Cytokines were measured by flow cytometry methods and catecholamine by gas chromatography. Blood samples were collected before and 1, 3, 6 and 24 hours after infusion. Continuous variables were compared by using t-test or repeated measures methods. Categorical variables were compared by using Chi-square. Nonparametric methods were used as appropriate. **Results:** 27 patients were enrolled from May 2001 to July 2002, 13 receiving HS. Control and intervention patients had similar age, gender, mechanism of injury (70% vehicular), injuries severity (Injury Severity Score of mean 26 ± 10 SD) and pre-hospital time (mean 2.3 ± 1 h). After intervention, both groups received similar amounts of crystalloids, but HS patients required less blood (mean 2.2 ± 2.9 units versus 4.36 ± 6.7 for control patients, not significant) and less colloids (mean 0.36 ± 0.37 L versus .7 ± .7 L for control, p < .02). HS patients were ventilated for mean 4.3 ± 7 days while control patients received mean 5.3 ± 6 days of ventilation (not significant). ICU stay, sepsis, organ dysfunction and survival were not significantly different. HS resuscitation blunted neutrophil activation by abolishing shock-induced CD11b up regulation (mean 780 ± 15 MFI versus 690 ± 30 for HS, p < .02) and causing extensive CD62L shedding (mean 472 ± 50 MFI versus 353 ± 15 for HS, p < .05). HS prevented the marked lymphopenia observed in control patients (mean .72 ± 0.1 × 10<sup>9</sup>/L versus 1.16 ± .17 for HS, p < .05). HS also altered the post-hemorrhagic shock cytokine imbalance. It prevented shock induced increase of high pro-inflammatory monocyte subset (2 ± .03 × 10<sup>9</sup>/L versus .07 ± .01 for HS, p < .01). HS significantly reduced monocyte pro-inflammatory cytokine production (TNF-α, IL-1β) and increased anti-inflammatory cytokine production (IL-1ra, IL-10, IL-6, see figure). HS also inhibited the marked increase of serum nor-epinephrine levels, without affecting epinephrine concentration (see figure). **Conclusions:** This is the first human trial to demonstrate that HS has immunological and anti-inflammatory effects in trauma patients. A large randomized trial is feasible to compare HS versus NS in trauma patients. HS may be an immunomodulatory agent in other disorders associated with ischemia/reperfusion injury such as sudden cardiac arrest.



### The PAD Study: Input and Output but Not Outcome: The PAD Investigators.

Michael R Sayre; Cincinnati, OH

**Introduction:** The Public Access Defibrillation (PAD) Trial has as its goal to determine whether deployment of automatic external defibrillators (AED) in public facilities, concurrent with training of volunteers in CPR and AED use, will result in an improved survival rate from out-of-hospital cardiac arrest. We report here on facilities included, volunteers recruited, AEDs deployed, and cardiac arrests that have occurred. **Outcomes** are not reported, but we report on the impact that various denominators would have on outcome evaluation. **Results:** Twelve hundred and sixty facilities were enrolled at twenty-four sites (range 29 to 87). The distribution of facility by type was 14.6% residential, 5.9% hotel, 23.7% shopping areas, 17.4% meeting complexes, 28.9% participant recreation, 1.7% public transport, 7.0 office complex, 4.2% industrial complex, and 1.7% other. The average facility had a population that was 47.6% male, 23.1% non-white, and 52.7% over age 50. An average of 13.5 volunteers and 2.6 AEDs were involved at each facility. Volunteer turnover approximates 25% a year. Based on historical data or population size, the mean expected number of cardiac arrests during the course of the study was ~ 1 per facility. Tabulation of presumed cardiac arrest events occurring through January 31, 2003 is shown at right. Assuming a hypothetical 60 saves, the impact of the choice of

Presumed Cardiac Arrest Events	CPR	CPR & AED
Definite PAD OOH-CA	58	134
Total (All Cardiac Arrests)	230	242

		Null			Alternative(2x)		
		CPR	CPR&AED	P	CPR	CPR&AED	P
Numerator	Poisson (saves)	30	30	1.00	20	40	0.011
Denominator	Definite PAD OOH-CA	30/58	30/134	0.309	20/98	40/134	0.239
	All Events	30/230	30/242	0.891	20/230	40/242	0.028

denominator is shown for the null hypothesis and for the trial design alternative of a two-fold improvement in the CPR+AED arm. An intriguing back-of-the-envelope cost-effectiveness analysis can be made. Assuming a difference of 15 saves per year, \$50 training cost per volunteer, and \$3,000 AED cost spread over four years, the direct program costs are \$124,000 per additional save. **Conclusion:** Identifying facilities with a high incidence of out-of-hospital cardiac arrest is more difficult than anticipated. The distinct nature of the interventions appears to bias identification / classification of events. Unless there is substantially more than the two-fold hypothesized improvement with PAD, the cost per life saved may make this an unattractive strategy for improving outcome from out-of-hospital cardiac arrest.

# **The Effect of Hypertonic Resuscitation for Blunt Trauma**

IND Number: 10292

Protocol Version I  
September 2003



# PROTOCOL

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Part I

**Study Summary**

**Title:** Effect of Hypertonic Resuscitation for Blunt Trauma.

**Objectives:**

**1.** To determine the impact of prehospital administration of hypertonic saline/dextran on the risk of developing the Acute Respiratory Distress Syndrome (ARDS) following blunt traumatic injury with hypovolemic shock.

*Hypothesis: Resuscitation of hypovolemic shock following blunt trauma with HSD will result in lower rates of ARDS than conventional resuscitation.*

**2.** To determine the impact of prehospital administration of hypertonic saline/dextran on neurologic outcome following traumatic brain injury in patients with hypovolemic shock.

*Hypothesis: Patients with traumatic brain injury and hypovolemic shock will have reduced mortality and improved neurologic outcome following resuscitation with HSD versus conventional intravenous fluids.*

**3a.** When funding becomes available: To determine the effect of prehospital administration of hypertonic saline/ dextran on the activation of circulating inflammatory cells, neutrophils and monocytes.

*Hypothesis: Neutrophils and monocytes derived from trauma patients resuscitated with HSD will demonstrate a depressed proinflammatory response to in vitro inflammatory stimuli compared to cells derived from patients undergoing conventional resuscitation.*

**3b.** To determine the effect of prehospital administration of hypertonic saline/ dextran on the activation of T lymphocytes.

*Hypothesis: T lymphocytes from patients treated with HSD will produce increased levels of IL-2 and decreased levels of IL-4 & 10 thus manifesting a Th-1 profile rather than the enhanced Th-2 response seen after injury.*

**Study Design:** Single center, prospective, randomized, double blinded, placebo controlled clinical trial. Subjects will be randomized to receive either 250cc of 7.5% hypertonic saline/dextran or 250cc of placebo (lactated ringers).

1. Enrollment: approximately 24 months.
2. Subjects will be followed clinically for 28 days or until hospital discharge whichever occurs first.
3. Subjects with head injuries will have follow up questionnaires administered at 6 months and one-year post randomization.

**Sample Size/Interim Monitoring:**

1. The study will accrue a maximum of 400 subjects.
2. Progress of the trial will be review by an independent Data and Safety Monitoring Board to determine if randomization should stop for futility, lack of safety, or proven efficacy. Three interim analyses are planned equal quartiles of enrollment. Specifically, we will perform an interim analysis at 25%, 50% and 75% of total enrollment. These analyses will coincide with meetings of the data monitoring and safety board (DMSB). This committee will evaluate whether there are clinically significant differences between the study groups that would require early cessation of the trial. Stopping for futility or efficacy will be based on formal group sequential stopping boundaries.

**Inclusion Criteria:**

1. Blunt trauma patients
2. Age >17 or of adult size if age is unknown
3. Prehospital SBP  $\leq$  90 mmHg
4. Altered mental status
5. Patients transported directly to Harborview Medical Center from the injury event

**Exclusion Criteria:**

1. Patients with ongoing CPR
2. Patients transferred from outside
3. Pregnant women or suspected pregnancy
4. Patients with injuries from penetrating trauma

**Efficacy:** The primary efficacy variable is incidence of ARDS within 28 days following injury, measured by ARDS-free survival as defined in the protocol.

Secondary efficacy variables include:

1. The number of ARDS free days and the validated Multiple Organ Dysfunction Score (MODScore) at day 28 after randomization
2. Several other secondary efficacy variables will be analyzed, as well as outlined in the protocol.

## Part II

### Study Description

#### Effect of Hypertonic Resuscitation for Blunt Trauma

Protocol for the Study July 15, 2003

#### 1 Background

Traumatic injury is the leading cause of death among Americans between the ages of 1 and 35 years, resulting in nearly 150,000 deaths per year in the United States (1). 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 (2). 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 (3, 4) (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

**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

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 (5). 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.

HSD (7.5% saline with 6% dextran-70) has been investigated as an alternative resuscitation fluid in critically injured patients (6-10). HSD results in an increase in serum osmotic pressure, which results in 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. This 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, HSD may have additional beneficial effects by modulating the excessive immuno-inflammatory response following systemic ischemia/reperfusion injury. HSD, therefore, has the potential to impact both early and late mortality following traumatic injury.

## **1.1 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 (11). 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 to the trauma patient (12).

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 (13-19). 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%) (20). 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 this country, however, results from blunt injury as a result of motor vehicle collisions. Furthermore, these patients often have a prolonged transport time and multisystem injury including brain injury. 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 (15, 18). Animal models of uncontrolled arterial and venous hemorrhage have demonstrated reduced mortality and no increase in pre-operative hemorrhage with hypertonic resuscitation. 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.

## **1.2 Resuscitation of the Patient with Traumatic Brain Injury**

Traumatic brain injury is a major public health problem in the United States, affecting nearly 500,000 patients per year (21). Approximately 100,000 of these patients will die from their injury and 90,000 will suffer a long-term neurologic disability. This translates into a societal cost of \$75 to 100 billion per year for medical care and lost productivity (22). 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 (23). Likewise, hypotension on arrival to the hospital and in the operating room have been associated with adverse outcome (24, 25). Inadequate cerebral perfusion from hypotension results in an ischemic insult that extends the primary injury, thus creating a secondary brain injury (26). 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 (27). The injured brain loses its ability to autoregulate the vasculature in response to changes in blood flow, thus increasing its sensitivity to hypotension(28). 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.

### **1.3 Effects of HSD 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(29). 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 (10). 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(6, 30-37). This effect is due to plasma volume expansion secondary to the increased osmotic load, along with centrally mediated effects on cardiac output (27). Rapid restoration of mean arterial pressure results in improved cerebral perfusion pressure, which supports the injured brain.

In addition to the systemic effects of HSD, HSD has been shown to lower ICP in several clinical trials and animal models (38-47). The effect of hypertonic saline 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 extracellular space by several mechanisms thus contributing to the rise in ICP (27). Increasing extracellular sodium levels by administration of hypertonic saline restores the active cellular sodium-osmolyte cotransporters, 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(45).

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 (27). 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. HSD counteracts hypoperfusion and vasospasm by increasing vessel diameter via volume expansion. In addition, HSD 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 (48). Hypertonic saline (HTS) infusion has also been associated with the release of nitric oxide, endothelins, and eicosanoids that alter vasomotor tone (49-51). The systemic immunomodulatory effects of HSD (described in detail below) 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. HSD may be beneficial in this regard, as increasing extracellular sodium reestablishes the normal direction of the sodium/glutamate transporters, which restore intracellular glutamate levels (52).

In summary, HSD meets the criteria outlined as an optimal resuscitation fluid for patients with traumatic brain injury. Its favorable effect 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 HSD on long term functional outcome for patients with traumatic brain injury.

#### **1.4 Prehospital Administration of HSD**

There have been 8 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 hospital. 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. 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 (29, 53, 54). The first was a traditional meta-analysis of all the trials using HSD or HTS published as of 1997. The conclusion from this paper was that HSD offers a survival benefit for the treatment of traumatic hypotension while there was no benefit from HTS 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.

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 immunoinflammatory response. Thus, critical evaluation of these effects in humans has not been undertaken. We propose the definitive clinical trial, focusing on the blunt, multisystem trauma population, which will maximize the statistical power to detect changes in outcome and provide a detailed analysis of the immunoinflammatory effects of HSD resuscitation. Furthermore, an emphasis on the functional outcome of brain-injured patients will define the clinical utility of this resuscitation approach for these patients.

**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

### 1.5 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- $\kappa$ 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 $\alpha$ , 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) (55). 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 (56). This systemic, over expression of the host inflammatory response results in ARDS and MOFS. ARDS occurs in up to 50% of severely traumatized patients (57).

The monocyte and macrophage are a key cells in coordinating the inflammatory response leading to organ injury. These cells produce all the pro-inflammatory cytokines and chemokines that have been implicated in the development of ARDS. This leads to further activation and recruitment of neutrophils, resulting in the release of proteolytic enzymes and reactive oxygen intermediates, which contribute to direct tissue injury. Current research has defined several key intracellular signaling pathways involved in the activation of mononuclear cells. These include phosphorylation of the mitogen activated protein kinases (MAPK): p38 kinase and extracellular regulated kinases (ERK 1 & 2), and the nuclear translocation of the transcription factor NF- $\kappa$ B. The activation status of these cascades may be predictive of the development of subsequent inflammatory organ injury. A recent study from our institution demonstrates that that the activational status of p38 kinase in alveolar macrophages from trauma patients is predictive of the development of MOFS (Unpublished communication, Dr. Rosengart). Understanding the effects of HSD resuscitation on the intracellular signaling pathways responsible for pro-inflammatory gene transcription will aid in determining the mechanisms responsible for its functional effect.

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

Several studies suggest that HTS can have profound effects on neutrophil function. In vitro studies have shown that HTS 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 (58-60). 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 (61). HTS 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 (62). Lung injury was also attenuated by HTS resuscitation in a hemorrhagic shock model secondary to suppression of the hemorrhage-induced neutrophil oxidative burst(63). Finally, the timing of HTS administration appears critical, as lung injury is attenuated by administration at the time of reperfusion but was enhanced in animals given HTS after partial resuscitation with crystalloid (64). These data support the prehospital administration of this fluid as the initial fluid to resuscitate hemorrhagic shock.

The effect of HTS on monocyte/macrophage activation is less well defined. Studies from our laboratory suggest, that similar to the neutrophil effect, hypertonic preconditioning inhibits the macrophage responsiveness to inflammatory stimuli, such as endotoxin (65). These studies demonstrated a significant reduction in TNF- $\alpha$  production in response to endotoxin following hypertonic saline pretreatment. In addition, this effect appeared to be mediated by the down-regulation of ERK1 & 2 kinase activation. 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.

### **1.7 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 of the patient to nosocomial infection. Nosocomial infection rates among trauma patients admitted to the ICU are reported to range from 30 to 40%(66, 67). In addition, nosocomial infection in this population has been associated with a two fold increased risk of death(67). 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 (68). Th1 cells secrete interferon- $\gamma$  (IFN- $\gamma$ ), TNF- $\alpha$ , and IL-2 and are involved in monocyte/macrophage mediated inflammatory responses. Th 2 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 (69). 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(70).

Several investigators have demonstrated a switch from the Th1 to Th2 phenotype in critically injured patients (70-72). 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(57, 73). 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.

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

The levels of hypertonicity achieved following HSD resuscitation have been shown to double T cell proliferation of mitogen-stimulated human PBMC (74). HTS has also been shown to enhance mitogen-stimulated IL-2 production by both Jurkat T-cells and human PBMC (75). 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 HTS, *in vitro* (76).

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 HTS 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 HTS group (77). Furthermore, HTS 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 (78). Taken together, these studies suggest that HTS resuscitation of the trauma patient may enhance cellular immune function and thus decrease susceptibility to subsequent nosocomial infection.

### **1.9 Significance and Study Implications**

Despite the many previous clinical trials of HSD resuscitation, it has not been adopted in the U.S. 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 focused on the trauma population as a whole with survival to hospital discharge as a primary outcome. By including penetrating trauma victims with a very short transport to the hospital, the effect on survival may be less evident, as the outcome for these patients depends on rapid surgical intervention. Furthermore, it is evident that patients with traumatic brain injury may have the greatest benefit from HSD therapy and there have been no trials to evaluate the impact of HSD therapy on 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. Our proposal, which focuses on the blunt trauma population, will provide a greater number of patients with traumatic brain injury and a greater incidence of ARDS to assess these outcomes.

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. Our study is designed to not only evaluate the clinical outcome parameters, but to also provide a detailed analysis of the activation status of inflammatory cells from these patients.

The data achieved from these studies will provide insight into the clinical and biological advantages of HSD resuscitation following blunt trauma, and thus contribute to the development of a resuscitation strategy to improve clinical outcome. By providing insight into the effect of HSD resuscitation in the blunt trauma population, this study will address the major clinical questions remaining regarding the utility of this approach.

## **2 Endpoints**

### **2.1 Primary Endpoint**

The primary efficacy measure is ARDS-free survival to day 28 after randomization so death prior to ARDS determination and loss-to-follow-ups can be appropriately accounted for. This efficacy measure has been used to calculate sample size and to develop interim stopping boundaries.

The primary clinical outcome of interest is the incidence of ARDS within 28 days following injury. ARDS is the most common manifestation of inflammatory organ injury following mulitsystem trauma. Previous studies demonstrate that the majority of trauma patients (>90%) who develop ARDS will meet the clinical criteria by 7 days post injury and thus by 28 days, we should capture all patients with ARDS(90). The widely accepted clinical criteria for ARDS is based on the American-European Consensus Conference on ARDS published in 1994(91). These criteria include: (a) hypoxia with a  $\text{PaO}_2/\text{FiO}_2$  ratio < 200, (b) bilateral infiltrates on chest X-ray, and (c) no clinical evidence of increased left atrial pressure or a pulmonary artery wedge pressure of < 18mmHg. Most patients will have pulmonary artery catheter monitoring. For those that do not, clinical evidence of left atrial hypertension includes: (a) acute myocardial infarction *or* known cardiomyopathy *or* severely reduced ejection fraction (<30%) *or* known critical valvular disease; b) chronic or acute oliguric renal failure with fluid input

that exceeds output by  $\geq 3$  liters in previous 24 hour period. Acute Lung Injury (ALI) has been defined as a milder form of ARDS with the same clinical criteria except for a  $\text{PaO}_2/\text{FiO}_2 < 300$ . The clinical research nurse will identify the development of ARDS and ALI by daily screening of the patients for these clinical criteria. The date of onset will be recorded. Patients will be followed for 28 days regardless of whether the primary endpoint has been achieved to track the secondary outcome variables.

Since patients with ARDS may be affected by many other factors that are indirectly or remotely related to an ARDS diagnosis, several secondary outcome variables will also be examined. They are chosen to reflect morbidity and cost of medical care:

## 2.2 Secondary Endpoints

### a. Multiple Organ Failure Syndrome

The development of additional system organ dysfunction will be tracked by the well-

<b>Table 3: Multiple Organ Dysfunction Score</b>					
<i>Sum the worst scores of each of the individual systems over the course of the ICU stay</i>					
	Score				
Organ system	0	1	2	3	4
Respiratory ( $\text{PO}_2/\text{FiO}_2$ )	>300	226-300	151-225	76-150	$\leq 75$
Renal (serum creatinine - mmol/l)	$\leq 1.1$	1.2-2.3	2.4-3.9	4.0-5.6	>5.7
Hepatic (serum bilirubin - mmol/l)	$\leq 1.1$	1.2-3.5	3.6-7.1	7.2-14.1	>14.2
Cardiovascular (PAR*)	$\leq 10.0$	10.1-15.0	15.1-20.0	20.1-30.0	>30.0
Hematologic (platelet count $\times 10^3$ )	>120	81-120	51-80	21-50	$\leq 20$
Neurologic (Glasgow coma score)	15	13-14	10-12	7-9	$\leq 6$

\*PAR - pressure adjusted heart rate is calculated as the product of heart rate (HR) multiplied by the ratio of the central venous pressure to the mean arterial pressure (MAP):  $\text{PAR} = \text{HR} \times \text{CVP}/\text{MAP}$

validated Multiple Organ Dysfunction Score (MODScore) (Table 3) (92). Its continuous nature allows detection of subtle differences in organ dysfunction not identified by dichotomous measures. The MODScore assigns points to each of the six organ systems indicated and the summary score is calculated by summing the worst scores of each organ system over the course of the ICU stay. Because the MODScore is designed to measure stable alterations in organ function, the first 48 hours post-injury are excluded. Those who die in first 48 hrs will be assigned the maximum MODS score of 24, and those who are discharged before 48 hrs will have a MODS score of 0

### b. Nosocomial Infection

All post-injury infections will be tracked based on the criteria defined in Table 4.

### **Bacteremia**

To diagnose bacteremia then criteria #1 and #2 must be satisfied on the same day:

1. Recognized pathogen isolated on one blood culture or, if organism is a common skin contaminant (diphtheroids, bacillus, propionibacterium, coagulase negative staphylococci, or micrococci) two positive blood cultures are required.
2. At least one of the following:
  - a. fever  $>38$  C or hypothermia  $< 36$  C
  - b. chills
  - c. hypotension (SBP  $< 90$  mmHg)

### **Pneumonia**

To diagnose pneumonia all three criteria must be satisfied within a three-day period during days 1-28:

1. Radiologic criteria (both a and b)
  - a. new infiltrate corresponding in size to one segment or more of lung, or cavitation with an air fluid level
  - b. radiographic finding persists  $\geq 24$  hrs.
2. Clinical criteria (both a and b)
  - a. fever ( $\geq 38.3$  °C) or hypothermia ( $\leq 36.0$  °C)
  - b. WBC  $> 10\,000/\text{mm}^3$  or 25% increase over last available value or bands  $> 10\%$  of total WBC or new decrease in WBC to  $< 4000/\text{mm}^3$
3. Bacteriologic confirmation by at least one of:
  - positive blood culture for bacterial pathogen also identified in sputum or other respiratory culture
  - protected specimen brushing with  $\geq 10^3$  cfu/ml bacterial pathogen
  - BAL with  $> 10^4$  cfu/ml bacterial pathogen
  - positive gram stain from BAL fluid
  - positive sputum gram stain with  $\geq 3+$  of one type of bacteria
  - positive semi-quantitative sputum culture with  $\geq 3+$  growth of one type of pathogenic bacteria (if not quantitative, then must be moderate or heavy growth)

### **Wound Infection**

To diagnose wound infection must meet all the following criteria:

1. Erythema or wound drainage
2. One of the following:
  - a. fever ( $\geq 38.3$  °C) or hypothermia ( $\leq 36.0$  °C)
  - b. WBC  $> 10\,000/\text{mm}^3$  or 25% increase over last available value or bands  $> 10\%$  of total WBC or new decrease in WBC to  $< 4000/\text{mm}^3$
3. Intervention: wound drainage and/or treatment with antibiotics

### **Intra-abdominal abscess**

To diagnose intra-abdominal abscess must meet both of the following criteria:

1. Intra-abdominal fluid collection requiring percutaneous or surgical drainage
2. Growth of bacteria on culture of the drainage fluid.

### **Urinary tract infection**

To diagnose UTI must meet 1 & 2 on same day

1. Urine culture with  $> 100,000$  colonies of an organism
2. One of the following:
  - a. fever ( $\geq 38.3$  °C) or hypothermia ( $\leq 36.0$  °C)
  - b. WBC  $> 10\,000/\text{mm}^3$  or 25% increase over last available value or bands  $> 10\%$  of total WBC or new decrease in WBC to  $< 4000/\text{mm}^3$

## **c. Resource Utilization and Mortality**

Additional secondary outcome variables to be assessed will include: 28 day mortality, survival to hospital discharge, duration of hospital and ICU stay, and ventilator-free days through day 28. Ventilator-free days is another marker of pulmonary morbidity that may be influenced by both organ dysfunction and

nosocomial pneumonia. This is calculated by the number of days during which no ventilator support is required over the first 28 days. These parameters will provide an assessment as to whether HSD resuscitation reduces resource utilization and mortality.

### **3 Study Population and Enrollment**

#### **3.1 Number/Source/Screening**

The trial will accrue a maximum of 400 subjects over a 2 year period. Patients within the King County area with blunt trauma will be recruited from the prehospital agencies that are responsible for the management of the trauma patient at the scene of injury and in transport to HMC include the Seattle/ King County Medic One program and Airlift Northwest.

#### **3.2 Inclusion Criteria**

*All the following inclusion criteria must be met prior to administration of study drug:*

Blunt Trauma in the field with:

1. Age >17 or of adult size if age is unknown
2. Prehospital SBP  $\leq$  90 mmHg
3. Altered mental status
4. Patients transported directly to Harborview Medical Center from the injury event

#### **1.3 Exclusion Criteria**

*Any one of the conditions listed below will disqualify a subject:*

1. Patients with ongoing CPR
2. Patients transferred from outside
3. Pregnant women or suspected pregnancy
4. Patients with injuries from penetrating trauma
5. Airlift patients who received more than 500cc of any other resuscitative fluid prior to study enrollment.

#### **3.4 Enrollment and Study Initiation Time Window**

The study drug must be the first fluid hung (may be hung simultaneously with other fluids) at the time of reperfusion. However, the subjects must be enrolled prior to receiving more than 500cc of any other resuscitative fluid.

### **3.5 Informed Consent**

These patients will be identified at the scene of injury by the prehospital providers. As a result, these patients will be unable to provide consent at the time of enrollment due to the severity of injury and altered sensorium secondary to hypotension, head injury, or other intoxicating substances. In addition, legal next-of-kin are rarely available to provide immediate consent, nor is it practical for the prehospital provider to engage in a consent discussion when managing an unstable trauma patient. Thus, in accordance with the regulations from the U.S. Food and Drug Administration and the Office for Human Research Protections, we have been approved by the University of Washington's Human Subjects Division for a waiver of consent for initial enrollment. We will attempt to obtain informed consent when either the subject is able to provide consent, or their legal representative is available. The exceedingly short interval for obtaining consent in this population, and the fact that HSD has been used in several previous prehospital studies of trauma patients, without adverse event, make waived consent a viable option to enable a study to answer these important clinical questions. If consent is obtained by the legal-next-of-kin, and the subject regains the ability to consent, we will re-consent the subject for continued participation. Informed consent, for outpatient contact and use of survey information, will be obtained by the study coordinator prior to discharge.

### **3.6 Randomization and Blinding**

The study fluids will be purchased from Biophausia Inc, Sweden in 250cc infusion bags. HSD is marketed by this company as RescueFlow ® and widely used in Europe. An IND has been approved by the FDA for use of this product in this study. These bags will then be blinded by the HMC pharmacy and a randomly generated numeric code will be applied to each bag and kept by the research pharmacist. The control fluid (250cc lactated ringers) will be prepared in IV bags which are identical to the HSD fluid. They will be randomized by computerized number generation in blocks of 6 and 6 bags will be placed at each base station where they can be retrieved by the medic units. Two bags of study fluid will be kept on each ambulance or helicopter. The numbering on each block of 6 will be sequential so they must be taken in order by the paramedics and thus there is no potential for selection bias. Our pharmacy personnel will keep inventory records for each site and conduct site visits to confirm inventory status every three months. When a site has less than 3 bags of fluid remaining, an additional set of 6 will be distributed. Each bag will have several stickers denoting its number and these will be placed on the medic report, ER nursing admission record and on the blood sample provided by the paramedic. In this manner, the subjects, investigators, study coordinators, and all persons caring for the patient will be blinded to the study treatment assignment. To avoid the risk that blinding will be compromised by initial changes in serum sodium, all caretakers will be blinded to

the serum sodium and chloride levels for the first 12 hours. Critical serum sodium and chloride levels will be reported to a Critical Care Physician who is not responsible for the clinical management of the patient, who will advise the management team if intervention is required.

### **3.7 Minorities and Women**

All comers that meet the study entry criteria and have no exclusions will be enrolled in the trial.

### **3.8 Community Notification**

Because the population eligible for enrollment includes all adult citizens in King County, WA and surrounding areas it was not possible to target any particular small group. We achieved community consultation with IRB approval in the form of a random digit dialing survey. The survey which explained the proposed study protocol asked for input from 500 respondents in the King County area. Citizens were asked about any concerns they may have about potential enrollment. The results of the survey showed that 75% has no issues with the waiver of consent, and 77% would like to receive the study drug. Lectures to the community and medical providers have also been performed.

Public disclosures have been performed prior to study enrollment and will continue at the completion of the study in the form of multimedia press releases organized by the Harborview Injury Prevention and Research Center community relations office. These have included plans for the study including potential risks and benefits and a summary of the results of the study upon completion.

## **4 Procedures**

### **4.1 Administration of Study Drug**

The study drug (250cc of HSD or LR) must be the first fluid hung for reperfusion (it may be hung simultaneously with other fluids). 6 bags of study drug will be placed at each base station where they can be retrieved by the medic units. Two bags of study fluid will be kept on each ambulance or helicopter. The numbering on each block of 6 will be sequential so they must be taken in order. When a patient meets the entry criteria a study drug bag will be hung. Each bag will have several stickers denoting its number and these will be placed on the medic report, ER nursing admission record and on the blood sample provided by the paramedic. In this manner, the subjects, investigators, study coordinators, and all persons caring for the patient will be alerted to the subject's enrollment into the study.

## 4.2 Infection Monitoring

All post-injury infections will be tracked based on the following criteria:

### Bacteremia

To diagnose bacteremia then criteria #1 and #2 must be satisfied on the same day:

1. Recognized pathogen isolated on one blood culture or, if organism is a common skin contaminant (diphtheroids, bacillus, propionibacterium, coagulase negative staphylococci, or micrococci) two positive blood cultures are required.
2. At least one of the following:
  - a. fever  $>38$  C or hypothermia  $< 36$  C
  - b. chills
  - c. hypotension (SBP  $< 90$  mmHg)

### Pneumonia

To diagnose pneumonia all three criteria must be satisfied within a three-day period during days 1-28:

1. Radiologic criteria (both a and b)
  - a. new infiltrate corresponding in size to one segment or more of lung, or cavitation with an air fluid level
  - b. radiographic finding persists  $\geq 24$  hrs.
2. Clinical criteria (both a and b)
  - a. fever ( $\geq 38.3$  °C) or hypothermia ( $\leq 36.0$  °C)
  - b. WBC  $> 10\,000/\text{mm}^3$  or 25% increase over last available value or bands  $> 10\%$  of total WBC or new decrease in WBC to  $< 4000/\text{mm}^3$
3. Bacteriologic confirmation by at least one of:
  - positive blood culture for bacterial pathogen also identified in sputum or other respiratory culture
  - protected specimen brushing with  $\geq 10^3$  cfu/ml bacterial pathogen
  - BAL with  $> 10^4$  cfu/ml bacterial pathogen
  - positive gram stain from BAL fluid
  - positive sputum gram stain with  $\geq 3+$  of one type of bacteria
  - positive semi-quantitative sputum culture with  $\geq 3+$  growth of one type of pathogenic bacteria (if not quantitative, then must be moderate or heavy growth)

### Wound Infection

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To diagnose intra-abdominal abscess must meet both of the following criteria:

3. Intra-abdominal fluid collection requiring percutaneous or surgical drainage
4. Growth of bacteria on culture of the drainage fluid.

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To diagnose UTI must meet 1 & 2 on same day

1. Urine culture with  $> 100,000$  colonies of an organism
2. One of the following:
  - a. fever ( $\geq 38.3$  °C) or hypothermia ( $\leq 36.0$  °C)
  - b. WBC  $> 10\,000/\text{mm}^3$  or 25% increase over last available value or bands  $> 10\%$  of total WBC or new decrease in WBC to  $< 4000/\text{mm}^3$

### **4.3 Clinical Management**

No colloids will be given to study subjects during the hospital stay. In the case of high intracranial pressure where clinicians may opt to use 3% hypertonic saline for management, it will be avoided for the first 24 hours after admission. Otherwise, clinical management of the patient is left up to the attending physician.

### **4.4 Duration of Study**

Subjects will be followed clinically for 28 days or until hospital discharge whichever occurs first. Subjects with head injuries will have follow up questionnaires administered at 6 months and one -year post randomization.

### **4.5 Schedule of Events**

## **5 Data Collection**

### **5.1 Baseline Assessments**

Because 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 nurse. This initial data, including demographics, mechanism of injury, prehospital and ED hemodynamic variables, time to definitive care & mode of transport, Injury Severity Score, and total fluids in the first 12 hours will be obtained by the research nurse within 24 hours of admission. This will include review of the prehospital report and documentation of initial events in the ED. It is anticipated that the subject or the legal representative will be available for consent at the time of this assessment, however, if this is not the case, baseline data will be obtained while continued attempts at localizing next-of-kin are made. All trauma admissions during this time period will also be tracked to identify any patients meeting the entry criteria but not enrolled. This will identify any selection bias.

### **5.2 Assessments During study**

The following information will be recorded daily for 28 days or until hospital discharge between 4-10 am. If more than one value is available during this window the values closest to 8 am will be recorded.

1. Vital signs: Heart rate(b/min),systolic and diastolic BP (mmHg), body temperature.
2. Respiratory parameters: Fio<sub>2</sub>, Vent status (ventilated or not) minute ventilation, compliance. ARDS/ALI criteria.

3. Arterial PO<sub>2</sub>,
4. Serum electrolytes to exclude NA<sub>2</sub>CO<sub>3</sub> during study enrollment, BUN
5. Glasgow Coma Score
6. Frontal chest radiograph (when available)
  - a. Radiographic Lung Injury Score (# of quadrants)
7. Administration of vasopressors
8. Organ Failure Data
  - a. Platelet
  - b. Bilirubin,
  - c. GCS
  - d. Creatinine

**Blood draws:**

Serial blood specimens will be obtained from patients enrolled in the clinical trial. Thirty milliliters of whole blood in a citrate anticoagulant will be drawn within:

06-12 hours of injury (day 0)

24-36 hours of injury (day1)

Between days 3-5

Between days 7-9

The initial samples are designed to capture initial effects of hypertonicity on cellular function, with subsequent samples to assess the duration of this effect and to capture changes in both early and late immunoresponsiveness.

For follow up on long-term neurologic outcomes, for subject with head injuries, a questionnaire (Appendix B) has been prepared, which includes the key components of the Glasgow Outcome Score (GOS), Glasgow Outcome Score Extended (GOSE), and the Disability Rating Score (DRS). The questionnaire will be administered to patients or their caregivers at day 28, 6 months and 12 months after injury. The questionnaire will be administered by a single, trained interviewer, to avoid problems with inter-rater variability.

## **6 Statistical Considerations**

### **6.1 Analysis of Endpoints**

Outcomes will be evaluated on an intention to treat basis using all randomized patients as the cohort. The primary endpoint will be the development of ARDS within 28 days of injury. Operationally, to account for patients who are lost to follow-up or die within 28 days before ARDS status can be determined, ARDS-free survival up to 28 days will be the actual measure analyzed. ARDS free survival is defined as the duration from study entry to development of ARDS or death, whichever occurs first. The duration is considered as having been 'censored' at the time of last contact for patients lost to follow-up <28 days and

prior to ARDS determination. Both an unadjusted analysis (logrank test) and an adjusted analysis (Cox model regression accounting for relevant baseline variables) will be performed. Results will be reported as the relative hazard of developing ARDS or death for those receiving HSD resuscitation vs. conventional isotonic therapy.

We hypothesize that the impact of HSD therapy will be greatest for patients surviving greater than 48 hours as these patients are more likely to manifest the inflammatory organ dysfunction associated with resuscitation and thus meet the primary endpoint of ARDS. The majority of patients who die in the first 48 hours following injury die from either exsanguination or devastating head injury. These patients are not likely to be impacted by HSD resuscitation. Subset analysis will thus be performed for patients surviving greater than 48 hours. In addition, a pre-defined subset analysis will be performed for patients with and without traumatic brain injury as outlined under the design for objective #2.

## **6.2 Randomization of Ineligible Subjects**

It is anticipated that there will be a small number of patients randomized who in retrospect do not meet the entry criteria. These patients will be analyzed according to the group to which they were randomized. Subgroup analysis based on the eligibility criteria will be performed if greater than 10% of the population is involved. Based on the simple inclusion and exclusion criteria we do not expect this to be a significant problem.

## **6.3 Non-adherence**

In some circumstances it is possible that the patient will not receive the full amount of the study solution or the solution may be inadvertently administered after isotonic fluid resuscitation. In this circumstance, these patients will remain in the intention to treat analysis within their respective groups.

## **6.4 Analysis of Secondary Outcome Parameters**

MODSscore, ventilator-free days, duration of ICU stay and duration of hospital stay are all continuous variables that will be analyzed using a t test for normally distributed data and the Wilcoxon rank-sum test for non-parametric data. Differences in the rate of nosocomial infection will be evaluated by the Chi-square test. Mortality will be analyzed by Kaplan-Meier survival curves, which will be plotted with an unadjusted log-rank test to compare the groups. Cox model regression analysis will also be conducted to adjust for any confounding baseline parameters. Patients lost to follow-up due to discharge prior to 28 days and failure to achieve a subsequent telephone contact will be censored at the time the patient was last observed to be alive.

## **6.5 Interim Analysis**

Progress of the trial will be reviewed by an independent Data and Safety Monitoring Board to determine if randomization should stop for futility, lack of safety, or proven efficacy. Three interim analyses are planned at equal quartiles of enrollment. Specifically, we will perform an interim analysis at 25%, 50% and 75% of total enrollment. These analyses will coincide with meetings of the data monitoring and safety board (DMSB). This committee will evaluate whether there are clinically significant differences between the study groups that would require early cessation of the trial. Stopping for futility or efficacy will be based on formal group sequential stopping boundaries.

## **7 Data Collection and Site Monitoring**

### **7.1 Data Collection**

The research nurse will enter data on an access data capture system. The database is designed with a series of checks to avoid missing or incorrect data. The research nurse will identify all patients enrolled by review of the ED log for the previous 24 hours. Each patient will be assigned a study code number and the randomization number from the study fluid will be recorded in the database for that patient. The research nurse will approach the patient or legal next-of-kin for consent to track patient outcomes and for blood specimen collection as soon after admission as possible. Baseline data will be collected at that time and follow-up data will be collected by review of medical records and computer charting daily. We will also keep a log of all admissions to the trauma service during the study enrollment period and will have access to the trauma registry data on these patients to allow comparison for selection bias.

### **7.2 Data Integrity**

The data collection form and software have been used in several previous clinical trials at HMC and thus the research nurses responsible for data collection are familiar with the definitions of the baseline variables and outcome parameters. To ensure consistency and identify data collection problems, a random audit of the database will be conducted at 2, 4, 8, and 12 months.

### **7.3 Safety and Monitoring**

In accordance with the FDA, we have developed 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. 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 DMSB.

#### Serious Adverse Events

1. Any evidence of anaphylactic reaction to HSD
2. Seizure activity associated with hypernatremia
3. Hypernatremia ( $\text{Na} > 160 \text{ mEq/L}$ ) requiring therapeutic intervention
4. Evidence of increased intracranial hemorrhage on Head CT scan
5. Unexplained coagulopathy
6. Any death not explained by the injury severity

#### Other Adverse Events

7. Irritation at the site of infusion
8. Minor allergic reaction, skin rash with no hemodynamic effects
9. Evidence of increased bleeding based on blood & fluid requirements in the first 24 hours (evaluated at interim analyses)

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 prehospital 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 adverse event will be reported by fax/telephone to the FDA, IRB and chairperson of the DSMB within 24 hours of discovery of the event. 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 of the DSMB as necessary to investigate adverse events.

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

For all patients:

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

For patients with Traumatic Brain Injury:

- a. Results of all Head CT scans obtained in the first week after injury
- b. Intracranial pressure (ICP) and Cerebral perfusion pressure (CPP) at the time of ICP monitor placement.
- c. Highest ICP and lowest CPP recorded for every 12 hour period in the first 5 days after injury.
- d. Total amount of Mannitol administered ever 12 hours for the first five days.
- e. All reports of seizure activity and anti-convulsant medications administered.

As described in detail above, due to blinding issues, all serum sodium and chloride levels in the first 12 hours, including the baseline level from the pre-infusion blood sample, will be recorded in the laboratory and significantly high or low levels will be reported to the safety officer who is a critical care physician, not directly involved in the care of the patient, to determine whether intervention is required. This physician will report any patient with hypernatremia who is deemed to require a therapeutic intervention to the investigators as a serious adverse event.

#### **7.4 Reporting of Adverse Events**

The principle Investigator will determine daily if any clinical adverse experiences occur during the period from when the study drug is administered until hospital discharge or day 28, whichever comes first. The investigator will evaluate any changes in laboratory values (except the NACL level which will be evaluated by a critical care physician not related to the study), and physical changes and will determine if the change is clinically important and different from what is expected in the course of treatment of patients with blunt trauma. If clinically important and unexpected adverse experiences occur, they will be recoded on the adverse event case report form.

The principle investigator will report all serious, unexpected, and study-related adverse events, as defined in Appendix A to the FDA within 24 hours of discovery of the event by fax/telephone and by writing within 10 working days. The University of Washington's IRB will also be notified in a timely manner.

### **8 Human Subjects**

Each study participant or appropriate surrogate must sign and date an informed consent form as soon as reasonably possible after enrollment under the waiver of consent. Institutional Review Board approval will be required before any subject is entered into the study. All study participants or their surrogates will be

informed of the objectives of the study and the potential risks. To maintain confidentiality, all laboratory specimens, evaluation forms, and reports will be identified only by a coded number. All records will be kept in a locked file cabinet, and in a password protected computer. Clinical information will not be released without the written permission of the patient, except as necessary for monitoring by the FDA, or National Heart Lung, and Blood Institute (per 21CFR sec. 50 and 312)

## 9 Appendices

### A. Adverse Events

#### 1. 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 her 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.

The investigator will report all *serious, unexpected, and study-related* adverse events to the FDA within the required time frame. The Institutional Review Board must all also be informed in a timely manner.

#### 2. Definitions of Adverse Events

A *serious adverse* event is any event that is fatal or immediately life threatening, is permanently disabling, or severely incapacitating, or prolongs inpatient hospitalization. Important medical events that may not results in death, be life threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical, surgical intervention to prevent one of the outcomes listed above.

Life-threatening means that the patient was, in the view of the investigator at immediate risk for death from the reaction as it occurred. It does not include the reaction that, had it occurred in a more serious form, might have caused death. Assessment of the cause of the event has no bearing on the assessment of the event's severity.

An *unexpected* event is any experience not identified by type, severity, or frequency in the current study protocol or an event that occurred unexpectedly in the course of treatment for blunt trauma. Averse events will be considered to be study-related when the event follows a reasonable temporal sequence from administration of the study drug.

**B. Structured Interview for Outcome Following Traumatic Brain Injury  
6 month/1 year evaluation**

Study No \_\_\_\_\_

Date: \_\_\_\_\_

Date of Injury: \_\_\_\_\_

Interval Post Injury: \_\_\_\_\_

Respondent:

- a) Patient alone (1)             $\theta$
- b) Caregiver alone (2)         $\theta$
- c) Patient and Caregiver (3)  $\theta$

If caregiver, identify:

- a) Relative (1)  $\theta$
- b) Friend (2)  $\theta$
- c) professional (RN, employed caretaker) (3)  $\theta$

**Consciousness**

- (i) Is the head injured person able to obey simple commands or say any words?  
 $\theta$  Y(1)  $\theta$  N(0) (VS-GOS)

Anyone who shows ability to obey even simple commands, or utter any word or communicate specifically in any other way is no longer considered to be in a vegetative state. Eye movements are not reliable evidence of meaningful responsiveness. If unclear, corroborate with nursing staff.

1a. Does the patient open eyes: (DRS)

- a) spontaneously            (0)  $\theta$
- b) to speech                (1)  $\theta$
- c) to pain                    (2)  $\theta$
- d) none                      (3)  $\theta$

1b. Is the patients speech: (DRS)

- a) oriented                    (0)  $\theta$
- b) confused but conversant (1)  $\theta$
- c) inappropriate words      (2)  $\theta$
- d) incomprehensible        (3)  $\theta$
- e) none                        (4)  $\theta$

1c. What is the patients best motor response: (DRS)

- a) obeys commands            (0)  $\theta$
- b) localizes pain              (1)  $\theta$
- c) withdraws from pain        (2)  $\theta$
- d) flexor posturing            (3)  $\theta$
- e) extensor posturing         (4)  $\theta$
- f) none                        (5)  $\theta$

*Independence in the Home*

- 2a. *Is the assistance of another person at home essential every day for some activities of daily living?  $\theta$  Y(1)  $\theta$  N(0) (GOS, Y=SD)*

*For a No, the patient should be able to care for himself at home for 24 hours if necessary. Independence includes the ability to plan for and carry out the following activities: bathing, dressing, preparing food, dealing with callers, and handling minor domestic crises. The person should be able to carry out these activities without prompting or reminding and should be capable of being left alone overnight.*

- 2b. *Does the patient require frequent help or someone to be around the home most of the time?  $\theta$  Y(1)  $\theta$  N(0) (GOSE, Y=Lower SD, N=Upper SD)*

*For a No, the patient should be able to care for himself for up to 8 hours a day if necessary.*

- 2c. *Was assistance at home required before the injury?  $\theta$  Y(1)  $\theta$  N(0)*

- 2d. *Does the patient have the cognitive ability to feed himself? (DRS)*

- a. complete (0)  $\theta$*
- b. partial (1)  $\theta$*
- c. minimal (2)  $\theta$*
- d. none (3)  $\theta$*

- 2e. *Does the patient have the cognitive ability to bath and toilet? (DRS)*

- e. complete (0)  $\theta$*
- f. partial (1)  $\theta$*
- g. minimal (2)  $\theta$*
- h. none (3)  $\theta$*

- 2f. *Does the patient have the cognitive ability to groom and dress? (DRS)*

- i. complete (0)  $\theta$*
- j. partial (1)  $\theta$*
- k. minimal (2)  $\theta$*
- l. none (3)  $\theta$*

*[Note: 2d,2e,2f Focus specifically on cognitive ability not physical ability to perform these tasks]*

- 2g. *Would you describe the patient as currently: (DRS)*

- a) completely independent (0)  $\theta$*
- b) independent in a special environment (1)  $\theta$*
- c) mildly dependent (needs limited assistance, non-resident helper) (2)  $\theta$*

- d) moderately dependent (needs person in home for some assistance) (3)  $\theta$
- e) markedly dependent (needs assistance with all activities at all times) (4)  $\theta$
- f) totally dependent (24 hr nursing care required) (5)  $\theta$

Independence Outside the Home

3a. Can the patient shop without assistance?  $\theta Y(1) \theta N(0)$  (GOS, N=SD)

*This includes being able to plan what to buy, take care of money independently and behave appropriately in public.*

3b. Was the patient able to shop without assistance prior to the injury?  $\theta Y(1) \theta N(0)$

4a. Is the patient able to travel locally without assistance?  $\theta Y(1) \theta N(0)$  (GOS, N=SD)

*This includes either driving or use of public transit. Ability to use a taxi is sufficient, provided the person can call for the taxi and instruct the driver independently.*

4b. Was the patient able to travel without assistance prior to the injury?  
 $\theta Y(1) \theta N(0)$

Work

5a. Is the patient working at his/her previous capacity?  $\theta Y(1) \theta N(0)$  (GOS, N=MD, Y=GR) (DRS: Y=0 points)

*If they were working before, then their current capacity for work should be at the same level. If they were seeking work before, then the injury should not have adversely affected their chances of obtaining work at the level to which they were eligible. If the patient was a student before the injury, then their capacity for study should not have been adversely affected.*

5b. How restricted are they? (GOSE, 1=upper MD, 2=lower MD) (DRS, 1=1 point, 2= 2 points, 3=3 points)  
 $\theta (1)$  Reduced work capacity  
 $\theta (2)$  Able to work only in a sheltered workshop or non-competitive job, or unable to work  
 $\theta (3)$  unable to work at all

5c. Prior to injury was the patient:

$\theta$  Working full-time: List occupation: \_\_\_\_\_ (5)

$\theta$  Working part-time: List occupation: \_\_\_\_\_ (4)

$\theta$  Seeking Employment (3)

$\theta$  Student: Level of education: \_\_\_\_\_ (2)  
 $\theta$  Unable to work (1)

**Social & Leisure Activities**

6a. *Is the patient able to resume regular social and leisure activities outside the home?*  
 $\theta Y(1) \theta N(0)$  (GOS, Y=GR)

*They need not have resumed all their previous leisure activities, but should not be prevented by physical or mental impairment. If they have stopped the majority of activities because of loss of interest or motivation then this is also considered a disability.*

6b. *What is the extent of restriction on their social and leisure activities? (GOSE a= lower GR, b= upper MD, c= lower MD)*

5. <i>Participate a bit less: at least half as often as before injury</i>	(1)	$\theta$
6. <i>Participate much less: less than half as often</i>	(2)	$\theta$
7. <i>Unable to participate: rarely, if ever, take part</i>	(3)	$\theta$

6c. *Did the patient engage in regular social and leisure activities outside the home before the injury?*  $\theta Y(1) \theta N(0)$

**Family & Friendships**

7a. *Have their been psychological problems which have resulted in ongoing family disruption or disruption to friendships?*  $\theta Y(1) \theta N(0)$  (GOS, N=GR)

*Typical post-traumatic personality changes: quick temper, irritability, anxiety, insensitivity to others, mood swings, depression, and unreasonable childish behavior.*

7b. *What has been the extent of the disruption or strain? (GOSE, a= lower GR, b= upper MD, c= lower MD)*

a) <i>Occasional-less than weekly</i>	(1)	$\theta$
b) <i>Frequent- once a week or more, but tolerable</i>	(2)	$\theta$
c) <i>Constant-daily and intolerable</i>	(3)	$\theta$

7c. *Were there problems with family or friends before the injury?*  $\theta Y(1) \theta N(0)$

*If there were some problems, but the problems have become markedly worse since the injury then the answer should be No.*

## Return to Normal Life

- 8a. *Are there any other current problems relating to the injury that affect daily life?*  
 $\theta Y(1) \theta N(0)$  (GOSE, Y= lower GR, N= upper GR)

*Other typical problems reported after head injury include: headaches, dizziness, tiredness, sensitivity to noise/light, slowness, memory failures, and concentration problems.*

- 8b. *Were similar problems present before the injury?*  $\theta Y(1) \theta N(0)$

*If there were some problems, but the problems have become markedly worse since the injury then the answer should be No.*

9. *What do you feel has had the greatest impact on outcome following this injury?*
- a. *effects of the head injury (1)*  $\theta$
  - b. *effects of the injury to another part of the body (2)*  $\theta$
  - c. *a combination of these (3)*  $\theta$

### **Scoring**

**GOS:** The overall rating is based on the lowest outcome category indicated

1. dead
2. vegetative state (VS)
3. severe disability (SD)
4. moderate disability (MD)
5. good recovery (GR)

**GOS-extended:** The overall rating is based on the lowest outcome category indicated:

- 1 dead
- 2 vegetative state (VS)
- 3 lower severe disability (Lower SD)
- 4 upper severe disability (Upper SD)
- 5 lower moderate disability (Lower MD)
- 6 upper moderate disability (Upper MD)
- 7 lower good recovery (Lower GR)
- 8 upper good recovery (Upper GR)

**DRS:** *Score is based upon point total*

<u># points</u>	<u>Level of disability</u>
0	None
1	Mild
2-3	Partial
4-6	Moderate
7-11	Moderately Severe
12-16	Severe
17-21	Extremely severe
22-24	Vegetative state
25-29	Extreme vegetative state
30	Death

\*Interview adapted from Wilson et al, J Neurotrauma 1998 and Rappaport et al, Arch Phys Med Rehabil, 1982

### C. Schedule of Events for HSD Study

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	14,21	Day 28	Follow up
Randomization	X										
Demographics/History	X										
MODSscore	X	A	A	A	A	A	A	A	A	A	
Physical exam	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	
	X										
<b>Blood tests:</b>	X										
Electrolytes	X	A	A	A	A	A	A	A	A	A	
Creatinine	X	A	A	A	A	A	A	A	A	A	
BUN	X	A	A	A	A	A	A	A	A	A	
CBC, plts	X	A	A	A	A	A	A	A	A	A	
ABG	X	A	A	A	A	A	A	A	A	A	
HCG (f)	X										
<b>Medications:</b>	X										
Fluid therapy*	X	X	X	X	X	X	X	X			
I/O 24 hrs	X	X	X	X	X	X	X	X			
<b>Other:</b>	X										
Glascow Coma Score	X										
Chest X-ray	X	A	A	A	A	A	A	A	A	A	
Specimen collection +	X+	X+		X+					X+		
Study Completion										X	
For brain Injured Subjects Questionnaireα										X	X

\* Fluid Therapy: Blood products, colloids, crystalloid

+Specimen Collection: 30cc of whole blood in a citrate anticoagulation to be drawn at:

06-12 hours of injury (day 0)

24-36 hours of injury (day1)

Between days 3-5

Between days 7-9

αStructured Interview for Outcome Following Traumatic Brain Injury 6 month /1 year evaluation

X = required by protocol

A = record if available