

2008-05-10 Version 4

# **HYPERTONIC RESUSCITATION FOLLOWING TRAUMA**

## **MANUAL OF OPERATIONS**

## TABLE OF CONTENTS

SUMMARY .....	3
BACKGROUND .....	3
RESEARCH DESIGN.....	4
INCLUSION AND EXCLUSION CRITERIA.....	5
STUDY OUTCOME MEASURES.....	6
Primary outcome measure.....	6
Secondary outcome measures .....	6
SCREENING.....	7
CONSENT.....	7
Informed consent.....	7
ADMINISTRATION OF STUDY DRUG AND DURATION OF INTERVENTION .....	8
Storage and tracking of study fluids.....	8
Blinding and Randomization .....	8
UNBLINDING.....	9
STANDARDIZATION OF CARE .....	12
Pre-hospital Care.....	12
In-hospital Care .....	12
SITE MONITORING.....	13
SAFETY AND MONITORING .....	14
Randomization.....	14
Randomization of ineligible subjects.....	14
Non-adherence.....	14
Protocol violation/deviations .....	14
Definitions of Adverse Events.....	15
Serious Adverse Events .....	15
Procedures for Reporting Adverse Events.....	16
REGULATORY ISSUES .....	18
IRB/REB .....	18
Federal Wide Assurance (FWA).....	19
Office of Human Research Protection (OHRP).....	19
Investigational New Drug (IND) .....	19
Human subjects research training .....	19
List of Acronyms.....	20
DATA COLLECTION.....	22
Confidentiality and Privacy .....	22
Duration of Study.....	22
Source of Data Collection.....	22
Baseline Assessments.....	22
Study Patient Oversight during Hospitalization.....	23
Summary of Hospital Data Collection .....	24
Serum Sodium Monitoring .....	24
QA assessments.....	25
Follow-up assessments .....	25
TBI follow-up.....	25
ROC Web-data transmission.....	26
Web-Entry Setup .....	26

Electronic Signature Agreement .....	26
Accessing Data Forms.....	27
Web-data Entry and Navigation.....	27
CTC Request System.....	36
Data Collection Forms.....	38
Hypertonic Resuscitation Schedule of Case Report Forms Collection.....	39
Patient Enrollment Form.....	41
Pre-Hospital Time Record.....	45
Pre-Hospital Form.....	47
ED Admit Form.....	51
Resuscitation /Injury Characteristics .....	55
ICU Form.....	57
Neurologic Function/TBI Management Form.....	61
Care Guidelines .....	63
Hospitalization form.....	65
Alert CTC Form.....	71
Pt/Family Consent Form.....	73
Patient Information Form.....	75
First Follow-up Form .....	77
6 month Follow-up Form .....	79
TBI Outcome Interview Form .....	81
QUICK REFERENCE.....	89
Adverse Events .....	89
Potential Serious Adverse Events (SAEs) in the HS study.....	90
ALI/ARDS definitions.....	91
Predicted Body Weight (PBW) calculations.....	91
Base Deficit Calculations.....	92
Infectious and non-infectious complications tracked in the data forms defined .....	93
Injury scoring systems: AIS, NISS and TRISS.....	97
Normal Lab Values .....	101
Care Guidelines .....	103
Summary of HS Care Guidelines, March 7, 2006.....	103
Glue Grant Guidelines:.....	107
TR1: Clinical Protocol for Trauma Resuscitation .....	107
TR2: Clinical Protocol for Mechanical Ventilation .....	111
TR3: Clinical Protocol for the Prevention, Diagnosis and Treatment of Ventilator-Associated Pneumonia .....	119
TR4: Insulin Infusion Orders.....	123
TR5: Transfusion Guidelines for Trauma Patient.....	125
TR6: VTE prophylaxis Algorithm.....	127
TR7: Sedation Protocol     Draft (07/12/04).....	129
Guidelines for Management of Traumatic Brain Injury.....	131
Attachment A.....	133
Attachment B.....	135
Attachment C .....	137

## **SUMMARY**

This study simultaneously conducts two multicenter trials of hypertonic resuscitation in two populations of trauma patients using the same intervention and infrastructure. Study 1 seeks to determine the impact of hypertonic resuscitation on survival for blunt or penetrating trauma patients in hypovolemic shock. Study 2 seeks to determine the impact of hypertonic resuscitation on long term (6 month) neurologic outcome for blunt trauma patients with severe traumatic brain injury. Both studies will be three arm, randomized, blinded intervention trials comparing hypertonic saline/ dextran (7.5% saline/6% dextran 70, HSD), hypertonic saline alone (7.5% saline, HS), and normal saline (NS) as the initial resuscitation fluid administered to these patients in the prehospital setting.

## **BACKGROUND**

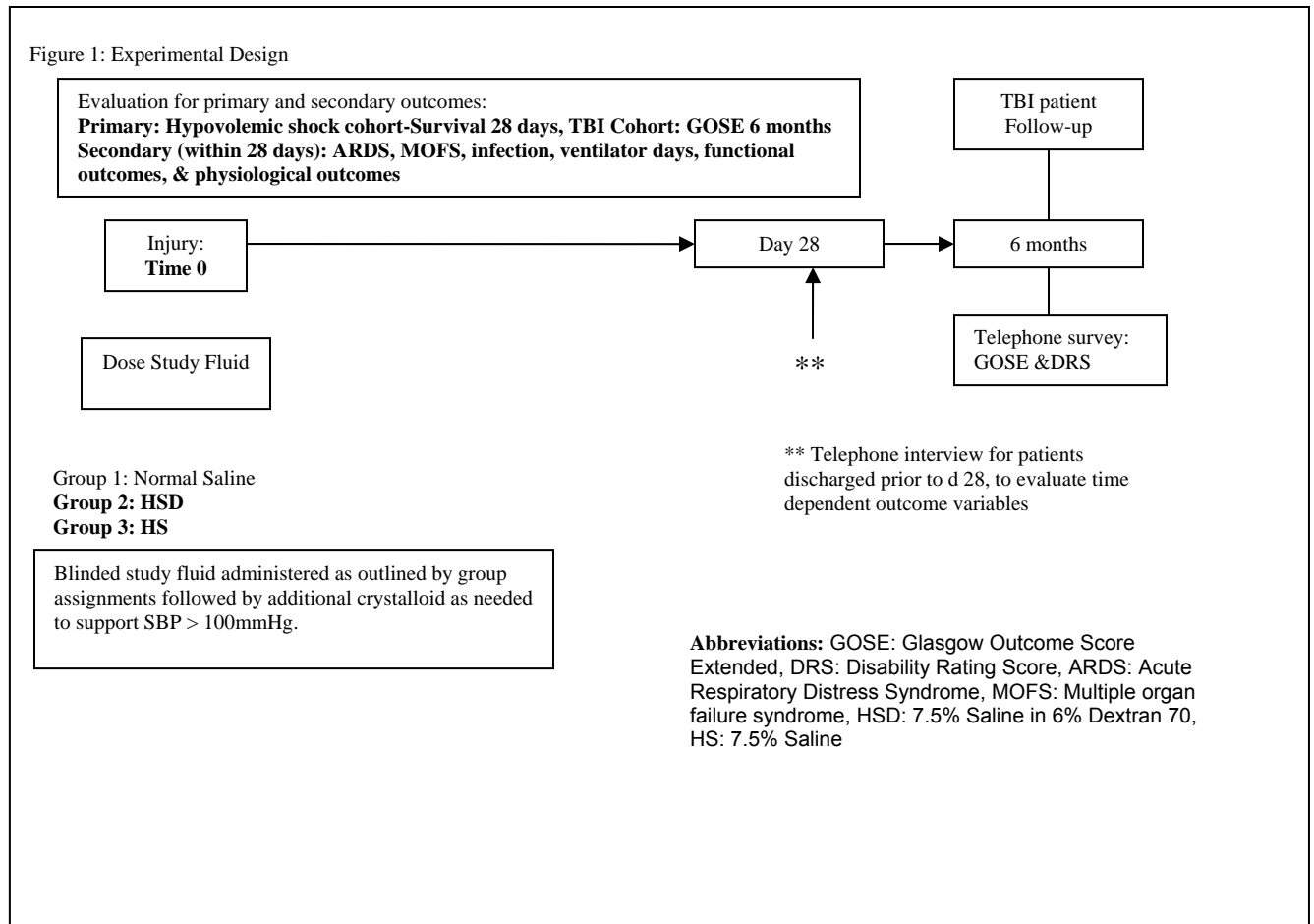
Trauma is the leading cause of death among North Americans between the ages of 1 and 44 years. The majority of these deaths result from hypovolemic shock or severe brain injury. Patients in hypovolemic shock develop a state of systemic tissue ischemia with a subsequent reperfusion injury at the time of fluid resuscitation. Conventional resuscitation involves the intravenous (IV) administration of a large volume of isotonic (normal saline, NS) 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. 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 (prehospital SBP $\leq$ 90) 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.

This study will be conducted by the Resuscitation Outcomes Consortium (ROC). This is a consortium of 10 clinical centers in the United States and Canada along with a Data Coordinating Center, which is tasked with conducting prehospital clinical trials for cardiac arrest and life threatening trauma.

## RESEARCH DESIGN

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 normal saline (250cc) as the initial fluid for prehospital resuscitation. The study design is illustrated in Figure 1.



## **INCLUSION AND EXCLUSION CRITERIA**

### **Inclusion Criteria**

#### Hypovolemic Shock Cohort

1. Blunt or Penetrating Trauma
2. Prehospital SBP  $\leq$  70 OR  
Prehospital SBP 71-90 AND HR  $\geq$  108
3. Age  $\geq$ 15yrs or  $\geq$ 50kg\*\*

#### TBI Cohort

1. Blunt trauma
2. Prehospital GCS  $\leq$ 8\*
3. Age  $\geq$ 15yrs or  $\geq$ 50kg\*\*

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

\*\*Field criteria of "greater than 50kg" may be used as an equivalence for age  $\geq$ 15yrs when age unknown.

### **Exclusion criteria (both cohorts)**

- 1) Known or suspected pregnancy
- 2) Age  $<$ 15 or  $<$ 50kgs if age unknown
- 3) Ongoing prehospital Cardiopulmonary Resuscitation (CPR)
- 4) Administration of  $>$  2000cc crystalloid or any amount of colloid or blood products or Mannitol
- 5) Severe hypothermia (suspected T  $<$ 28C)
- 6) Drowning or asphyxia due to hanging
- 7) Burns TBSA  $>$  20%
- 8) Isolated penetrating injury to the head
- 9) Inability to obtain prehospital intravenous access
- 10) Time of call received at dispatch to study intervention  $>$  4 hours
- 11) Known prisoners

## **STUDY OUTCOME MEASURES**

### **Primary outcome measure**

#### **Hypovolemic Shock Cohort**

- 28 day survival

#### **Severe TBI Cohort**

- Neurologic outcome: GOSE 6 months after injury

### **Secondary outcome measures**

#### **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

#### **Severe TBI Cohort**

Additional neurological outcomes:

- Disability Rating Score (Discharge & 6 months)
- GOSE at discharge
- 28 day survival

## **SCREENING**

All patients who have suffered blunt or penetrating trauma will be screened at the scene of injury by prehospital providers. Those who are identified as meeting entry criteria will receive study fluid. (See inclusion and exclusion criteria above).

## **CONSENT**

### **Informed consent**

This study qualifies for the “Exception from informed consent required for emergency research” outlined in FDA regulation 21CFR50.24 (Attachment A). The study fluid needs to be administered as the first resuscitation fluid following traumatic injury. These patients will be identified at the scene of injury and enrolled by the prehospital providers. 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 exception from informed consent a viable option to enable a study to answer these important clinical questions. 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 potential intoxication with sedating drugs or alcohol. 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. Attempts to obtain informed consent will be made when either the subject is able to provide consent, or their legally authorized representative (LAR) is available. If subjects or their LAR deny consent, then no further data will be collected. 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.

We expect that children ages 15 to 21 years will achieve the same potential benefits from this resuscitation strategy as adults. This is an age range that has a high incidence of traumatic injury and thus we anticipate a significant number of these children to be enrolled. Parental consent and child assent will be obtained for those under age 18 years to remain in the trial.



## **ADMINISTRATION OF STUDY DRUG AND DURATION OF INTERVENTION**

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.

### **Storage and tracking of study fluids**

Study fluids are to be stored in a secure environment where they will not be exposed to extremes of temperature. Only authorized individuals are allowed to access and dispense drugs to study subjects. Proper distribution and tracking of study drug use in study patients is essential in maintaining the integrity of a trial. Procedures for disposition of study drug (destruction or return to distribution center), due to end of study or expired drug lots, must comply with institutional study requirements. Accountability and storage requirements for all drugs must be followed.

Allocation and tracking logs should be kept for each base station that has study fluid. Inventory checks will be performed quarterly at the RCC and base stations levels. More frequent inventory checks and reconciliation may be advisable in sites that have wide distribution of the study fluids. As part of notification of randomization, EMS personnel should return the empty bags of fluid to the ED where they admit a patient if possible. The coordinator (or designee) will collect them and collate to inventory.

### **Blinding and Randomization**

The study fluids will be provided commercially from Biophasia Inc, Sweden. This company currently manufactures HSD and markets it in Europe as Rescue flow™. 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 tracked by the distribution center. The distribution center will ship study fluid bags to each RCC in variable size blocks to maintain sequential balance of the treatment arms within sites over time. This means that the bags sent to the clinical sites are "pre-randomized". Some sites may have more than one division for assigning randomized bags (e.g. North, South, East, West or Main, Outer etc.) Bags should not be mingled between these randomization divisions, i.e. bags designated for "north" should not be sent to "south", "east" or "west".

Bags will be placed at each base station where they can be retrieved by the medic or airlift units. No more than two bags of study fluid should be kept on each ambulance or helicopter. This allows for the possibility of more than one victim being treated per run while controlling for potential inventory losses. Study site personnel will keep allocation and tracking logs for each base station and conduct site visits to confirm inventory status. Pace of enrollment at individual sites will determine frequency with which supplies of study fluids need to be replenished. Sites may want to consider an automatic re-order “threshold”- that low point in inventory supply which would prompt reordering supplies. A 5 business day turn-around time, from order to receipt of additional study fluids, should guide re-ordering plans. Re-ordering study fluid will be done via the CTC request system accessible from the HS data entry area of the ROC web site. Orders are processed during business hours 8 am to 5pm Pacific time.

Each bag will have several stickers denoting its unique identification number and these will be placed on the medic report and Emergency Department (ED) report. 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 155 mEq/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.

## 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 should participate in this process. If the patient is to be unblinded, it would 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 should not be shared with other site personnel.*

An "Alert CTC Form" should be completed for all unblinding requests by the site coordinator. Additionally a brief summary about all unblinding events should be sent to the CTC which should 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.

## STANDARDIZATION OF CARE

### Pre-hospital Care

We recognize the significant variability in EMS systems and the difficulties associated with attempting to standardize care in this arena. We will not regulate prehospital airway management for these patients but will collect detailed prehospital data to determine if this is a potential confounding variable among the different study sites. We encourage the study fluid to be given as the initial resuscitation fluid prior to the start of additional resuscitation fluids; however, we recognize that there are some circumstances where air transport may arrive with the study fluid after an IV has been established. In this circumstance we will allow patient enrollment if less than 2000cc of crystalloid have been given and no blood products or colloids. The control fluid for the study will be normal saline but we will allow subsequent administration of either normal saline or lactated ringers with a goal to maintain the systolic blood pressure greater than 100 mmHg. We will collect detailed data for all prehospital fluid administration in these patients.

### In-hospital Care

In an effort to minimize variability in the subsequent care of trauma patients that could impact outcome, all sites agree to encourage the implementation of resuscitation and critical care management guidelines, which are supported by evidence based medicine. Where no pre-existing guidelines exist in an institution, it is expected that a site will use the following protocols (already developed by the NIH funded, multi-center GLUE grant, which is studying a similar population of trauma patients) as examples of good clinical practice. Glue Grant Guidelines include:

1. Clinical Protocol for Trauma Resuscitation
2. Transfusion Guidelines for the Trauma Patient
3. Insulin Infusion/Blood Glucose Control in the ICU
4. Sedation/Analgesia Protocol for Mechanical Ventilation
5. Mechanical Ventilation Protocol
6. Venous Thromboembolism Prophylaxis guidelines
7. Clinical Protocol for the Prevention, Diagnosis & Treatment of Ventilator Associated Pneumonia
8. Management of Severe Traumatic Brain Injury

Compliance with these guidelines will be monitored. The care guidelines are described in detail in the protocol appendices.

## **SITE MONITORING**

Site monitoring is done to provide a progress report to the CTC and study sponsors regarding the RCC site protocol execution, adherence to study procedures, availability of applicable regulatory documents, data quality, and that the subjects' rights and safety are protected. The CTC will conduct annual site visits at each of the Regional Clinical Centers. On-site monitoring will be performed by a CTC research nurse, coordinator, project director or designee 1-2 times during the course of the study; once during the enrollment phase, and possibly a second time during the follow-up. Re-visits to RCC's will be based on the following situations: those with high enrollment; very low enrollment; protocol adherence issues; those with data inconsistencies; or those with tardy data.

The site visit usually takes between 6-8 hours to conduct and includes time spent with the Coordinator and the PI and time spent in episode chart review of source documentation. Items to be reviewed include:

- Administrative Items (protocol, MOO, IRB approval/consents, CTC/Industry communication)
- Patient enrollment/study progress
- Protocol Issues (enrollment of ineligible subject, excessive exclusions)
- Adverse Events
- Completeness of Data (incomplete compliance, missing or late data)
- Review of patient data forms (compare PCR and hospital records) for eligibility, and individual data points.

After each on-site monitoring visit, a report will be sent (electronically and/or written) to the RCC-PI and RCC-Coordinator citing details of the site visit, findings, conclusions and action plan to correct deficiencies and data discrepancies. Site visit report copies are sent to the sponsor and CTC director. It is the prerogative of the Director to address with the CTC staff and the RCC any issues identified in the report that might interfere with the integrity of the study or the conduct of the trial.

## **SAFETY AND MONITORING**

Sequential monitoring will be used by the Data Safety and Monitoring Board (DSMB). All adverse events will be reported to the DSMB, the FDA and the local IRB.

### **Randomization**

The point of randomization for both cohorts of the study is when the outer wrapper of the study fluid is removed in the presence of a patient. If the wrapper is opened prior to being in the presence of the patient (e.g. on the way to the scene of an emergency) then this is considered a protocol violation and not enrollment of the patient. Once the study fluid is attached to an IV line, the patient is considered to have had study fluid administered.

### **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. Randomization of ineligible subjects will be tracked as a protocol violation on the "Alert CTC" form.

### **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 2 liters of isotonic fluid resuscitation, or any amount of blood products, colloids or Mannitol. In this circumstance, these patients will remain in the intention to treat analysis within their respective groups. Non-adherence will be tracked as a protocol violation.

### **Protocol violation/deviations**

A protocol violation is an alteration from the agreed upon protocol whereas a protocol deviation is not a defined alteration but more a departure from the spirit of the protocol. Protocol violations will be documented on the case report form, as will potential safety issues related to the protocol and any other unusual circumstances. Several violations/deviations are listed.

- Incomplete study fluid administration
- Age obviously < 15 (wt < 50kg) and study fluid administered
- Age obviously < 15 but wt > 50kg and study fluid administered
- Prehospital GCS  $\geq$  9 and HS administered
- Prehospital BP > 90 and HS administered
- Prehospital BP 71-90 and HR < 108 and study fluid administered
- Pregnancy and HS administered
- Ongoing CPR in field prior to study fluid and study fluid administered
- 2000cc fluid prior to study fluid and study fluid administered

Any colloid, blood product or Mannitol given prior to study fluid and study fluid administered

Severe hypothermia (suspected temp < 28 C) and study fluid administered

Trauma due to hanging and study fluid administered

Trauma due to drowning and study fluid administered

Burns TBSA >20% and study fluid administered

Isolated penetrating injury to the head and study fluid administered

Study fluid given by route other than IV

### **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 result 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 or 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 or severe head injury. Adverse events will be considered to be study-related when the event follows a reasonable temporal sequence from administration of the study drug.

### **Serious Adverse Events**

- 1. Any evidence of anaphylactic reaction to HSD**
- 2. Seizure activity associated with hypernatremia**
- 3. Hypernatremia (Na> 160 mEq/L) requiring therapeutic intervention**
- 4. Unexplained coagulopathy**
- 5. Any death not explained by the injury severity**

### **Other Adverse Events**

1. Irritation at the site of infusion
2. Minor allergic reaction, skin rash with no hemodynamic effects
3. Evidence of increased bleeding based on blood and 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 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 and baseline data, the research coordinator 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 24 hours
- b. Coagulation parameters on admission
- c. Amount of blood loss reported in the operating room
- d. Potassium level on admission and presence of any cardiac arrhythmias
- e. All operative procedures performed during the hospital stay

For patients with Traumatic Brain Injury

- a. Results of the first 3 Head CT scans obtained within the first week after injury and the determination of any increased intracranial hemorrhage.
- 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 48 hours after injury
- d. Total amount of Mannitol administered every 12 hours for the first 48 hrs after injury
- e. All reports of seizure activity and anti-convulsant medications administered

The Principal 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 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 recorded on the adverse event case report form.

### **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 local IRB/REB 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.

## REGULATORY ISSUES

No investigational product may be released to a RCC until an IRB/REB has reviewed and approved the clinical study and until the FDA has permitted the investigational use of the product. Once released to the RCC's, all investigational product inventory will be monitored and must be accounted for at all times and handled according to applicable regulations from sponsor/funding agencies and institutional policies.

### IRB/REB

The HS protocol must be reviewed by the Institutional Review Board (IRB) or Review of Ethics Board (REB) at each site and it is up to the local IRB/REB to decide what actions must be taken by the site in order to protect the subjects of the study. Each clinical site must have IRB approval prior to the beginning of subject enrollment, randomization and data collection. The CTC will maintain copies of IRB approvals from each participating site.

- Canadian sites require Ethics Board approval but not necessarily community consultation and disclosure. Patient consent must be obtained for contact after discharge. Additional provincial approval may be required (in British Columbia a Provincial EMS board must also approve any study conducted by the EMS).
- US sites must conduct the study under 21 CFR 50 .45 (See Attachment A) “exception from informed consent requirements for emergency research”, which requires that the community be notified of the study and consulted regarding the study. This may require a site to set up web sites or other platforms for public comment, inform the public of the study by newspaper, radio, and/or TV announcements, etc. agreed upon by their IRB. A resource document to aid Institutional Review Boards with development of community consultation and public notification plans for the Resuscitation Outcomes Consortium has been prepared (See Attachment B). Additional information is located on the FDA website at [http://www.fda.gov/ora/compliance\\_ref/bimo/err\\_guide/htm](http://www.fda.gov/ora/compliance_ref/bimo/err_guide/htm).
- Community Consultation and Public Notification Summary Report: After a US site receives IRB approval, the CTC requires a follow-up report of what community consultation and public notification was done at that site. This should include specific details including descriptions of any feedback received. For community consultation, include the type and number of events, event dates, and attendance figures; for random digit dialing surveys, please indicate total number of calls made, and to what demographic, and the results (i.e. per cent approval); for public notification, include which type of media (print, broadcast, electronic) dates of publication(s) and any available links to news archives or study websites. This report should be on letterhead with the PI signature and will be submitted by the CTC to the UW IRB, the FDA and the NIH.

There are additional requirements for informing patients or their families of participation and requiring consent for further participation.

### **Federal Wide Assurance (FWA)**

Each participating institution (hospitals, EMS systems and the CTC) must have an appropriate assurance on file with the Office for Human Research Protections (OHRP).

### **Office of Human Research Protection (OHRP)**

Prisoner certification is required for all research involving prisoners that is HHS conducted or supported. This trial excludes known prisoners from enrollment. However there will be a certain percentage of those enrolled who become prisoners during the course of the study, and may be incarcerated when follow-up interviews are being conducted. Due to the fact that this study is funded by the Department of Human and Health Services (the parent organization for the NIH), the OHRP requires that IRB and REBs certify that they have reviewed the study and can state that the research will adhere to the applicable U.S. law regarding the involvement of prisoner in research (Title 45 CFR Sections 46.305). The main institutional IRB or REB from each site must submit a certification letter to the OHRP seeking approval of the research. A copy of the OHRP approval letter must be sent to the CTC.

### **Investigational New Drug (IND)**

The CTC will file and hold the INDs for the studies. The IND number for the TBI cohort is 12505 and the IND number for the Shock cohort is 12506.

### **Human subjects research training**

All personnel at each site who will have direct contact with patients (excluding EMS personnel) must complete human subjects research training and provide copies of their certificates of completion to the CTC prior to beginning enrollment. This link may be used to access online training:

<http://www.cancer.gov/clinicaltrials/learning/humanparticipant-protections>

## List of Acronyms

AIS	Abbreviated Injury Score
ALI	Acute Lung Injury
ACLS	Advanced Cardiac Life Support
ATLS	Advanced Trauma Life Support
AMA	Against Medical Advice
ARDS	Acute Respiratory Distress Syndrome
BLS	Basic Life Support
CAD	Coronary Artery Disease
CPP	Cerebral Perfusion Pressure (MAP – CVP)
CPR	Cardio pulmonary Resuscitation
CT	Computerized tomography (CAT scan)
CTC	Clinical Trial Center (see DCC)
CVP	Central Venous Pressure
CXR	Chest x-ray
DCC	Data Coordinating Center (see CTC)
DNAR	Do Not Attempt Resuscitation (also known as DNR/Do Not Resuscitate)
DOA	Dead On Arrival
DRS	Disability Rating Score
DSMB	Data Safety Monitoring Board (aka Data Monitoring Committee or DMC)
DVT	<u>Deep Venous Thrombosis is the formation of a blood clot (“thrombus”) in a deep vein. It commonly affects the leg veins, such as the femoral, popliteal or peroneal veins or the deep veins of the pelvis.</u>
ED	Emergency Department
ESR	Emergency System Responder
ETT	Endo-tracheal tube (or ET tube)
Ex-lap	Exploratory laparotomy (also called an e-lap)
FiO <sub>2</sub>	Percent inhaled oxygen
FFP	Fresh frozen plasma
GCS	Glasgow Coma Score
GOSE	Glasgow Outcome Score – Extended
GSW	Gun shot wound
HR	Heart rate
ICH	Intracranial hemorrhage OR intracranial hypertension
ICP	Intra-cranial pressure
ICU	Intensive Care Unit
IND	<u>Investigational New Drug (a regulatory classification assigned by the U.S. Food and Drug Administration to an unproven drug, allowing its use in approved studies with human patients.</u>
INR	International Normalized Ratio
ISS	Injury Severity Score (derived from the AIS)
LMA	Laryngeal mask airway
LPVS	<u>Lung protective ventilation strategy, a low volume ventilation strategy used in patients with ALI/ARDS to minimize potential damage to the lungs from mechanical ventilation.</u>
MAP	Mean arterial pressure. $MAP = [(2 \times \text{diastolic}) + \text{systolic}] / 3$

MI	Myocardial infarction
MODS	Multiple Organ Dysfunction Score
MOF	Multiple Organ Failure
MVC	Motor vehicle crash (also known as motor vehicle accident/MVA)
PaO <sub>2</sub>	The partial pressure of oxygen in the plasma phase of arterial blood
PAC	Pulmonary Artery Catheter
PCR	Patient Care Report (also called “run report”, “incident report”)
PE	Pulmonary Embolus
PEEP	Positive End Expiratory Pressure
P/F	ratio of PaO <sub>2</sub> to FiO <sub>2</sub>
Plt	Platelets
PNA	Pneumonia
PT	Pro-thrombin time
PTT	Partial thromboplastin time
QOD	Every other day
RBCs	Red blood cells (also called packed red blood cells/PRBCs)
RR	Respiratory rate (breaths per minute)
SaO <sub>2</sub>	Oxygen saturation
SBP	Systolic blood pressure (mm Hg)
TBI	Traumatic Brain Injury
UTI	Urinary Tract Infection
VATS	Videoscopic-assisted Thoracic Surgery
Vt	Tidal Volume
<u>VSA</u>	<u>Vital signs absent</u>
VTE	Venous Thrombo-Embolism

## **DATA COLLECTION**

### **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/REB.

### **Duration of Study**

Subjects will be followed clinically for 28 days or until hospital discharge whichever occurs first. Subjects who remain in the hospital after day 28 will have the date of discharge and total ICU days noted on the hospital form, but no further clinical data collected (e.g. no operative procedures, complications or infections occurring after day 28). Subjects with head injuries will have the TBI Outcome Interview (the combined GOSE/DRS structured interview) administered at discharge, at 1 month post discharge and at 6 months post injury. The six month TBI outcome interview is the primary outcome-every effort should be made to capture this endpoint.

### **Source of Data Collection**

Data will be collected prospectively as patient care progresses. Baseline assessments may include information from the PCR or forms from a transferring facility or transport team. Review of the medical records and results of diagnostic studies should be done routinely as these will also be sources of data. Critically injured patients routinely receive repeated laboratory assessments of the markers of organ dysfunction that will be tracked for the MOD Score.

### **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 research coordinator. Initial data will be collected as soon as possible and includes the following categories:

Demographics- Age, Gender, Race, Ethnicity

Injury characteristics-Injury time, date, mechanism, AIS, ISS scoring

Prehospital care- Time call received, vital signs, volume of fluids administered in the field, transport time and mode of transport, procedures in the field, time of study intervention, length of transport time

Emergency Care – Arrival date and time, initial VS and blood chemistries, interventions

Resuscitation – For the first 24 hours, both types of fluids and amounts given will be monitored as well as resuscitation endpoints and interventions.

It is anticipated that the subject or the legally authorized 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 locating next-of-kin are made.

### **Study Patient Oversight during Hospitalization**

Monitoring of patients following hospitalization is critical to detect expected and unexpected adverse events and address any concerns related to the study intervention. To standardize this across all sites the following patient oversight requirements must be met at every hospital before patient enrollment can begin at that hospital. The components of this plan are as follows:

1. A study coordinator or investigator will be on call 24 hours a day, 7 days a week to begin data collection, implement the sodium monitoring plan as outlined above, and address any concerns from care providers. This coordinator will be notified of enrollment by the EMS provider after arrival at the hospital. The coordinator will also have a 24hr/7day a week backup by a ROC investigator physician from each site.
2. Each hospital accepting patients enrolled in the trial will have a named physician (co-investigator or sub-investigator) on the medical staff responsible for facilitating communication with study personnel and addressing any concerns regarding patient management. In the high volume centers this will usually be a co-investigator and at the low volume centers this person will be a sub-investigator in direct communication with the site PI. The name and contact information for the hospital investigator will be provided to the CTC prior to enrollment in that hospital. These sub-investigators will be listed on the 1572 forms and reported to the FDA.
3. Investigative personnel will assess the patient's clinical status daily after ICU admission for the first 5 days after injury and then if the patient is stable, every other day for the remainder of the ICU stay. This assessment will include a review of the sodium monitoring, screening for potential SAEs, and the current clinical status of the patient consistent with the data collection outlined in the data collection forms (see summary table below). This includes information regarding the initial resuscitation of the patient, ICP monitoring and management, neurologic assessment based on the Glasgow coma score, and adherence to the clinical care guidelines. Should the study coordinator identify any concerns related to the patient's condition or management, he/she will notify the local investigator and PI who will communicate with the treating physician.



### Summary of Hospital Data Collection

Admission & ED Care	Initial Resuscitation 0-24 hours	Intensive Care & TBI Management 1-5 days	Subsequent ICU Care 5-28 days	Outcome 28d to 6months
<ul style="list-style-type: none"> <li>◆ <u>Vital signs</u></li> <li>◆ <u>Temperature</u></li> <li>◆ <u>GCS score</u></li> <li>◆ <u>Electrolytes</u></li> <li>◆ <u>Osmolarity</u></li> <li>◆ <u>Arterial Blood Gas ± lactate</u></li> <li>◆ <u>Hemoglobin</u></li> <li>◆ <u>Coagulation studies</u></li> <li>◆ <u>Ventricular arrhythmias</u></li> <li>◆ <u>Intubation status</u></li> <li>◆ <u>ED procedures</u></li> <li>◆ <u>Angiography</u></li> <li>◆ <u>Adverse Events</u></li> <li>◆ <u>Disposition</u></li> </ul>	<ul style="list-style-type: none"> <li>◆ <u>Type and Quantity of IV fluids</u></li> <li>◆ <u>Blood products transfused</u></li> <li>◆ <u>Highest lactate or worst base deficit</u></li> <li>◆ <u>Q8 hr serum sodium values (ICU pts)</u></li> <li>◆ <u>ICP monitor placement</u></li> <li>◆ <u>Highest ICP, #hrs ICP&gt;25, #hrs CPP&lt;60</u></li> <li>◆ <u>Total grams Mannitol</u></li> <li>◆ <u>GCS score</u></li> <li>◆ <u>Interventions for elevated ICP</u></li> <li>◆ <u>Any seizures</u></li> <li>◆ <u>Adverse Events</u></li> </ul>	<ul style="list-style-type: none"> <li>◆ <u>ARDS/ALI</u></li> <li>◆ <u>MODS score*</u></li> <li>◆ <u>Highest ICP, #hrs ICP&gt;25, #hrs CPP&lt;60</u></li> <li>◆ <u>Total gm Mannitol</u></li> <li>◆ <u>GCS score</u></li> <li>◆ <u>Interventions for elevated ICP</u></li> <li>◆ <u>Any seizure activity</u></li> <li>◆ <u>Results of 1st 3 head CT scans with Marshall score</u></li> <li>◆ <u>All Infections &amp; Non-infectious complications</u></li> <li>◆ <u>All operative procedures</u></li> <li>◆ <u>Compliance with guidelines d3-5: Glucose levels and insulin use</u></li> <li>◆ <u>Lowest Hgb &amp; transfusion rate</u></li> <li>◆ <u>Sedation used for mechanical ventilation</u></li> <li>◆ <u>Type of nutrition</u></li> <li>◆ <u>Adverse Events</u></li> </ul>	<ul style="list-style-type: none"> <li>◆ <u>MODS score QOD</u></li> <li>◆ <u>ARDS/ALI</u></li> <li>◆ <u>All Infections &amp; Non-infectious complications</u></li> <li>◆ <u>All operative procedures</u></li> <li>◆ <u>Duration of ventilation and ICU stay</u></li> <li>◆ <u>Adverse Events</u></li> </ul>	<ul style="list-style-type: none"> <li>◆ <u>TBI outcome interview prior to discharge, 1 month after discharge and 6 months after injury</u></li> <li>◆ <u>Survival follow-up to 28 days after injury</u></li> </ul>

\*MODS score includes QOD review of platelet count, creatinine, bilirubin, GCS score, CVP, use of pressors, vital signs, oxygenation.

### Serum Sodium Monitoring

All hospitals are required to obtain, at a minimum, serum sodium values upon admission to the hospital and every 8 hours for the first 24 hours for all patients requiring ICU admission. (Allowing for some variability in lab draws, this means that all ICU patients should have 4 serum sodiums drawn in the 26 hours following ED admission, with no lab values being drawn more than 10 hours apart.) Patients with minor injuries that do not require ICU admission will not be subject to q8 hour monitoring. When q8 hour sodium values are not considered standard of care by the hospital provider, the ROC will incur the cost of these laboratory studies. Additionally, any patients who receive treatment for intracranial hypertension (e.g. Mannitol or 3% saline drips) will have serum

sodium values monitored every 6 hours during such treatment and once more 6 hours after the treatment is halted. The CTC will monitor compliance with sodium monitoring.

### **QA assessments**

Run records, trauma admissions and ED deaths should be tracked to identify any patients meeting the entry criteria but not enrolled. This will identify personnel with educational needs or opportunities for information updates and reminders about the study.

The care guidelines recommended in the study protocol will be monitored via sampled data points included in the data collection forms. (Imbedded in the “Respiratory” and “Cardiovascular Failure” forms; the “Other Organ Failure” form and in the “Care Guidelines” form.)

Real-time checks and balances will occur as data is entered using software programming with defined data parameters. Source documents will be reviewed during annual site visits to assess for accuracy in collecting and reporting data.

### **Follow-up assessments**

All patients who are discharged prior to day 28 will require a follow up phone call after day 28 to assess for survival data, and any complications (such as infections) that may have occurred since discharge.

### **TBI follow-up**

To obtain meaningful outcome data for this study, we need nearly complete 6 month follow-up for the TBI cohort. To facilitate this, the coordinator’s will use a detailed contact list collected from the patient prior to discharge and a log for tracking follow-up attempts. Study coordinators are encouraged to establish a relationship with the patient and family while in the hospital which will enhance 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 not possible despite our efforts. We also will initiate telephone contact at 1 month post discharge to complete a one-month TBI outcome interview and firm up commitment for the 6 month TBI interview.

For follow-up on long-term neurologic outcomes, the Glasgow Outcome Score-Extended (GOSE) and Disability Rating Score (DRS) will be assessed at the time of hospital discharge, one month from discharge and 6 months after injury. Whenever possible, the survey will be administered by the same trained interviewer, to avoid problems with inter-rater variability. 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.

## ROC Web-data transmission

### Web-Entry Setup

A new user who wants access into the data entry area of the ROC web site should do the following:

1. Register for access to the main ROC web site. Be sure that **all** of the entries are completed, especially the person's name and e-mail address (crucial if this person will be entering data on the web forms).
  - The CTC will verify with the site Principal Investigator and Main Coordinator that it is OK to provide access for the new person.
  - The Main Coordinator will add this person to the Contact Directory, which is accessed through the internal ROC web link listed on the left navigation column (username: resus, password: call911).
2. The Main Coordinator will then have the person complete the Electronic Signature Agreement found in the Data Entry area of the web site. See below for more information about electronic signatures.
  - Fax this form to the CTC at 206-543-0131, attention Umberto Lenzi, or
  - Scan and e-mail as a PDF file to Umberto at [ulenzi@u.washington.edu](mailto:ulenzi@u.washington.edu).  
Indicate what protocols this person will be allowed to access (EMS Structures, Epistry, Hypertonic Saline, or PRIMED protocols).
3. The Main Coordinator will then provide the person with a copy of the Web-Entry Instructions to review. The Web-Entry Instructions can be found in the Data Entry area at <https://roc.uwctc.org/tiki/roc-data-entry>.
4. The new person will receive an e-mail from Umberto Lenzi ([ulenzi@u.washington.edu](mailto:ulenzi@u.washington.edu)) at the CTC with instructions to take the data entry evaluation. The 'Web Entry Instructions' may be referenced during this exercise.  
After the above steps are completed, the CTC will then allow access to the data entry area.

### Electronic Signature Agreement

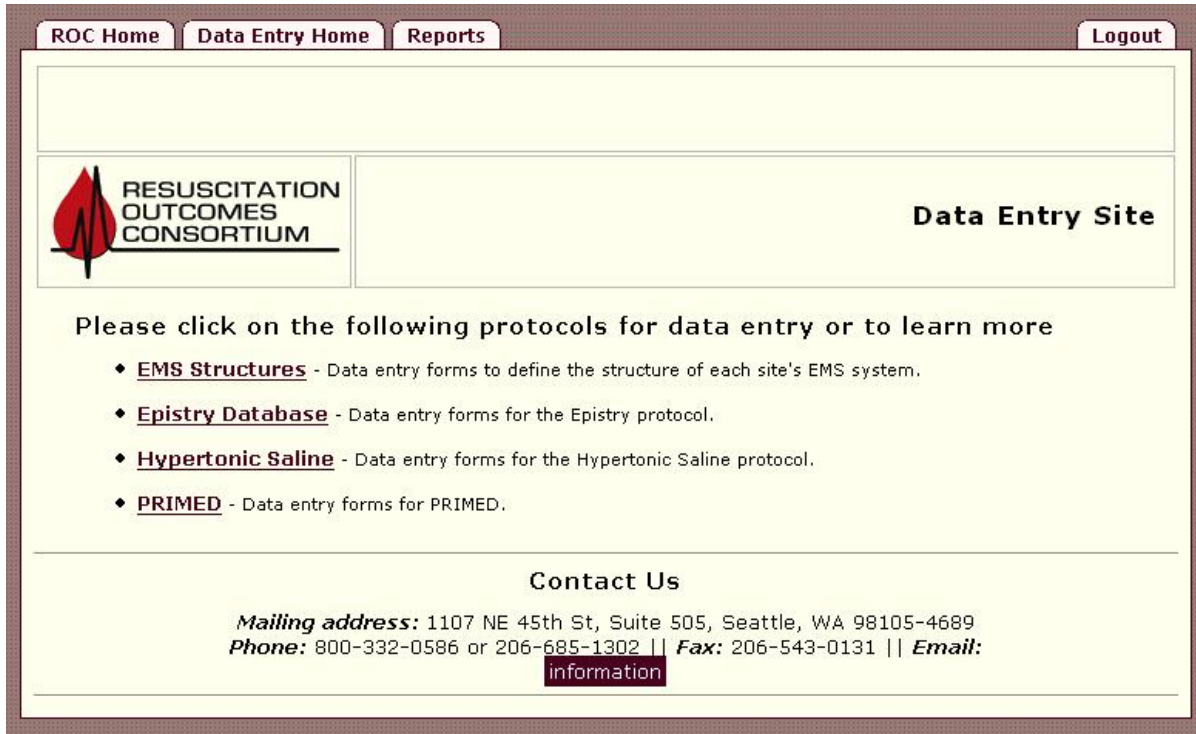
Before data can be submitted via the web, each ROC member must complete an Electronic Signature Agreement. This form can be found on the Data Entry main page at the ROC web site (<https://roc.uwctc.org/>). A signed copy of the Electronic Signature Agreement must be submitted to the CTC. This agreement stipulates that the use of your username and password to participate in ROC web-data transmission constitutes your signature on any document transmitted electronically. The electronic signature is considered equivalent to a handwritten signature.

The electronic signature is composed of a username and password, which were established during registration to the ROC web site. The username and password should be kept confidential and not shared by other site members.

## Accessing Data Forms

1. Data forms for all protocols can be accessed via the ROC web site. To access data forms:
2. Go to the ROC web site (<https://roc.uwctc.org/>).
3. Enter your user name and password.
4. Click 'Data Entry' on the left navigation bar.
5. Click 'Continue to Data Entry.'

Choose protocol of interest on the ROC data entry menu page as depicted below:



## Web-data Entry and Navigation

**Entering a new episode.** Click 'New Episode' and then fill out the PATIENT ENROLLMENT FORM. Several key data fields are required for the database to accept the form. These are:

- date of episode
- time call received at dispatch
- source of the time information
- HS study fluid bag number

The Episode ID is assigned after the form is successfully submitted. The Episode Information at the top of the form will be pre-filled on all other forms that are required for an episode.

**Person responsible for data.** The name of the ROC member who initiates the entry of data on a form automatically appears at the bottom of the form. This person is

responsible for the data. This name will remain unchanged on the form even if another ROC member reloads the form to edit the data or supplies missing information. The names of the ROC members who edit data on existing forms will be stored in the database.

**Navigating data fields.** To navigate between questions on the form, use the mouse or the keyboard (the TAB key will navigate forward and Shift-TAB will navigate backward). More instructions on using the keyboard to navigate and fill out forms can be found in 'Keyboard Shortcuts,' in the instructions section of Data Entry.

**Types of data fields.** There are four main types of data-input fields on the data forms.

**Text Boxes:**

The first type of data field is the text box, which requires the entry of characters into a box.

- **Example 1.** The format and type of characters that should be entered are specified in parentheses:

Time call received at dispatch (24hr clock)  
[ ] : [ ] : [ ] (hh:mm:ss)

- **Example 2.** The maximum number of characters that can be entered is specified in parentheses:

specify: [ ] (30)

A combination of numbers, letters and certain special characters may be entered in this text box. The following special characters are allowed: plus sign (+), minus sign (-), comma (,), period (.), pound (#), and apostrophe ('). All other special characters, including the carriage return (ENTER key), are not allowed.

**Drop-Down Boxes:**

The second type of data field is the drop-down box, which lists all the available responses:

Arriving Vehicle	Agency Name	Vehicle Name
1	[ ]	[ ]
2	[ ]	[ ]

To view the response options, click on the down arrow in the drop-down box. This will activate the drop-down box and display the response options. Once the options are displayed, click the desired response.

**IMPORTANT!** To move to the next question, use the TAB key. Avoid using the mouse wheel or arrow keys while in the drop-down box because they will alter your selection.

**Radio Buttons:**

The third type of data field is the radio-button choice field, where you must select the button that corresponds to your choice:

Service Level			
BLS	BLS-D	BLS+	ALS
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

To select an answer, click the desired radio button. Only one button may be selected for each radio-button question. Once an answer has been selected, it is possible to de-select that answer by clicking a different button in that field.

**IMPORTANT!** There are two ways to undo the mark on a radio button:

- Click on the marked radio button and press the DELETE key, or
- Double-click on the marked radio button.

**Check Boxes:**

The fourth type of data field is the check-box field, which allows multiple answers for one question:

<input type="checkbox"/>	Hispanic or Latino
<input type="checkbox"/>	White
<input type="checkbox"/>	African-American/Black
<input type="checkbox"/>	American-Indian/Alaska Native

**Searching for an existing episode.** On the main page of a protocol, search for an existing episode by typing the Episode ID. It is not necessary to type the leading zeros or all the digits of the Episode ID of interest. The resulting list will display all IDs that contain the string of digits typed (such as '45' in the following example). From the list, choose the correct episode and then click 'Find Episode.'

**Enter data for an existing episode:**

*To find the episode in the box below, begin typing an episode ID or date. Then click the button to display the episode details.*

CTC-

004507-1	Date: 04-28-2006 23:23:23
004509-8	Date: 04-28-2006 23:23:23
004549-7	Date: 04-12-2006 11:11
004584-5	Date: 02-15-2006 08:20:22

05, Seattle, WA 98105-4689

**Episode list.** To get to this list, click the 'Episode List' tab above any form. This list shows all the episodes for a site and the status of all the forms for each episode. Sorting can be applied on all the columns by clicking on the gray bar below the column names. The direction of the arrows on the gray bar indicate whether a column is sorted

in ascending (△) or descending (▽) order. Note: Clicking on these arrows will sort only the episodes currently displayed on the page. To sort **all** episodes, the 'Filter/sort Selections' function described below must be used.

Row	Episode ID	Date of episode	Time	Date episode entered	Site-linking ID	Cardiac Trauma	Patient Enrollment	Pre-hospital time record	Pre-hospital data	CPR Process	ECG Uploads	ED/hospital admit	Trauma Ventilation
1	<a href="#">CTC-036158-5</a>	04-03-2007	21:10	06-01-2007		Trauma	C	R	R	-		?*	?
2	<a href="#">CTC-035885-1</a>	04-25-2007	20:15	05-22-2007		Trauma	C	R	R	-		?*	?
3	<a href="#">CTC-035882-7</a>	04-10-2007	05:20	05-21-2007		Trauma	C	R	R	-		?*	?
4	<a href="#">CTC-035718-9</a>	05-10-2007	07:07:07	05-15-2007		Cardiac	E	R	E	R		R	-
5	<a href="#">CTC-035717-0</a>	08-12-2006	21:05	05-15-2007		Trauma	E	R	E	-		E	?
6	<a href="#">CTC-035716-2</a>	03-18-2007	12:13:13	05-15-2007		Trauma	E	R	R	-		?*	?
7	<a href="#">CTC-035715-4</a>	03-17-2007	12:01:02	05-15-2007		Cardiac	E	E	E	E	0/?	E	-
8	<a href="#">CTC-035714-6</a>	03-01-2007	12:12:12	05-14-2007		Cardiac	C	R	R	E	0/2	P	-
9	<a href="#">CTC-035713-8</a>	04-30-2007	20:20	05-14-2007		Trauma	C	C	C	-		C	E
10	<a href="#">CTC-035711-1</a>	04-25-2007	02:50	05-14-2007		Cardiac	C	E	E	E	0/2	E	-

To go to a particular form, click the status code (e.g. C, R, E) for that form. To go to the episode summary for a particular episode, click on the Episode ID.

**Filter/Sort Selections.** Filtering and sorting the cases list allows for selecting cases based on a number of different variables. On the Episode List, click 'Filter/sort Selections' and a variety of choices will become available. The filters can be combined (e.g. allowing you to sort for episodes between certain dates that are in a given cohort that have patient enrollment forms designated 'C', and then sort those by date/time of episode, etc.):

- **Sort** a column by clicking on the gray bar below the heading.
- This grid displays the forms required for each episode and their status codes:
  - Click on a status code to go to the form details page
  - **C** = form was submitted without errors.
  - **R** = form is required and has not been submitted.
  - **?** = form may be required and has not been filled out yet.
  - **O** = form is optional and has not been filled out yet.
  - **E** = form was submitted with errors.
  - **P** = form was filled out already but is no longer required based on data from other forms. Please contact CTC
  - **?**\* = form may be needed in the future but currently it is not needed so you cannot access this form. Form will
  - **-** = form is not available as it is not required and thus cannot be accessed by coordinators.

**Filter/sort Selections**

---

**SELECT EPISODE SETTINGS**

Number of episodes per page:  (Be aware that a larger page takes longer to load and traverse.)

**FILTERS:**

Episode Date: Start  /  /  End  /  /  (mm/dd/yyyy)

Site-linking keyword:

Cohort:  All  Cardiac  Trauma

Status codes: Set all to

All	C	R	E	P	F	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Patient Enrollment
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Pre-hospital time record
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Pre-hospital data
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CPR Process
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	ED/ hospital admit
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Trauma Ventilation

RESULTS SORT:   Descending  Ascending

javascript;

- **Number of episodes per page:** To limit the number of records displayed on each page, change this setting. Larger numbers of episodes per page take longer to load and sort through.
- **Episode Date:** This function limits the number of records shown based on the Episode Date as listed in the Patient Enrollment form.
- **Site-linking keyword:** To search for site-linking keywords that contain certain letter or number combinations, use this function. A search for “Ma” will return all results that include “Ma,” such as “Mary” and “May.”
- **Cohort:** For protocols where patients are divided into cohorts, this function will separate the records so that the records for each cohort can be viewed independently.
- **Status Codes:** Selecting a status code allow only the records that meet that criteria to be included. For example, selecting a ‘C’ for Patient Enrollment will pull only the records that have a complete, correct Patient Enrollment form. Be aware that selecting ‘C’ and ‘R’ for Patient Enrollment will include all records that have EITHER a ‘C’ or an ‘R’ status on that form. Following the same logic, selecting a ‘C’ for Patient Enrollment and an ‘R’



for Pre-hospital Data will retrieve all cases that meet either of those criteria, not both of those criteria.

- **Results Sort:**
  - Date/time of episode: Sorts by the date of the episode, descending (present to past) or ascending (past to present).
    - Date of episode entry: Sorts by the date of when the episode was entered into the system, descending (present to past) or ascending (past to present).
    - Site-linking ID: Sorts by any included site-linking ID, either descending (Z-A) or ascending (A-Z).
    - Episode ID: Sorts by individual episode ID in numerical order, descending or ascending.

**Episode Summary.** This page shows the status of each form for an episode.

- The status codes are indicated in parentheses (see Status Codes Table for definitions of the different codes).
- To load a submitted form, click ‘Confirmation Page’ in the ‘Printable Page’ column.
- To load a form that is currently required, click ‘Custom WorkSheet’ in the ‘Printable Page’ column.
- To print a PDF of a form that is not yet required but may be needed in the future, click ‘WorkSheet’ in the ‘Printable Page’ column.
- ‘Date episode entered’ is the date the PATIENT ENROLLMENT FORM was initially submitted.

**Status codes.** Each form on the Episode List is assigned a status code as follows:

<u>Code</u>	<u>Description</u>
<b>C</b>	<b>Form was submitted without errors.</b> The form is complete; data errors that may have appeared at original submission have either been corrected or overridden.
<b>E</b>	<b>Form was submitted with errors.</b> The form is incomplete; data errors should be corrected or overridden as appropriate, for the status code to change to a ‘C.’
<b>R</b>	<b>Form is required but has not been filled out yet.</b> Example: In Epistry, if “Disposition” (question 4) on the Pre-hospital Data Form is marked as “Transported by EMS to ED/hospital,” the status code R will appear in the column for ED/hospital admit (i.e., the ED/hospital Admit Form is required).
<b>?</b>	<b>Form may be required and can be accessed by clicking on it.</b> This allows users to fill out a form before the rules confirming that the form is

<u>Code</u>	<u>Description</u>
	required are triggered. Example: In Hypertonic Saline, as soon as the Patient Enrollment Form is filled out, the ED Admit Form appears with a ‘?’ so it can be filled out before the Pre-hospital Form is submitted. The ED Admit Form turns to R when the Pre-hospital Form is submitted and indicates that the patient made it alive to the ED.
O	<b>Form is optional and has not been filled out yet.</b> The 'O' may appear as a designation for forms that are optional but not necessary.
F (Final)	<b>A blank or incomplete form was closed because no further data is expected.</b> If information becomes available, these forms can be reopened and information added at a later time.
F (Not Done)	<b>Form is required, but no source data is available to complete it.</b> If information becomes available, these forms can be reopened and information added at a later time. Rolling over the ‘F’ with your mouse will reveal whether an ‘F’ form is final or not done.
P	<b>Form was filled out already but is no longer required based on data from other forms. Please contact CTC to delete the form.</b> Example: In Epistry, a patient was originally classified as “Cardiac arrest” on the Patient Enrollment Form (question 2). After reviewing the records, the patient’s classification is changed to “Traumatic injury.” This change will make the CPR Process Form irrelevant (if filled out) and then ‘P’ will appear under the CPR Process column. Contact the CTC to delete the form.
?*	<b>Form may be needed in the future but currently it is not needed so you cannot access this form.</b> Form will be activated and coordinators can access it in the future when it is needed.
-	<b>Form is not available as it is not required</b> and thus cannot be accessed by coordinators.
U	<b>There was an error in calculating the status of this form. Therefore the status is unknown.</b> Resubmit the form. If you continue to have problems, contact the CTC.

These descriptions can also be found at the bottom of both the Episode Summary and the Episode List—clicking on ‘Status code descriptions’ at the top of the Episode List will quickly take you to the bottom of the page.

**Back to list.** To get to the Episode Summary page from a submitted form, click the ‘Back to List’ button which appears at the bottom of each form. Or, click the Episode Summary tab above the form.

**Next Form.** To get to the next available form in a packet of forms for an episode, click ‘Next Form.’ This button appears at the bottom of each form, except on the last form in a packet.

**Help Links.** To obtain instructions on a form question, first move the cursor to the question prompt while in edit mode. This will highlight the question green. Next, click the link to open the help window. The item you clicked on will open a help box from the Manual of Operations. The item in question will be at the top of the box.

4) Device used: (check all that apply)

Phillips Feedback:  On  Off

Zoll

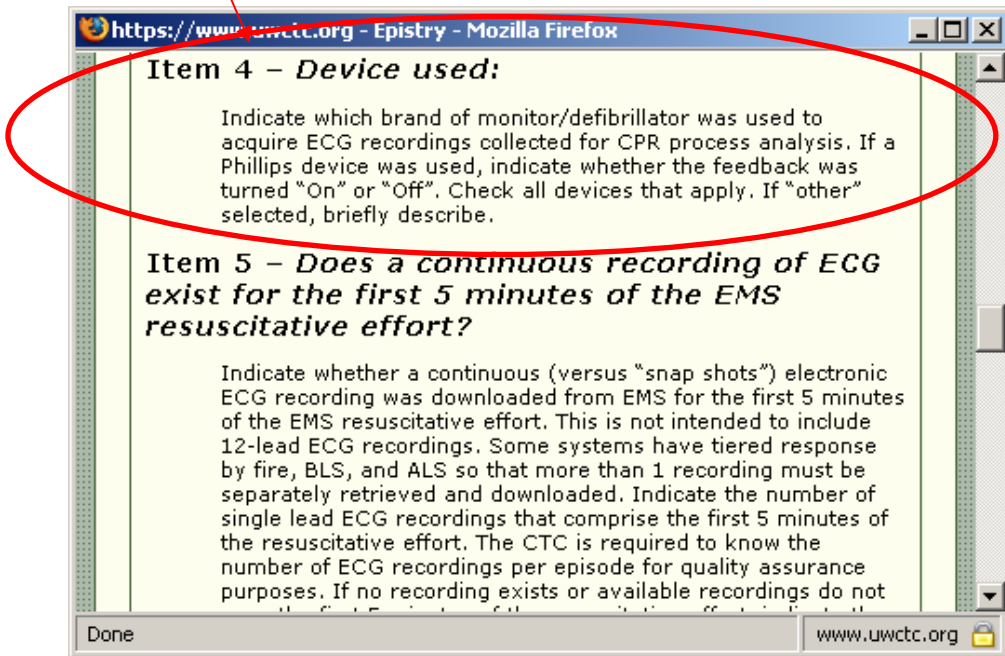
Medtronic

Other, specify:  (30)

5) Does a continuous recording of ECG exist for the first 5 minutes of the EMS resuscitative effort?

Yes → How many recordings make up the first 5 minutes?

No → Why not?



## Submitting and Editing Data

**IMPORTANT!** Before submitting completed forms, review entries for accuracy and completeness.

**Submitting a form.** To initially submit a form, click the 'Add' button, which appears at the end of the form. If there are no data errors, print a hardcopy for your paper records or create a PDF copy for your electronic records.

**Data errors and error overrides.** If data errors exist after initial submission, a list of 'Form Corrections Requested' will appear above the form:

Error messages that involve key data fields, which are critical for data acceptance, are indicated with an exclamation point (!). Review and address

each error message on the list. Certain error messages may be addressed by *overriding the error*. Instances where error messages can be overridden include:

- the value entered in a field is outside the acceptable range, but the value is legitimate

Please direct any questions about overriding error messages to the CTC. If there are error messages that cannot be resolved immediately, the form may be saved with errors (see 'Save' and 'Save with Errors'). Once all errors have been addressed, print a hardcopy for your paper records or create a PDF copy for your electronic records.

**Editing a form.** To edit an existing form, click 'Edit Form.' A 'Form Corrections Requested' list will appear above the form. Review and address each error message on the list.

**Marking a form as not done.** If insufficient data is known, or if no more data is expected, some forms can be marked as 'Not Done.' All information currently in the form is saved but the form is unable to be edited unless the process is reversed with the 'Make Available' button.

**Canceling.** While in edit mode, clicking 'Cancel,' which appears at the end of a form, will discard any corrections to the data. If the form has been saved previously, it will revert back to its prior status. If the form has not been saved, all data will be discarded and you will be returned to the episode summary.

**Save and Save with Errors.** While in edit mode, click 'Save,' which appears at the end of a form, after resolving all error messages. If all the corrections and overrides are accepted, 'Form Corrections Requested' will not appear above the form. Print a hardcopy for your paper records or create a PDF copy for your electronic records.

If an additional 'Form Corrections Requested' list appears:

- Address the error messages and click 'Save,' or
- Click 'Save with Errors' if resolutions to error messages need to be deferred to a later time

Note that any information entered has not been completely saved, whether saving with or without errors, until 'Confirmation Page' appears at the top of the form.

**Deleting an episode.** Please use the CTC Request System to delete an episode.

## Reports

Click the 'Reports' tab to display reports (e.g. Error Report, Cross-form Error).

## Instructions

Click the 'Instructions' tab to display general instructions including Web Entry Instructions and Keyboard Shortcuts as well as more specific instructions for each form.

## Logging Out

To prevent unauthorized use of your ROC username and password, click the 'Logout' tab at the top-right-hand part of the screen. To ensure that all access to the web-data transmission system is terminated, close your web browser.

## CTC Request System

The CTC Request System is available to make requests to the CTC related to the protocols or for general requests. Examples of requests include: deletion of a case or deletion of specific forms related to a case, date or cohort changes, form not done, form close out and ordering of supplies.

To access the system enter the ROC data entry site. Once at the Data Entry Main Menu, click on the tab labeled "Request Home" on the upper part of the page. This is the Request Home page noting the various requests by each protocol and the request status. You can also reach the Request Home tab if you are within the data entry area by clicking on the Request Home tab on the top of the screen.

### Request Home

Each request lists an ID number (basically just a number which notes the order of the requests), a description of the request supplied by the site, date submitted and who at the site made the request. By clicking on the request link the site can view the entire request and add comments to respond to further questions from the CTC.

Once your request has been submitted the status will read "New (waiting for CTC)". When the CTC has additional questions the status will read "Pending (waiting for site)". Requests that are pending require the site to click on the request and reply to the question in the comment box.

The status of each request is on the far right. The CTC will address requests within 3-5 business days of submission. When the status is "Approved", the request has been granted. When the status is "Rejected", the request has not been granted. "Pending" indicates that the CTC has requested further clarification to determine whether to approve or reject the request. "Closed" indicates that the request is no longer being considered (e.g. it may have been entered in error). Once approved or rejected the requested changes are made and no further action can be taken on the request.

### Make a Request

To make a request, start at the "Request Home" page and click "Make Request," which takes you to a page that describes the process for making any request.

- **Form-related Requests**-All form related requests are made within the form itself. Buttons to make the requests are in the upper, right corner of the form. Additionally, once a request has been made, a warning will appear on the form and episode summary page noting that there is an active request for this form. The request can be viewed by clicking on the "View Request" button.
- **Cohort or Date Changes**-Requests to change the cohort or date are made on the Enrollment form. Specify the reason for the change and in the case of a date change enter the correct date (in the correct date format) and submit.
- **Form Specific Requests**-  
*Form Deletion*-Request form deletion if the form was completed in error or the form is in "P" or problem status (for example a treated cardiac arrest case is actually untreated and the CPR Process form is no longer required). Note the reason for the deletion and submit.

*Episode Deletion*-To request deletion of an entire case, go to the Enrollment form for a specific case and click on the “Request Case Deletion” button on the right. Enter the reason for the deletion and submit. If the request is due to a duplicate case, enter the case ID exactly as it appears on the form (e.g. XXX-XXXXXX-X) and the date.

*Form Not Done*-Request form not done if no data can be entered on a form (for example a patient or family requests that all data be deleted from the database).

*Form Close Out (F status)*-Request form close out when all available data has been entered on the form but there is missing data with non-overridable error checks (for example, prehospital disposition is not entered due to a missing PCR or ED/Hospital chart cannot be located).

### **Ordering Hypertonic Saline Study Fluid study fluid**

Each site will have their site-specific distribution divisions already available on this page. Simply enter the number of bags requested for each of the distribution divisions. For example, Air Agency A = 5 bags, North Distribution Point = 10 bags, etc. Remember, bags must stay in the distribution block where assigned to and be given only to those agencies in that division and not be shared between distribution divisions. Sites should allow 5-7 days for shipping from the distribution center.

### **Generic Requests**

Select the protocol needing the request (non-protocol requests can also be made). Describe the request and submit the form. Examples of non-protocol requests might include changes to EMS structures such as rigs moving from one station to another, etc.

### **Refresh List**

This button (on the Request Home page) will refresh the list of requests including any that have been recently submitted while working on this page.

### **Old Requests**

Requests that are completed by being either approved or refused will stay on the main list until they are 14 days old. Older requests are archived on a separate page. Click this button to review old requests.

### **Active Request Indicators**

On the **Episode List**, the right-most column tells sites how many (if any) requests each case has. On the **Episode Summary** page, the right-most column links to any active requests for each form. Also on this page, a warning will be displayed if there is an active episode deletion request for the currently displayed episode. And finally, sites will also see warnings on any form where you have made a request; after making the request, the request button is replaced by a link to the active request.

## Data Collection Forms

Data are received by the CTC directly over a secure internet connection through web-based entry system. Sites log-on through a user name and password verification process. All persons who plan to enter data must complete an electronic signature agreement (see Attachment C). Password protected access is granted by the CTC database manager in consultation with each RCC PI. File and specific page access is controlled by software protocols. Regular data verification is performed by the CTC database manager and the data are also monitored for and protected against any suspicious or inappropriate use.

### Timelines for HS web data entry (by form)

Within **3 days** of episode date:

- Enrollment form

Within **2 weeks** of episode date:

- Pre-hospital Time record
- Pre-hospital form
- ED form
- Care Guidelines

Within **2 weeks of hospital discharge or Day 28** (whichever comes first):

- Neuro function/TBI management form
- ICU form
- Pt/family Consent

Within **2 weeks of hospital discharge**

- Hospital form

Within **2 months of hospital discharge or Day 28** (whichever comes first):

- Resus/injury Characteristics form

Within **one month of “activation date”**:

- First follow-up
  - No sooner than 28 days from episode date for SHOCK
  - 1 month from discharge date for TBI and “Both”
- TBI outcome interview
  - At discharge
  - At 1 month from discharge
  - At 6 months from episode date
- 6 month follow-up
  - No sooner than 180 days from episode date

## Hypertonic Resuscitation Schedule of Case Report Forms Collection

Fill form out on these pts → Name of Form ↓	Baseline (Both TBI & shock pts)	Pts admitted to ED	Pts admitted to ICU	Pts admitted to Hospital	TBI & shock pts d/c'd alive before day 28	TBI Pts only**	TBI Pts Alive at Hospital d/c	CTC Alert ‡
Patient Enrollment	✓							
Pre-hospital Time Record	✓							
Pre-hospital Data	✓							
ED Admit		✓						
Resuscitation / Injury Characteristics	✓							
ICU			✓					
Neuro						✓		
Care Guidelines				✓				
Hospital				✓				
CTC Alert‡								✓
Patient/Family Consent	✓							
Patient Contact Information					✓			
First F/U					✓			
6-Month F/U (from injury)							✓	
TBI Outcome Interview							✓	
EMS Records	✓							
Hospital Records	As requested by CTC							

‡ CTC Alerts are used to report any adverse events, unusual situations, protocol violation/deviation, safety concerns, damaged bags etc.

\*\*Shock only patients with an incidental finding of a positive head CT (Marshall Score >1) on initial work-up will also be required to have a Neuro form completed for safety monitoring purposes, but no TBI follow-up will need to be completed on these pts





## Patient Enrollment Form

Complete this form on any patient who has the outer wrapping of the HS study fluid opened in their presence even if the study fluid is never attached to the IV, no fluid is given or are later determined to be ineligible. All enrollments/episodes should be reported to the CTC within 72 hours. This can be accomplished by entering the minimum amount of data needed to successfully save the form: the date and time of the call received at dispatch and the study fluid bag number.

### **Enrollment, randomization and Intention-to treat patients**

The point of randomization for the study (both cohorts) is when the outer wrapper of the study fluid is removed in the presence of a patient. If the wrapper is opened prior to being in the presence of the patient (e.g. on the way to the scene of an emergency) then this is considered a protocol violation and not enrollment of the patient. Once the study fluid is attached to an IV line the patient is considered to have had study fluid administered. This randomization process is called “intention to treat” and all patients in this situation will have data collected.

Effectiveness population: The primary analysis for both cohorts (TBI and Shock) will be a modified intent to treat analysis which will include all patients who had the study fluid connected to their IV line regardless of how much fluid was administered.

Secondary Intent-to-Treat population: To ensure there is no bias on the part of the enrolling EMS personnel, we will also do a secondary intention to treat analysis, which will include all randomized patients even if the fluid was not administered. Hence, if the wrapper is opened in the presence of the patient, but then is not connected to the IV line, then that patient is considered an intent-to-treat patient. In this circumstance we will collect prehospital and hospital data but no long term (post- hospital discharge) data.

Safety population: Analysis of treatment safety will be conducted on all patients who had the study fluid connected to their IV line. Hence, the safety population is the same as the Effectiveness population.

The CTC will analyze all patient data where the bag was opened as above but this is not the primary analysis. The primary analysis will only include patients where the HS fluid was attached to an IV (even if it appears that none of the fluid was administered). This type of analysis is called “modified intention to treat”.

If the HS fluid bag was opened on the way to the scene of an emergency this is considered a protocol violation, not an enrolled patient.

Opening a study fluid bag in the presence of a patient is considered an episode.

*Episode information* includes the date of episode and the time the call was received at dispatch. If the time the call was received at dispatch varies from the PCR, the time that is recorded by dispatch should be used. To begin an enrollment form you may initially use an estimated “time of call received at dispatch”, but ultimately you should enter the

actual dispatch time. For cases where the first EMS on scene are from a non-ROC agency who then hand off to ROC personnel, the ROC personnel should ask what the time the first responders were dispatched or what the estimated time of injury was. The *Incident Number* is the number that the ESR uses to track an episode. Its use is optional. The site may put the incident number on the form when entering an episode on the web, but this number will not appear on the CTC records.

The Site-Linking ID is an optional number assigned by a site to link multiple data forms (e.g. HS, Epistry) on the same individual. This number will be displayed on the episode list.

The *Episode ID* will be given to the site after the above information plus the study bag number (Item 2) is entered onto the web. The episode ID will be the number used to refer to this subject on all future forms and any communications between the CTC and RCC regarding data forms.

Item 1 – *Agency name that provided the intervention*– Select the agency name and number from the drop down menu. If more than one agency was present at scene, list the agency that gave the intervention, choosing from the drop down menu. Please select the vehicle name from the drop down menu provided.

Item 2 – *Study fluid*:

*2a - Bag number* – The number on the study fluid bag. All opened or empty bags must be returned to the study coordinator or disposed of as directed by the study coordinator. Each bag comes with extra stickers with the bag number for placement on the PCR and hospital record.

*2b – Was fluid given?* If “No” (as in “**Bag-Opened-but-No-fluid-Given**” or “BONG” scenario) complete an Alert CTC form and STOP HERE; if “Yes” complete c and d.

*2c - Amount of study fluid given:* Indicate the milliliters of study fluid given to the patient. A patient who has the study fluid hung in their IV line is considered to have had study fluid administered and at least 1 ml should be listed as given, even if the EMS personnel state the fluid was not running or the IV infiltrated. If the all the fluid was not given (i.e. <250mls) complete an Alert CTC form.

*2d – Where was the fluid started?* Indicate whether the fluid was started in the pre-hospital or ED/Hospital setting. If the fluid was started in the ED/hospital setting, complete an Alert CTC form as this is considered a protocol violation.

**Protocol violation: Inter-facility transfer patients enrolled**

Occasionally an inter-facility transfer patient will be enrolled by an enthusiastic EMS crew who forgets that transfer patients are not eligible for enrollment. In this case, please indicate that the HS study fluid was given in the ED/hospital setting – even if they got the fluid in the rig on the way to the second ED. The idea is to capture that the fact that the fluid was not given prior to the first ED arrival. Don't forget to note on the first ED form that the patient's disposition was “Transfer to another ED”.

Item 3 – *Was more than one victim given study intervention during this incident?*  
Indicate number of patients treated with HS study fluid. (If more than one victim treated, complete separate data collection forms for each victim).

Item 4 – *Inclusion criteria* – Indicate “Yes” or “No” for all three inclusion criteria. (Please note that to qualify for enrollment into the TBI cohort, the patient must have had Blunt head trauma but for the Hypovolemic Shock cohort, the patient may have had blunt OR penetrating trauma or both.)

If “No” to all 3 criteria (which might happen in the event that a patient is enrolled who actually didn’t meet any inclusion criteria), indicate which cohort the patient was “intended to be enrolled in” by the medics and fill out an Alert CTC form. Otherwise skip to question 5. (E.g. patient with an altered LOC is enrolled by medics intending that he would be a TBI patient – review of the records reveals that the prehospital GCS was actually >8. Even though this enrolled patient turned out not to have met inclusion criteria– the patient stays in the study, data is collected and consent sought in the usual manner and he is assigned to an analysis group. In this case, the patient was “intended to be enrolled” as a TBI patient and his data will be analyzed with that cohort).

Item 5 – *Exclusion criteria* – Indicate “Yes” or “No” for all listed exclusion criteria. Enrolled patients who turn out to not be eligible (in other words those who have a YES checked in this category) must have an “Alert CTC” form filled out. Data will continue to be collected and consent sought in the usual manner on these patients.

A patient with a gunshot wound to the head is enrolled based on his pre-hospital GCS of 3 (his pre-hospital VS did not meet the inclusion criteria for the Shock cohort). On question 4, you would answer “no” to all 3 inclusion criteria and then check the “Intended to enroll in TBI cohort” box AND, in Question 5, check “Yes” to the exclusion criteria of “Isolated penetrating injury to the head”. An Alert CTC form will become required regarding the exclusion.

**Item 6 is only visible for those few sites which use the “modified scene” approach with their air-medical teams (e.g. Toronto)**

Item 6 – *Was this a “modified scene” patient?* – If “No” stop here. A “Yes” means that this patient was taken to an Emergency Department in anticipation of transportation to a ROC hospital by an air EMS agency. The patient should not have been admitted to that hospital nor have any treatment beyond what a typical ALS EMS could provide and typically stay less than 20 minutes. If “yes” continue with parts a-d

*6a – Name of hospital where taken to the ED.*

*6b – Arrival time at the ED:* Indicate the time the patient arrived at the ED in hours and minutes

*6c – Treatments while in the ED* – for each of the treatments listed select either “NA/NR” (Not Available/Not Recorded) or “Done”. If “Done” is selected, indicate all IV lines and airway that were attempted or done; and indicate

all tests that were done, selecting from the lists provided. If any of the tests are done, complete an Alert CTC form as this is a protocol violation. If "Other" is selected, further describe in the text box provided.

*6d – Departure time from ED* - indicate the departure time from the modified Scene ED.

After web entry, print the form and verify it against the worksheet or source document. If it matches, date and sign the verified information and place in your site file.

## Pre-Hospital Time Record

The purpose of the Pre-Hospital Time Record is to determine the correct times and sequence of events. The items listed in the time record are the typical sequence of events that would occur when a call is received at dispatch for a potential traumatic injury.

Fill in Event Order, Watch (PCR) time, and Dispatch time for all events that occurred. If an event did not occur enter, "0" for that event order. (E.g. if the patient survived to ED, then the "Resus terminated due to death" should have an event order of "0"). If no documented time exists (from PCR or dispatch), check the "No Doc Time" box.

Item 1 – *1<sup>st</sup> 911 Call received at dispatch*: Call time at Public Safety Answering Point (may be the primary or secondary PSAP) that was responsible for the dispatch of the first responding vehicle. (This first responding vehicle may or may not have the study intervention)

Item 2 – *Enrolling vehicle dispatch time*: This refers to the time when the enrolling vehicle (the vehicle that administered study fluid) was notified by dispatch.

Item 3 – *Enrolling vehicle w/study fluid arrived*: This refers to the time the enrolling vehicle (the vehicle that administered study fluid) arrived.

Item 4 – *Time study fluid hung*: This is the time that the study fluid was hung. (For "BONG cases" enter an event order of zero).

Item 5 – *Resus. terminated due to death*: This is the time the patient died OR efforts at resuscitation are halted in the field (DNR status discovered, for example).

Item 6 – *1<sup>st</sup> ED arrival*: The time that the patient arrives at the 1<sup>st</sup> emergency department or hospital, when the vehicle stops moving. *If the patient dies in the pre-hospital setting, the ED arrival event order should be "Zero"*.

Buttons at the bottom of the form:

- "Sort Event Order" - Sorts events into numerical order, but does not align times.
- "Align times" - moves watch time, dispatch time or a computer aligned time into the "Aligned Time" column. Pressing "Align Times" will also calculate the time intervals and cumulative time. Events with watch time only will be aligned via computer algorithm if other event(s) have both a watch time and a dispatch time.

A question mark between the "Adj" column and the "time interval" indicates that the time is computer aligned. Clicking on the question mark tells you which event(s) the aligned time is based on. Once you have pressed align times, it will keep aligning times until they press "Turn Align Off". ***The align times button must be pressed to "finish" the form and save it without errors.***

- “Turn Align Off” – This blocks the Align function and erases any previous computer aligned times and computer calculated intervals. These will be recalculated the next time the user presses “Align Times”
- “Original Order” – this returns the event order to that seen on the paper copy and erases any computer aligned time and calculated intervals.
- “Reset form” – Pressing this button erases/blanks out the form so you can start over.

After web entry, print the form and verify it against the worksheet or source document. If it matches, date and sign the verified information and place in your site files.

### **Quirky Pre-hospital time record scenarios**

1. BONG pts have an event order of “Zero” for study fluid hung
2. Inter-facility transfer patients will have the “Time study fluid hung” occurring AFTER the arrival at the first ED. The ‘1<sup>st</sup> call received at 911’ may be a non-ROC agency dispatch time. Because of this, pre-hospital time record may show a longer-than-usual time between “1st 911 call received at dispatch” and “Enrolling vehicle dispatch time”.

## Pre-Hospital Form

The purpose of the Pre-Hospital form is to collect information from the time the patient was screened in the field and enrolled through the time that the patient either died or was admitted to the emergency department. The information for the form will come from the PCR and dispatch, with the possibility of other information from family members or witnesses, depending on the episode and site.

The episode date/time and episode ID will be pre-filled by the web data entry program and will be consistent with the date and time recorded on the Patient Enrollment form. It should be reviewed here for accuracy.

Item 1 – *Vital Signs*: “Initial, SBP, RR and GCS” are collected to allow calculation of the Revised Trauma Score (calculated automatically and pre-filled on the Resuscitation/Injury Characteristics form, Item #4). The GCS is broken down into its component parts of Eye, Verbal and Motor.

There may be rare instances in a shocky patient where the enrolling EMS personnel list the BP as “unable to be detected” but a pulse is recorded. In this instance do not estimate a numeric value for the qualifying BP, instead select the “Not Detectable” box.

“Qualifying GCS” is that GCS which prompted enrollment of subject with TBI. It is assessed in the absence of paralytics. (Qualifying GCS and Initial GCS may be the same.) For patients who are in the hypovolemic shock cohort only, you will not be able to access the “Qualifying GCS” field.

“Qualifying SBP prior to study fluid” is the SBP which prompted enrollment of subject with hypovolemic shock. (For a patient who is in the TBI cohort only, the “Qualifying SBP” data field is not accessible). In the rare case where the patient has a pulse, but no detectable SBP, you may check “Not Detectable” for “Qualifying SBP”. If the “Qualifying SBP prior to study fluid” value is 71-90, or you checked “Not Detectable” please enter the qualifying HR.

If the patient meets both TBI and hypovolemic shock cohorts, please enter data in both the Qualifying GCS and SBP/HR fields.

List the “Best field SBP after the study fluid was given” that the patient had in the field and prior to admit to the ED. In the rare case where the patient has a pulse, but no detectable SBP, you may check “Not Detectable” for “Best field SPB after study fluid”.

“Highest field heart rate” is a data point which when combined with information about SBP provides information about depth of shock as does “Lowest Field SBP”. (Lowest Field SBP or may not be the same as “qualifying SBP prior to study fluid”).



*Please note that the “Not Detectable” option for Initial SBP, Best field SBP after study fluid” and Lowest Field SBP is only checked in those instances where the patient had a detectable pulse, but the blood pressure was not able to be detected. Implied in this is that there was an attempt to get a blood pressure. This is different than a patient who is in full arrest and has no detectable blood pressure AND no detectable pulse, in which case the values for HR and SBP would be zero.*

Item 2 – *Procedures*: If none of the listed procedures were attempted, check “No”. If an advanced airway was attempted, indicate which kind of airway. Check “Failed” for LMA, Combitube, ET tube or cricothyrotomy if that airway type was unable to be placed. Indicate whether or not the patient had a needle thoracostomy. If another significant procedure was performed in the field, check other and briefly describe. Please note that for the purposes of this study the use of an LMA, Combitube or any type of King Airway does **not** constitute intubation (these patients will have all those airways replaced in the ED or hospital with intubation suitable for long term ventilation). Field placement of an ET tube or a cricothyrotomy DOES constitute intubation.

Item 3 – *Medications Given*: If no medication were given in the field, skip to item #4. If “Yes”, indicate which medicines the patient received choosing from the list provided. If other checked, please free text what other medication was given in the space provided.

Item 4 – *Fluids Given*: List amount of all fluids given in milliliters (ml). If no fluid given in the pre-hospital setting, enter “0”. If the amount of crystalloids given is > 2L, Indicate whether it was administered prior to the study fluid (If the total crystalloid listed is not greater than 2 liters, you should not answer this question.) If the patient received any rbc's, colloid or Mannitol prior to study fluid or if the patient received greater than 2 liters of fluid total *before receiving study fluid*, an “Alert CTC” form must be filled out.

#### **Crystalloids vs. colloids**

Crystalloids are fluids that contain a combination of water and electrolytes. **Common examples are NS, LR, D5W, D51/2 NS, D5 ¼, NS and Plasmalyte.** Crystalloid solutions closely mimic the body’s extra cellular fluid. Given I.V., crystalloid solutions diffuse through the capillary walls that separate plasma from interstitial fluid. They can be used to expand both intravascular and extra vascular fluid volume.

Colloids are fluids that contain undissolved particles, such as protein, sugar, and starch molecules, which are too big to pass through capillary walls. (Technically speaking, blood is a colloid.) A colloid solution draws fluid from the interstitial and intracellular spaces, increasing intravascular volume. The degree of osmotic pull that a colloid exerts depends on its particle concentration. **Albumin and Hetastarch are examples of colloid solutions.**

Item 5 – *Transportation*: Select the agency and vehicle(s) that transported the patient from the drop down menus provided. Indicate whether a selected vehicle was air or ground transport. Two spaces are provided in the event a land vehicle is used to meet an aero-medical team for further transport.

Item 6 – *Demographics*: Use data collected from the pre-hospital records only.  
*6a - Age*: Indicate the age of the patient if noted, or approximated, on the PCR (do not use information from the hospital records to give age – we want to document information here from the pre-hospital providers).  
*6b - Race/ethnicity*: Check- all that apply. If “other” is checked, free text a description.  
*6c - Gender*: Indicate “male” or “female”.

Item 7 – *Adverse Events*: Choose “yes” if any AE occurred and explain. Also complete an “Alert CTC form”. (For example, anaphylaxis or seizure activity)

Item 8 – *Disposition*: Outcome for the pre-hospital time period, check one only. Admittance to the ED is defined as both completion of Emergency Department admission paperwork or treatment of the patient by the ED staff. A patient who was transported to the ED in order to be pronounced dead or was pronounced DOA by ED staff is not considered to have been admitted to the ED. If patient expires prior to arrival to ED, please fill out item 9.

Item 9– *Cause of death*: If patient expires in the pre-hospital setting, indicate the primary and secondary causes of death, choosing from the lists provided.

Additionally if patient expires prior to ED arrival, fill out Resuscitation/Injury Characteristics forms, Pt/Family consent form and, if needed, an Alert CTC form.

Enter your name. After web entry, print the form and verify it against the worksheet or source document. If it matches, date and sign the verified information and place in your site files.



## ED Admit Form

The purpose of this form is to document information occurring during the Emergency Department (ED) admission. Admittance to the ED is defined as both completion of Emergency Department admission paperwork or treatment of the patient by the ED staff. A patient who was transported to the ED in order to be pronounced dead or was pronounced DOA by ED staff will not have the ED Admit form completed.

Patients that are admitted directly to the hospital (ICU/CCU) will not have an ED Admit form completed.

Patients that are admitted to more than one ED will have one ED Admit form completed for each ED admission.

The episode date/time and episode ID will be prefilled by the web data entry program and will be consistent with the date and time recorded on the Patient Enrollment form. It should be reviewed here for accuracy.

Item 1 – *ED admit information*: Enter the date and the time the patient was admitted to the ED. This would be typically located on the ED admit sheet or the paperwork completed by the admit nurse. In the event that the injury occurred near midnight, it is possible the date of the injury and the date of ED admission could differ by one day.

Item 2 – *Demographics*: Enter demographic information here which comes from ED or Hospital records. Race and Ethnicity demographics are requested and tracked by the NIH.

*2a: Birth year*: Enter the 4 digit number corresponding to the year of birth.

*2b: Race*: Check all that apply from the list provided.

*2c: Ethnicity*: Choose one from the list provided.

Item 3 – *Vital Signs within 4 hours of ED admit*: All vital signs noted are within 4 hours of the 1<sup>st</sup> ED admit. Pre-filled time guidelines here are based on the information entered in Item one on the first ED admit form.

“First ED GCS”, enter component parts of the GCS: Eye (also note size and reactivity of right and left pupils), Verbal (note whether intubated at time of Verbal assessment) and Motor (note whether chemically paralyzed at time of motor assessment).

“First ED BP” and “Lowest ED BP” should be entered; as well as “First ED HR” and “Highest ED HR”. (*Lowest ED BP is based on the systolic value, not the MAP*). Note “First temperature” as well as the source of the temperature.

**A WORD ABOUT LAB VALUES AND UNITS OF MEASURE**

To accommodate the variety of units of measure across the RCC's, there are several places through the forms that require indication of the units of measure **prior to entering a lab value.**

Item 4 - *Labs*: All lab values noted are within four hours of admission to the first ED. Pre-filled time guidelines here are based on the information entered in Item one on the first ED admit form. To accommodate the variety of units of measure across the RCCs, there are several places in Item 4 that require you to indicate your units of measure prior to entering your lab value.

Indicate whether or not arterial blood gases (ABGs) were drawn. If ABGs have been drawn, enter the time of the first and worst ABG ("worst" based on lowest pH), and the values (FiO<sub>2</sub> (as a decimal), pH, pCO<sub>2</sub>, pO<sub>2</sub> and SaO<sub>2</sub> (as a whole number)) associated with those times. (If only one ABG is drawn, only enter data for "first". In other words, Worst ABG = the worst ABG subsequent to the "First ABG".) The base deficit will be calculated by the computer.

Indicate whether or not a lactate was obtained within 4 hours of arrival to the ED. If drawn, enter the units of measure used at your site, the first lactate value and the time drawn.

Indicate whether or not hemoglobin was obtained within 4 hours of arrival to the ED. If drawn, enter the units of measure used at your site, the first hemoglobin value and the time drawn. *Sites which draw hematocrits first in the ED may calculate the "first hemoglobin" and use the calculated value until hemoglobin values are available. Calculate hemoglobin by dividing the hematocrit by three for g/dL or dividing the hematocrit by 0.3 for g/L.*

Indicate whether or not a coagulation panel was drawn within 4 hours of arrival to the ED. If drawn, select and enter all applicable lab values ("First INR", "First PT", "First PTT", "First Platelet count", "First fibrinogen") in the space provided. In the "First platelets" and "First Fibrinogen" areas, you **must** indicate your units of measure prior to entering the value.

Item 5 – *Arrhythmias*: Indicate whether or not the patient experienced any ventricular arrhythmias requiring intervention, defined for our purposes as either shock or drug therapy (drug therapy might include Lidocaine, Procainamide etc). (This question is a safety check required by the protocol.)

Please note that for the purposes of this study, pre-hospital placement of an LMA, Combitube or any type of King airway does **not** constitute intubation (these patients will have all those airways replaced in the ED or hospital with intubation suitable for long term ventilation) while the placement of an ET tube or getting a cricothyrotomy does constitute intubation.

- Item 6 – *Intubation*: Indicate if the patient was not intubated, or arrived intubated, or was intubated in the ED or had a surgical airway placed in the ED.
- Item 7 – *Angio Suite for hemorrhage control*: Indicate whether or not the patient went to angio. If “yes” – please indicate whether or not they received embolization.
- Item 8 – *Were any adverse events uncovered during the ED Admit?* (For example, anaphylaxis, and seizure activity associated with hypernatremia.) Choose yes if any AE occurred and explain. Also complete the “Alert CTC form”. Please note that you do not need to report here an AE for which you have already filled out an “Alert CTC” form, i.e. you need report each AE only once.
- Item 9 – *Disposition*: Note the outcome of the ED admit. Typically most patients will be admitted to the hospital. If transferred to a second hospital ED, you must fill out a second ED admit form. If transferred to another ED, indicate type of transport.
- Item 10 – *Date and time of ED discharge*: Note date and time patient left ED. If the patient died in the ED, note the date and time of death here and complete items 11 and 12.
- Item 11 – *For patients who die in the ED, please indicate cause of death*: If the patient died in the ED, indicate the primary and secondary causes of death, choosing from the lists provided.
- Item 12 – *For patients who die in the ED, please list ED Procedures performed here*: If the patient died in the ED, indicate whether any of the listed procedures were performed in the ED, using the ED procedures Key provided.

*Additionally if patient expires in ED, fill out Resuscitation/Injury Characteristics forms, Patient/Family consent form and, if indicated, Alert CTC form.*

Enter your name. After web entry, print the form and verify it against the worksheet or source document. If it matches, date and sign the verified information and place in your site files.



## Resuscitation /Injury Characteristics

The purpose of this form is to document information about the mechanism, type, location, and severity of the injuries suffered, and how the patient was resuscitated. The injury information will be translated into injury scores used as predictors of mortality.

The episode date/time and episode ID will be prefilled by the web data entry program and will be consistent with the date and time recorded on the Patient Enrollment form. It should be reviewed here for accuracy.

- Item 1 – *Injury type/mechanism*: Note whether injury is blunt and/or penetrating (may have both) and by which mechanism the patient was injured.
- Item 2 – *Head CT done within 7 days of injury episode date*: Enter the date, time and Marshall Score for the first three head CT's for patients during the 7 days immediately following the episode date. (It is recommended that one person at each institution, familiar with the Marshall Head CT scoring system do all the head CT scores for that institution to ensure consistency.) If no head CT's were done, so indicate. For a patient with > 1 head CT during the first 7 days following the injury episode date, indicate whether or not there is "Evidence of increased intracranial hemorrhage" on the 2<sup>nd</sup> and 3<sup>rd</sup> CT's. If "Yes" you will be prompted to fill out an alert CTC form.
- Item 3 – *Anatomic Injuries*: The Abbreviated Injury Scale, a seven digit number, will be used to describe diagnosed injuries and their severity. Injuries described in this area should be related to the original injury episode only (e.g. do not list the broken hip the patient got after falling out of bed on day 4) The first part of each injury description is a unique 6-digit numerical code followed by a decimal point. The second part of each injury description, the severity score, is the digit to the right of the decimal point. Using the Abbreviated Injury Scale codes enter the three worst injuries for each of the six anatomic areas listed. (Enter zero in the area to the left of the decimal point if there is no injury to an anatomic area.) The AIS is the foundation for the Injury Severity Score which is the sum of the squares of the highest AIS code in each of the three most severely injured ISS body regions. It will be automatically calculated from the data entered here. The six body regions of injuries used in calculating the ISS are:
- Head/ neck: Includes injury to the brain or cervical spine, and skull or cervical spine fractures;
  - Face: Includes injuries to the mouth, ears, eyes, nose and facial bones;
  - Chest: Includes injuries to the chest and the contents of the chest cavity, and also injuries to the diaphragm, rib cage and thoracic spine;
  - Abdominal or pelvic contents: Includes injuries to organs (and associated vasculature) in these cavities, including lumbar spine lesions;
  - Extremities or pelvic girdle: Includes injuries to the extremities or to the pelvic or shoulder girdle including sprains, fractures, dislocation and amputations, except for the spinal column, skull and rib cage. Included here are injuries to the femoral and popliteal vessels.
  - External: Includes lacerations, contusions, abrasions and burns independent of their location on the body surface.



Item 4 – *Injury Severity Scores*: The database will automatically compute the NISS, ISS, RTS and TRISS from data entered on preceding forms. The New Injury Severity Score (NISS) is calculated from the worst three injuries suffered regardless of anatomical region. The ISS is calculated from the worst injuries from each of three different anatomical regions. The Revised Trauma Score (RTS) is calculated from the first pre-hospital Glasgow Coma Score, Systolic Blood Pressure and Respiratory Rate. The TRISS calculates the probability of survival from the ISS, RTS and patient's age. Injury scoring systems are used as predictors of mortality and may be used in subgroup analyses. (For further descriptions of injury scoring systems, including an AIS 98 “cheat sheet”, see pages 89-92).

Item 5 – *Fluids*: Document the amounts given (in mls) of each fluid, during the first 24 hours of hospitalization. If none given, enter zero. Please note that the computer generated time periods here are based on the “time call received at dispatch”, to capture the fluid information for the first 24 hours from the time of injury. Also note that Crystalloid, Mannitol and RBCs given in the prehospital setting will be prefilled here by the computer based on information entered on the prehospital form.

Item 6 – *Labs*: (Please note that the time periods here are based on “ED arrival” from the Pre-Hospital Time Record).

*a. Labs*: Select your unit of measure, and then enter the lab values for “highest lactate” and “worst base deficit” during the time periods indicated, if available. If labs not drawn or not recorded please, check (NA/NR)

*b. Electrolytes in the first 24 hours*: (*Na, Cl and K+ are measured in either mEq/L or mmol/L at all RCCs which are equivalent*). Please enter all sodium (Na), chloride (Cl), and potassium (K+) values for the first 24 hours. Sodium values are expected to be drawn, at a minimum, on admission and every 8 hours for all patients admitted to the ICU. (Sodium levels should be drawn every six hours if the patient receives Mannitol, 3% saline infusion or another non-study hypertonic saline solution for the treatment of increased intracranial hypertension – see the Neuro form). If labs are not drawn or not recorded, please check (NA/NR). If you enter a sodium value > 160 you will be prompted to fill out an “Alert CTC form”, keeping in mind that serum sodium > 160 mEq **and** requiring intervention is an SAE.

*Highest sodium value from 24-28 hours*: Enter the highest sodium value for the time period indicated (please note that the time period here is based on “ED arrival” from the Pre-Hospital Time Record).

Item 7 – *Osmolality*: Enter the highest serum osmolality for the dates/times indicated. (1<sup>st</sup>/ED is asking for the first value drawn in the ED. Day one is, as before, one calendar date after the date of the injury episode. ***Osmolality is measured in either mOsm/kg or mmol/kg at all RCCs, which are equivalent.*** If labs not drawn or not recorded, please check (NA/NR)

After web entry, print the form and verify it against the worksheet or source document. If it matches, date and sign the verified information and place in your site files.

## ICU Form

This form should be filled out on all patients who are admitted to an ICU. Pre-anesthesia Care Unit or Recovery Room stays as part of routine pre- or post-op care, do not count as ICU stays. If the patient was not admitted to the ICU, please skip ICU forms.

Data from the ICU forms document organ dysfunction which is used to calculate the Multiple Organ Dysfunction Score (MOD Score), a secondary outcome measure for the hypovolemic shock cohort. The MOD Score assigns points to each of six organ systems. The total MOD score is given by the sum of score of six major organ systems. The MOD score will be calculated **every other day** while the patient is in the intensive care unit. Because the MOD Score is designed to measure stable alterations in organ function, the first 48 hours post-injury are excluded. Those who die in the first 48 hrs will be assigned the maximum MOD score of 24, and those who are discharged before 48 hrs will have a MOD score of 0.

<b>Multiple Organ Dysfunction Score</b>					
<b>Sum the score from each organ system</b>					
<b>Organ system</b>	<b>Score</b>				
	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>
Respiratory (PO <sub>2</sub> /FiO <sub>2</sub> )	>300	226-300	151-225	76-150	≤75
Renal (serum creatinine - μmol/l)	≤1.1	1.2-2.3	2.4-3.9	4.0-5.6	>5.7
Hepatic (serum bilirubin - μmol/l)	≤1.1	1.2-3.5	3.6-7.1	7.2-14.1	>14.2
Cardiovascular (PAR*)	≤10.0	10.1-15.0	15.1-20.0	20.1-30.0	>30.0
Hematologic (platelet count -x 10 <sup>3</sup> )	>120	81-120	51-80	21-50	≤20
Neurologic (Glasgow coma score)	15	13-14	10-12	7-9	≤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): PAR = HR x CVP/MAP

The episode date/time and episode ID will be prefilled by the web data entry program for each of the four ICU forms and will be consistent with the date and time recorded on the Patient Enrollment form. It should be reviewed here for accuracy.

Item 1 – *Date of ICU Admit*: Indicate date and time (required) of initial ICU admit. This will set up the blocking scheme for all information entered on the ICU form. The fact that most data for this form are collected only on alternate days has led to a complicated program to block data entry on days where data collection is not expected. This will help to guide the entry of data only for the days needed and will help to ensure that a day's data are entered on the same day across the 3 tables for cardiovascular failure, respiratory failure and "Other" organ failure.

Item 2 – *Cardiovascular failure*: In order to track total ICU days (a subset analysis) indicate only if the patient was admitted or discharged on day zero or day one. (Day Zero is the date of injury; Day One is the first calendar day after the date of injury, and so on.) Otherwise, fill in the CV failure information (heart rate (HR), mean arterial blood pressure (MAP), central venous pressure (CVP), Pressors – “Yes/No”) every other day for those days that the patient is in the ICU (starting with Day 2 if the patient was admitted to the ICU on day zero). **It is strongly recommended that you enter the ICU admit date (item one) which sets up the blocking scheme, prior to collecting any ICU data to ensure that you are collecting data on the correct days.** In the case where a patient may be admitted to the ICU or readmitted to the ICU later in their hospital course, please enter data beginning with their day of admit and continuing every other day until ICU discharge (e.g. if the patient isn't admitted to the ICU until day one, you would enter data on days 1, 3, 5,7, etc until ICU discharge; if the patient isn't admitted to the ICU until day 4, you would enter data on days 4,6,8 etc until ICU discharge).

The calendar date will be prefilled by the web data program based on the date entered on the Patient Enrollment form. HR, MAP, CVP data should be collected together from one point in time, 0800, each day. If there is no charted information at 0800, go back in time and use the data closest to 0800. If there is no CVP data, indicate “NA/NR”. (The data program will use an assigned CVP value of 10 to calculate pressure adjusted rate or PAR needed for MOD scoring.) **In the absence of an arterial line, MAP can be calculated according to this formula:  $MAP = [(2 \times \text{diastolic}) + \text{systolic}] / 3$**

Indicate whether or not the patient received any pressors (e.g. Dopamine, Dobutamine, Norepinephrine, or Vasopressin) during that 24 hour period.

In the far right column, indicate when the patient is discharged or readmitted, (this column is never “blocked”). Discharged from the ICU means the patient was out of the ICU for at least 24 hours. If the patient left the ICU but was readmitted less than 24 hours later, that does not count as being discharged from the ICU. If the patient is readmitted to the ICU for less than 24 hours, this does not count as an ICU admit.

Item 3 – *Never ventilated*: If the patient was never ventilated, skip to item 5. (For the purposes of this data collection form “never ventilated” means never ventilated through Day 28).

*Date and time of initial intubation*: Indicate date/time of initial intubation (required).

*Respiratory failure*: Fill in the information every other day for ventilated patients. **It is strongly recommended that you enter the ICU admit date (item one) which sets up the blocking scheme, prior to collecting any ICU data to ensure that you are collecting data on the correct days.** The calendar dates will be prefilled by the web data entry program based on the date entered on the Patient Enrollment form.

Indicate whether or not the patient is ventilated, **remember that *intubated* does not necessarily mean the patient is *ventilated*.** (Please note that patients who

are on a t-piece or straight CPAP during the day but who get ventilatory support during the night **are** considered ventilated). For the purposes of this protocol, all of the following are considered unassisted breathing/not ventilated:

- Extubated with face mask, nasal prong oxygen, or room air OR
- T-tube breathing, OR
- Tracheotomy mask breathing, OR
- CPAP  $\leq 5$  (with PS  $< 8$  or no pressure support; and without intermittent mandatory ventilation assistance).

If ventilated, enter PaO<sub>2</sub>, FiO<sub>2</sub> and PEEP settings from 0800. (If no data available at 0800, go back in time and use the data closest to 0800). Enter FiO<sub>2</sub> as a decimal, e.g. 35% FiO<sub>2</sub> should be entered as 0.35; 100% FiO<sub>2</sub> should be entered as 1 and so forth.

If the patient's p/f is  $\leq 300$ , assess whether or not bilateral infiltrates are present by reviewing the patient's chest films or having a designated clinician at your site review them for you. Do NOT just read the CXR report. Using the definitions given below indicate whether or not the patient had ALI or ARDS. (Please note that if you do not have ALL of PaO<sub>2</sub>, FiO<sub>2</sub> and CXR data available, you cannot verify either the presence or absence of ARDS or ALI. Simply leave the question blank and over-ride the error message).

**ALI:**

- (a) Hypoxia with a PaO<sub>2</sub>/FiO<sub>2</sub> ratio  $>200$ ,  $\leq 300$  and
- (b) bilateral infiltrates on chest X-ray and
- (c) no clinical evidence of increased left atrial pressure or a pulmonary artery pressure of  $<18$ mmHg\*

**ARDS:**

- (a) Hypoxia with a PaO<sub>2</sub>/FiO<sub>2</sub> ratio  $\leq 200$  and
- (b) bilateral infiltrates on chest X-ray and
- (c) No clinical evidence of increased left atrial pressure or a pulmonary artery pressure of  $<18$ mmHg\*

*\*For those without pulmonary catheter monitoring clinical evidence of left atrial hypertension includes:*

- a) Acute myocardial infarction or known cardiomyopathy or severely reduced ejection fraction ( $<30\%$ ) or critical valvular disease; b) chronic or acute oliguric renal failure with fluid input that exceeds output by  $\geq 3$  liters in the previous 24 hours.*

**TIME SAVING TIP:** Assess the p/f first - if the patient's p/f ratio is  $>300$ , then the pt cannot, by definition, have either ALI or ARDS and therefore it is not necessary to assess the CXR or answer the question regarding the presence of infiltrates. You may leave that field blank and over-ride the error message.

If yes to either ALI or ARDS, please indicate at what tidal volume the patient is ventilated, in mls per kg of predicted body weight. This allows us to assess whether or not the patient is getting a low tidal volume, lung protective strategy as recommended in the protocol guidelines for patients with ALI or ARDS.

If “Yes” to ARDS, no further CXR monitoring will be required, **and you should not indicate “Yes” or “No” for either ALI or ARDS on any subsequent dates that the patient is ventilated.** You must continue to enter PaO<sub>2</sub>, FiO<sub>2</sub>, PEEP and Vt data QOD until extubation.

**Calculate predicted body weight (PBW)**

**Males** = 50 + 2.3 [height (inches) – 60]

**Females** = 45.5 + 2.3 [height (inches) – 60]

**TIP: A patient’s height and/or weight is commonly listed or estimated on admission. Look in the H&P, the nursing admit assessment and the I&O section of the flow sheet. Weight is also used to calculate calorie needs and to guide decision making about anesthesiology: look for notes by the registered dietician or in the anesthesiologist’s pre-op assessment.**

*Extubated/Reintubated:* Indicate the date the patient was extubated. To count as “extubation”, the patient must be extubated for a period of at least 24 hours. If the patient is extubated, but gets reintubated within 24 hours, that does not count as extubation. If the patient is extubated for greater than 24 hours, but reintubated after that time period, indicate the date of reintubation and resume the every other day collection of respiratory failure data. If the patient is reintubated for less than 24 hours, that does not count as reintubation.

Item 4 – *ARDS qualifying CXR:* If the patient had a diagnosis of ARDS (as indicated in number 3 above) note the date of the qualifying CXR.

Item 5– *Other Organ Failure:* Fill in the information QOD for those days that the patient is in the ICU. **It is strongly recommended that you enter the ICU admit date (Item one) which sets up the blocking scheme, prior to collecting any ICU data to ensure that you are collecting data on the correct days.** The calendar date will be pre-filled by the web data program based on the date entered on the Patient Enrollment form. After indicating your unit of measure, enter lab values for *Platelets*, *Bilirubin* and *Creatinine* for the time period closest to 0800. If not available, so indicate. Enter the best *GCS* for the entire 24 hour period. The data program will pre-fill the *MOD score calculated*.

*Worst MOD Score:* The data program will assess and automatically pre-fill the worst score from data previously entered.

After web entry, print the form and verify it against the worksheet or source document. If it matches, date and sign the verified information and place in your site files.

## Neurologic Function/TBI Management Form

The purpose of this form is to assess the neurologic function of the TBI patient and to monitor the management of the traumatic brain injury. This form should be filled out on all patients randomized into the TBI cohort, even if subsequent CT scans do not document a head injury. (E.g. patients who were enrolled under influence of alcohol or drugs, but turn out to be uninjured). This form should also be filled out on hypovolemic shock cohort patients who had positive head CT findings for safety monitoring (although these patients will not need TBI outcome interviews).

The episode date/time and episode ID will be pre-filled by the web data entry program and will be consistent with the date and time recorded on the Patient Enrollment form. It should be reviewed here for accuracy.

Item 1 – *GCS*: List the best Glasgow Coma Scale for each day indicated. (The entire 24 hour period from 00:00 through 24:00)

Item 2 – *ICP Monitoring?* Indicate whether the patient had an ICP monitor. If "Yes", indicate what date the ICP monitor was placed and give the opening ICP and initial CPP, then press the "Prefill ICP Times" button. The computer will generate and prefill the time periods which encompass the five day period after the monitor was placed and for which data should be collected.

*Highest ICP*: List the highest ICP for the time periods indicated.

*# hrs ICP > 25*: List the total number of hours, in 15 minute increments that the ICP was > 25 for the time period listed. By measuring in increments of 15 minutes we hope to avoid tracking non-sustained spikes in the ICP which might be associated with procedures like turning or suctioning. If the ICP was not >25 for at least 15 consecutive minutes, then enter "0".

*#hrs CPP < 60*: List the total number of hours (in 15 minute increments) that the CPP was less than 60 during the time periods listed. By measuring the CPP in increments of 15 minutes we hope to avoid tracking non-sustained drops in the CPP which might be associated with procedures like turns or suctioning. If the CPP was not <60 for at least 15 consecutive minutes, then enter "0".

*Total gms/kg Mannitol*: Note the total grams/kg of Mannitol the patient received during the time periods indicated. If no Mannitol was given to the patient, enter "0".

*If the ICP monitor is removed prior to day 5, indicate NA for the affected time periods.*

Item 3 – *Other Interventions for intracranial hypertension?* Select "No" if the patient had no other interventions for intracranial hypertension and skip to the next item. If "Yes", indicate which treatments/interventions the patient received to treat intracranial hypertension during the time periods indicated. *The time periods are based on time of ED admit and will be computer generated.*

*Hyperventilation*: Indicate if the patient was hyperventilated (defined as the intentional use of an elevated ventilation rate to drive the patient's CO<sub>2</sub> to <30)

to treat intracranial hypertension during the time periods indicated. (This definition of hyperventilation does not include patient's who are "over-breathing the vent" on their own and have lowered CO<sub>2</sub> levels.)

*Craniotomy*: Indicate whether or not the patient received a craniotomy during the time periods indicated.

*Ventriculostomy*: Indicate if the patient received a ventriculostomy and how many milliliters of drainage were removed to treat intracranial hypertension during the time periods indicated.

*Other 1, 2, 3*: If patient had interventions other than those listed above for intracranial hypertension, please specify and give date.

Item 4 – *Any Seizures (from time of 1<sup>st</sup> ED admit?)*: Indicate if the patient had any seizure activity during the first 5 days from time of 1<sup>st</sup> ED admit. *The time periods are based on time of 1st ED admit and will be computer generated.* If "No", skip to next form. If the patient had seizure activity, indicate whether or not the patient was on anticonvulsants at the time of the seizure activity (anticonvulsant therapy might include Dilantin (phenytoin), valium (diazepam) or phenobarbital). If the patient had a seizure, indicate whether or not the seizure occurred in the setting of serum sodium >160. If yes, you must fill out an Alert CTC form, keeping in mind that seizure activity associated with hyponatremia (NA>160) is an SAE.

Item 5 – *Serum sodium monitoring during ICH treatment. Any treatments for intracranial hypertension which required serum sodium monitoring? (E.g. Mannitol, 3% saline infusion or any other non-study hypertonic saline solution).* If "No" skip rest of question, if "Yes" answer parts 'a' and 'b'.

a) *Treatments Day 0-5 – (Remember that Day "zero" is the day the patient is injured).* List the start date and time, which treatment the patient received and the stop date. Choose 3% sodium, Mannitol or other. "Other" would be any type of non-study hypertonic solution. Describe the concentration in the space provided. Use one line for each treatment.

b) *Sodium levels Day 0 – 5. Sodium must be monitored every 6 hours during treatment(s) described in part 'a' & once more 6 hours after treatment is discontinued. (Sodium levels from the first 24 hours are listed on the Resuscitation /Injury Characteristics form).* Enter sodium levels corresponding to the treatments listed in part 'a'.

After web entry, print the form and verify it against the worksheet or source document. If it matches, date and sign the verified information and place in your site files.

## Care Guidelines

The purpose of this form is to monitor the use of the resuscitation and critical care management guidelines recommended in the protocol. (See attached Care Guidelines page 93). The first 48 hours of hospitalization are considered the acute resuscitation period. Outside of that time period the queries look at days 3, 4 and 5. This is the time period when subjects will most commonly be in the ICU and be “eligible” for the guidelines. (E.g. the recommended transfusion trigger is Hgb  $\leq 7$ ; on days 3, 4 and 5 the Hgb levels are recorded and the chart is reviewed to see if the patient was transfused.)

Item 1 – *Resuscitation*: Indicate whether or not the patient had either CVP monitoring (not just a central line) or a PA catheter inserted during the 1<sup>st</sup> 48 hours after their admission to the ED (i.e. acute resuscitation phase).

If the patient was discharged prior to day 3, skip items 2 – 5.

Item 2 – *Insulin*: Indicate unit of measure, then list the highest blood glucose and whether or not the patient was on an insulin drip for each of days 3, 4 and 5.

Item 3 – *Transfusion*: Indicate unit of measure, and then list the lowest hemoglobin and whether or not the patient was transfused with red blood cells for each of days 3, 4, and 5.

Item 4 – *Sedation*: Indicate whether or not the patient was on the sedation drips listed for each of day 3, 4 and 5.

Item 5 – *Nutrition*: Indicate whether or not the patient was receiving any of the types of nutrition listed on days 3, 4 and 5. (Enteral nutrition is nutrition that uses the gut, e.g. via feeding tube or a knife and fork, or parenteral nutrition which is given intravenously (sometimes called total parenteral nutrition or TPN).)

After web entry, print the form and verify it against the worksheet or source document. If it matches, date and sign the verified information and place in your site files.





## Hospitalization form

The purpose of this form is to assess the incidence and nature of select major procedures, infectious and non-infectious complications in all enrolled patients. Data for this form is culled from hospital records.

The episode date/time and episode ID at the top of each page will be pre-filled by the web data entry program and will be consistent with the date and time recorded on the Patient Enrollment Form. It should be reviewed here for accuracy.

Item 1 – *Date Admitted to the Hospital*: List date of admission to the hospital (as distinct from the time of ED admission - usually this is listed as date/time patient arrives to a unit, the PACU or the OR).

Item 2 – *Major procedures*: If the patient had no major procedures, check "No" and skip to Item 3. If YES - Utilizing the choices in the procedures code key, indicate the code number for the type of major procedure(s) the patient underwent and the date of the procedure. You may enter multiple procedures for the same date. You may enter the same procedure more than once on the same date.

Item 3 – *Infection*: Indicate whether or not the patient had any infectious complications. If NO – skip to item 5.

If "YES"-list location of infection(s) using the numeric codes provided; list the date of each infection.

1 – Pneumonia: See definition of pneumonia on the following page.

2 – Bloodstream infection: See definition of bacteremia on the following page.

3 – UTI: See definition of urinary tract infection on the following page.

4 – Meningitis: Diagnosed by lumbar puncture with positive cultures. Symptoms include headache, malaise, nausea, fever, and neck stiffness.

5 – Cholecystitis: Acute inflammation of the gallbladder as diagnosed by ultrasound.

6 – Empyema: Positive bacterial cultures from a tap of the pleural fluid.

7 – Pseudo-membranous colitis: As evidenced by a stool culture positive for *C. difficile* toxin. The bacterium *Clostridium difficile* occurs normally in the intestine. In pseudo- membranous colitis, *c. diff* proliferates and releases a powerful toxin that causes symptoms which may include watery diarrhea, abdominal cramping, low-grade fever and bloody stools.

8 – Line Infection: This refers to a central line infection and is diagnosed by either a positive line tip culture *or* the presence of pus and erythema at the central line insertion site.

9 – Wound infection: See definition for wound infection on following page.

10 – Intra-abdominal abscess: See definition for intra-abdominal abscess on the following page.

11 – Osteomyelitis: A bacterial infection involving the bone as evidenced by radiographic changes suggestive of bone loss.

Item 4 – *Pneumonia Diagnosis*: If the patient had pneumonia, please indicate the diagnosis method.

Please note the definitions for nosocomial infections listed below.

### **Definitions for Nosocomial Infection**

#### **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, 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. Radiological 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/mm<sup>3</sup> **or** 25% increase over last available value **or** bands > 10% of total WBC **or** new decrease in WBC to < 4000/mm<sup>3</sup>
3. Bacteriologic confirmation by **at least one of**:
  - positive blood culture for bacterial pathogen also identified in sputum or pathogenic bacteria (if not quantitative, then must be moderate or heavy growth) 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

#### **Wound Infection**

To diagnose wound infection, it 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/mm<sup>3</sup> **or** 25% increase over last available value **or** bands > 10% of total WBC **or** new decrease in WBC to < 4000/mm<sup>3</sup>
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/mm<sup>3</sup> **or** 25% increase over last available value **or** bands > 10% of total WBC **or** new decrease in WBC to < 4000/mm<sup>3</sup>

Item 5 – *Non-infectious complication?* Select “No” if the patient had no non -infectious complications and skip to Item 5.

If “Yes”, enter the numeric code of the complication from the list on this page and enter the date the non-infectious complication occurred.

(1) – Fat embolism syndrome: Ultimately fat embolism syndrome is a clinical diagnosis of exclusion made by an attending or consulting physician and documented in the chart. This syndrome may include multiple signs and symptoms of varying subtlety (e.g. unexplained petechiae, unexplained hypoxia or difficulty ventilating, etc. usually occurring in the presence of a long bone fracture.)

(2) – Cardiac arrest: The complete cessation of cardiac activity (heart beat) as documented in the chart.

(3) – Myocardial infarction: To diagnose myocardial infarction, criteria one and two OR three must be satisfied:

i) A typical rise and fall of biochemical indicators of myocardial necrosis. (Defined by the Joint European Society of Cardiology/ACC as "maximal concentration of troponin T or I exceeding the decision limit (99th percentile of the values for a reference control group) on at least one occasion during the first 24 hours after the index clinical event; or maximum value of CK-MB (preferably CK-MB mass) exceeding the 99th percentile of the values for a reference control group on 2 successive samples, or the maximal value exceeding twice the upper limit of normal for the specific institution on one occasion during the first hours after the index clinical event." )

**AND** at least one of the following:

- ii) a. Ischemic symptoms
- b. Development of pathologic Q's on ECG
- c. ECG changes indicative of ischemia (ST elevation or depression)
- d. Coronary intervention.

**OR**

iii) For the purpose of this study, a patient with non-specific ECG changes and elevated troponin (for whom the differential diagnoses include acute coronary syndrome and blunt chest trauma) will be classified as an MI to ensure adequate review of potential complications.

(4) – Cerebral infarction: Infarction of brain tissue as documented by CT or MRI findings.

(5)– Deep venous thrombosis (DVT): The formation of a blood clot in a vein resulting in obstruction of venous flow, as documented by venous duplex testing.

(6)– Pulmonary embolus: A blood clot lodged in the lumen of a pulmonary artery as diagnosed by CT angiogram, pulmonary angiogram or ventilation perfusion scan.

(7)– Abdominal compartment syndrome: For the purposes of this study, a patient is considered to have abdominal compartment syndrome if they have a decompressive laparotomy. (Massive intestinal edema resulting in abdominal compartment syndrome may occur in any trauma patient who has undergone a period of profound shock. Crystalloid resuscitation, capillary leakage due to activated inflammatory mediators and reperfusion injury all contribute to this tissue swelling which can lead to significant cardiovascular, respiratory, renal and cerebral dysfunction. Clinically it is characterized by a fall in urine output associated with an elevated central venous pressure. The diagnosis can be confirmed by the measurement of intra-abdominal pressure.)

(8)– Extremity compartment syndrome: For the purposes of this study, a patient is considered to have extremity compartment syndrome if they have surgical decompression of the fascial compartments. (Swelling of tissue within its anatomical enclosure (e.g. a leg or arm muscle within its muscular sheath) producing pressure that interferes with circulation and adversely affects the function and health of the tissue itself.)

Item 6– *Date and time of final acute care hospital discharge or death? Enter date patient was discharged from the final hospital at which they received acute care related to this injury episode (if patient died in hospital, enter date and time of death).*

Item 7 – *Total ICU days:* Enter total number of ICU days. Count the first and last days in the ICU as one day each, even if in the ICU less than a full 24 hours.

Item 8 – *Since original hospital admission, was patient transferred to another acute care hospital for treatment of injuries suffered during original event?* Indicate whether or not the patient was transferred to another hospital since original hospital admission for continued care of acute injuries (as opposed to transfer to inpatient rehab or a vent weaning facility or a skilled nursing facility, etc). If “Yes” enter name and location of discharge hospital.

Item 9 – *Was the TBI Outcome Interview administered prior to hospital discharge for TBI patients? (TBI patients only)* Indicate whether or not the TBI Outcome Interview (TBIOI) was administered prior to discharge. If it was not, indicate why, choosing one answer from the list provided.

*If the patient is discharged prior to getting the TBIOI outcome interview done, you may use data you collect via a phone interview for up to seven days post-discharge. If you are unable to reach the patient for a phone interview you may, as a last resort, enter the data via chart review.*

Item 10 – *Disposition at discharge*: Choosing one from the list provided, indicate where the patient went at discharge.

*Inpatient rehab facility* is defined as being discharged from acute hospital care to either an adjoining rehab facility or admittance to a separate rehab facility with the purpose of providing temporary care that would allow the patient to regain strength and function with the intent of returning home or to an assisted living facility.

*Inpatient psychiatric facility* is a location where the patient receives 24-hour care by mental health professionals and healthcare providers.

*Skilled nursing facility* would indicate a location where the patient can receive high level nursing care, usually on a short-term basis. E.g. a nursing facility that could care for large wounds or manage someone with a trach.

*Nursing Home* would include any location where others are fully responsible for the care of the patient on a long-term basis. (E.g. where the patient lives)

*Home with services* means discharged to their home with a visiting nurse, chore services or outpatient physical therapy or occupational therapy.

*Home* is a relative term meaning that the patient was discharged to their own home or a home like situation (maybe with a relative) where they resumed independent care of themselves.

*Jail* means the patient was incarcerated upon discharge.

*Against Medical Advice* means the patient left the hospital against the advice of their doctor or medical team. This includes patients who leave without notifying their medical team or “elope”.

*Death*: Indicate the place of death choosing from the list provided.

Item 11 – *Cause of Death*: Indicate the primary and secondary causes of death, choosing from the lists provided. This information can be found by consulting the death note or the death certificate if one is available. It may be necessary to consult with the treating physician to determine the primary and secondary causes of death.

Item 12 – *Was care withdrawn prior to death?* If “No”, skip to item 8. If “Yes”, indicate why care was withdrawn. (May occur in situations where further treatment is deemed futile.) “CNS issues” may mean brain death, or a devastating or non-survivable head injury. “Organ failure” may mean single or multiple organ system failure deemed likely to be non-survivable making further interventions futile. “Other” - if this is selected, describe the reason that care was withdrawn, e.g. underlying terminal illness discovered.

Item 13 – *Were any adverse events uncovered during the hospitalization?* If yes, explain in the box provided and complete the CTC Alert form.

*Interim vital status: **Optional.** Complete this if the patient is still hospitalized at the time of hospital form completion or for a DSMB vital status sweep.*

After web entry, print the form and verify it against the worksheet or source document. If it matches, date and sign the verified information and place in your site files.

## Alert CTC Form

The purpose of the Alert CTC form is to notify the CTC regarding a potential adverse event, a protocol violation/deviation, or unusual circumstances related to the study. If any of the previously listed events occur, the CTC should be notified within 24 hours of discovery. The list provided below gives examples of the items that should be reported to the CTC. There are many other possible items that may be of interest. Basically, if there is any doubt whether an event should be reported, it should, at the very least, warrant a phone call to the CTC in order to discuss the situation. All potential events will be reviewed by CTC and RCC investigators.

It is possible to enter an Alert CTC form on the web that is not associated with an episode number (e.g. – leaking bag, damaged bag etc.) by going to the Main HS page and selecting the Alert CTC button on the right.

In cases associated with an episode, the episode date/time and episode ID will be pre-filled by the web data entry program and will be consistent with the date and time recorded on the Patient Enrollment Form. It should be reviewed here for accuracy.

Item 1 – *Date reported to CTC*: Enter the earliest date reported whether by phone or online form.

Item 2 – *Date of situation*: Date the situation or event occurred

Item 3 - *Type of situation*: Select one item from the lists provided in each category:

a) *Potential Safety Issues Related to Study Protocol* is defined as something directly related to the conduct of the study that may have adversely affected the patient, EMS personnel, or the community at large. Not all reported events will ultimately be classified as an AE. Each will be reviewed by the CTC staff as well as the ROC Investigators. All confirmed AEs must be reported to the IRB, FDA and the DSMB as required.

b) *Potential Protocol Violations/Deviations*: A protocol violation is a clear cut alteration from the agreed-upon protocol whereas a protocol deviation is not a defined alteration but a departure more from the spirit of the protocol. Many of these are derived from the inclusion/exclusion criteria.

c) *Potential Adverse Events*: Events which potentially have adverse effect. Adverse events will be considered to be study-related when the event follows a reasonable temporal sequence from administration of the study drug.

d) *Other Unusual circumstances*: Anything else that might be considered unusual and related to the study such as missing or damaged fluid bags.

Item 4 – *Explain circumstances*: Briefly explain the circumstances surrounding any issues identified above.

After web entry, print the form and verify it against the worksheet or source document. If it matches, date and sign the verified information and place in your site files.



**Guidelines for Alert CTC forms.**

Alert CTC forms can be triggered (become required automatically) in several ways which are summarized below:

**Enrollment form:**

**Question 2b** – Study fluid given?

Answering “No” (as in a “BONG” case); or if “Yes” indicating that <250 mls of study fluid was given or that the fluid was started anywhere other than the pre-hospital setting.

**Question 4** - Inclusion Criteria:

Checking “No” for “Blunt or penetrating trauma”

Checking “No” for **all** of “Pre-hospital SBP < 70 mm Hg”; “Pre-hospital SBP 71-90 **and** HR ≥ 108”; and “Pre-hospital GCS ≤ 8

**Question 5** - Exclusion Criteria:

Checking “Yes” to **any** of the listed exclusion criteria

**Pre-hospital form:**

**Question 4** – Fluids given:

Indicating that more than 2L of crystalloids or any rbc’s or any Mannitol were given prior to the study fluid.

If an Alert CTC is triggered in either of these situations from the Enrollment form, it need not be re-reported in another Alert CTC form.

**Resus/Injury Characteristics form:**

**Question 2** – Head CT Done within 7 days of episode date:

Answering “Yes” to Evidence of increased intracranial bleeding on the 2nd or 3rd head CTs.

Examples of Alert CTC situations

- Protocol violations will usually trigger an Alert CTC form based on information you enter on the Enrollment Form.
- <250mls of study fluid administered will trigger an Alert CTC form from the Enrollment Form
- Administration of study fluid anywhere other than the “Pre-hospital” setting will trigger an Alert CTC form based on information you enter on the Enrollment Form.
- Increased intracranial hemorrhage will trigger an Alert CTC form when indicated on the Resus/Injury form
- Hyponatremia (Na> 160mEq/L) should be reported as an adverse event based on what point the patient’s course that it occurred.

If in doubt about how to report an event or whether or not to report an event please call the CTC. Generally speaking it is worse for safety monitoring in any study to under-report than to over-report concerns.

## Pt/Family Consent Form

The purpose of this form is to document family/patient study notification and consent practices for any patient that is enrolled in the study. *This is not a substitute for your IRB/REB approved consent form(s).* Local IRB/REB requirements should be followed regarding notification of patients/families that either die in the field or in the ED/hospital. All patients and family should ideally be contacted by study personnel before they are discharged from the hospital. This situation allows time for discussion of study questions as well as consenting for medical records review and future contact by study staff. When consenting patients/family, it is prudent to seek permission from the patient's physician first and to have a member of the patient's care team, such as the bedside nurse introduce you. This may provide the patient/family with more confidence in participating in research. It will also establish your identity for follow-up phone calls as well as gathering contact information (phone/address for contacts). The patient and family should be informed that the follow up phone call(s) should only take about 10 or 15 minutes each.

The procedures for consent/notification will vary slightly from site to site. For example, some IRBs require an "assent" form for patients under the legal age of consent, in addition to having their parent(s) or LAR sign the consent form. Please check with your local IRB/REB.

The episode date/time and episode ID will be pre-filled by the web data entry program and will be consistent with the date and time recorded on the Patient Enrollment Form. It should be reviewed here for accuracy.

- Item 1 – *Was patient and/or family/LAR notified that patient was in study?* If "Yes", indicate who was notified and the date notification took place. If "No" is selected, explain why in the space provided.
- Item 2 – *Did patient and/or family and/or LAR consent to review of records?* If "Yes", indicate who gave consent and the date consent took place. If "No", indicate why not; if consent is refused, briefly explain why; if "Other" is selected, document and explain attempts to obtain consent in item 4. (Please note that selecting "Other" causes the form to stay in "E" status).
- Item 3 – *Did the patient and/or family and or LAR consent to a 1<sup>st</sup> follow-up call and a 6 month post-injury follow-up call?* If "Yes", indicate who gave consent and the date consent took place. If "No", indicate why not; if consent is refused, briefly explain why; if "Other" is selected document and explain attempts to obtain consent in item 4. (Please note that selecting "Other" causes the form to stay in "E" status).
- Item 4 – *Document and explain attempts to contact patient or patient representative:* Track all contact attempts here including date, type of attempt and results of attempts. This documentation will be necessary in cases where consent was not obtained and a "Form Close-out" is requested.

After web entry, print the form and verify it against the worksheet or source document. If it matches, date and sign the verified information and place in your site files.



## Patient Information Form

The purpose of this form is to provide the information necessary to contact the subject or the subject's representative who have consented for follow-up. *This form is kept at the site and not submitted to the CTC.*

Follow-up schedule:

- **First Follow-up - All subjects** who have left the hospital prior to Day 28 will get a follow-up call to assess vital status and complications since discharge (See the form "First Follow-up"). Shock subjects will be called 28 days after their injury. TBI subjects should be called one month after discharge. TBI subjects should have their contact information validated at this time.
- **TBI subjects ONLY** will be contacted additionally at:
  - **Six months after injury** to administer the TBI Outcome Interview for the final time.

Previous experience with follow-up studies in the trauma population has demonstrated variable success in achieving adequate response rates. This is a relatively young and mobile population and thus can be difficult to track once discharged from the hospital.

In the event that the patient changes his location of residence from the time of discharge, it is paramount that there are alternative names, addresses, and phone numbers that can be used to contact the patient or the patient's representatives. It may be necessary to contact the patient's family (or friends) at the time of discharge in order to complete the entire form. This contact information is vital in order to ensure adequate follow-up data for vital statistics and basic neurologic function. This form will be kept at the site.



## First Follow-up Form

The purpose of this form is to document the patient vital status at 28 days post injury. It will be filled out on all patients discharged alive prior to Day 28. For patients in the hypovolemic shock cohort fill this form out at Day 28 post injury. For the TBI cohort (for whom VS at Day 28 is a secondary endpoint), and for patients who are in both the hypovolemic shock cohort and the TBI cohort, fill this form out at 1 month from discharge and also administer the TBI outcome interview. This one month TBI interview could be used as back-up data for the primary end-point in case the patient cannot be interviewed at 6 months. (Administering the TIB outcome interview during the first follow-up call does NOT mean that you don't call the patient at 6 months. You must still get the primary outcome, e.g. the TBI outcome interview at 6 months from injury).

If the patient has left the hospital prior to Day 28, use the previously collected contact information to call them. This should be a relatively short (~10 minutes) phone call.

The episode date/time and episode ID will be pre-filled by the web data entry program and will be consistent with the date and time recorded on the Patient Enrollment Form. It should be reviewed here for accuracy.

Item 1 – *Was patient or patient representative successfully contacted?* If “No”, skip to item 5 and document and explain attempts to contact patient in item 6. (Please note that a “No” answer causes the form to stay in “E” status). If “Yes”, enter the date of the contact and note where contacted. If the patient died but you successfully contacted someone to confirm the death, answer “Yes” to this question.

Item 2 – *Was the patient difficult to contact?* Indicate whether or not the TBI cohort was difficult to contact.

Item 3 – *Follow-up conducted with whom?* Note whether the contact was with the patient, the family or “other”.

Item 4 – *Was the patient re-hospitalized after discharge?* If the patient was re-hospitalized, record LOS and reason for hospitalization (e.g. Infection) .

Item 5 – *Was vital status ascertained?* If “Yes”, complete items 5a & 5 b.

*5a: Vital status:* Note the vital status of the patient. If the patient died, note the date of death. If the exact date is unknown you may alternatively enter the month and year. Briefly note any available information on cause of death.

Please note that while you may use official public records such as state death registries, obituaries or court documents to confirm “death” as the vital status, you cannot conversely assume that they are alive if their name is **not** found on lists of this type.

*5b: How was vital status ascertained?* Choose one answer from the list provided, if “Other” is selected, explain briefly

Item 6 – *Attempts to contact patient or patient representative:* Document and explain all contact attempts here including date, type of attempt and results of attempts.

This documentation will be necessary in cases where follow-up was not obtained and a "Form Close-out" is requested.

After web entry, print the form and verify it against the worksheet or source document. If it matches, date and sign the verified information and place in your site files.

## 6 month Follow-up Form

The purpose of this form is to document the patient's vital status at six months after injury and to document six month follow-up for TBI patients.

The episode date/time and episode ID will be pre-filled by the web data entry program and will be consistent with the date and time recorded on the Patient Enrollment Form. It should be reviewed here for accuracy.

Item 1 – *Was patient or patient representative successfully contacted?* Note the date of the contact. If the patient died but you successfully contacted someone to confirm the death, answer “Yes” to this question. If “No”, document and explain attempts to contact patient in item 4.

Item 2 – *Follow-up conducted with whom?* Note whether the contact was with the patient, family or other.

Item 3 – *Vital status.* Note the vital status of the patient and the date that the vital status was ascertained. If the exact date of death is unknown you may alternatively enter the month and year. If dead, briefly list any information available on cause of death. If the patient is alive, complete the TBI Outcome Interview form. Please note that while you may use public records such as state death registries or obituaries to confirm “death” as the vital status, you cannot conversely assume that they are alive if their name is **not** found on lists of this type.

Item 4 – *Document and explain attempts to contact patient or patient representative:* Track all contact attempts here including date, type of attempt and results of attempts. This documentation will be necessary in cases where follow-up was not obtained and a “Form Close-out” is requested.

After web entry, print the form and verify it against the worksheet or source document. If it matches, date and sign the verified information and place in your site files.





## TBI Outcome Interview Form

This questionnaire combines the Glasgow Outcome Score-Extended (GOSE) and the Disability Rating Score (DRS) rating systems. Both the GOSE and the DRS are designed to classify patients based on their degree of function after brain injury. The intent of both scoring systems is to give a broad indication of disability, rather than specific information about particular impairments. For the TBI cohort, this is the primary endpoint when administered at 6 months after injury and a secondary endpoint when administered at discharge and one month post discharge. This interview is intended to be done in person; however a patient may occasionally be discharged from the hospital before the discharge TBI outcome interview (TBIOI) can be completed by the site personnel. In this situation, the **discharge** TBIOI can be done by chart review and so indicated on the web form itself. (Note -If the discharge TBIOI is done by chart review the “date of the interview” should be the date the patient was discharged from the hospital).

In some cases the subject may be conversant but not reliable due to their brain injury. To assess this, the interviewer will screen patients for cognitive impairment by explaining the study to them at the phone contact and then asking them two cognitive screening 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 subject is unable to answer these questions, then a care giver 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 at 6 months.*** Using the patient contact form and tracking contact attempts will increase your follow-up success rate. Using the same interviewer for consecutive interviews is recommended to maintain consistency and accuracy.

Remember these points when conducting the interview:

1. Disability due to head injury is identified by a change from pre-injury status.
2. Only pre-injury status and current status should be considered. (How sick they were while they were hospitalized, is not considered in rating their disability).
3. Disability must be a result of mental or physical impairment. (E.g. the fact that their car was totaled and therefore they **do not** drive does not mean that they **cannot** drive).
4. Use the best source of information available. (e.g. use the cognitive pre-screening questions to determine who should be responding to the interview questions).

The episode date/time and episode ID will be pre-filled by the web data entry program and will be consistent with the date and time recorded on the Patient Enrollment Form. It should be reviewed here for accuracy.

Item 1 – *Interview?* Note the date of the contact. Enter the name of the RCC personnel who conducted the interview. The web will automatically calculate the interval post injury by subtracting the date of contact from the episode date.

Item 2 – *Respondent:* Please note the respondent. If the respondent is a caregiver, identify the caregiver and indicate how many hours a day that person spends with the patient. Regardless of who the respondent was, please indicate if the patient was able to answer the two “cognitive screening questions”.

This interview is intended to be done in person; however a patient may occasionally be discharged from the hospital before the discharge TBI outcome interview (TBIOI) can be completed by the site personnel. In this situation, you may conduct the discharge TBIOI by phone for up to one week after discharge, other wise the discharge TBIOI may be done by chart review. Indicate this on the form and briefly explain why the in person interview was not able to be obtained.

Item 3a–*Is the head injured person able to obey simple commands or say any words?* A “yes” answer indicates the patient is not in a vegetative state. Eye movements are not reliable evidence of meaningful responsiveness. If unclear, corroborate with nursing staff.

Item 4a – *Is the assistance of another person at home essential every day for some activities of daily living?* For a “no”, the patient should be able to care for himself at home for 24 hours if necessary. Independence include the ability to plan for and carry out the following activities: bathing, dressing, preparing food, dealing with callers, and handling minor domestic crises (e.g. broken glass, tap is left running, a light goes out, it begins to get cold, stranger comes to the door). The patient should be able use the telephone to summon help or report problems if needed. Indicate “Yes” or “No. If “No” answer item C only.

Item 4b – *Does the patient require frequent help or someone to be around the home most of the time?* For a “no”, the patient should be able to care for himself for up to 8 hours a day if necessary, though they need not actually look after themselves.

Item 4c - *Was assistance at home required before the injury?* Indicate “Yes” or “No. This information distinguishes between a pre-existing condition and a change due to injury.

Item 5a - Shopping includes being able to plan what to buy, take care of money independently and behave appropriately in public.

i – *Can the patient shop without assistance?* Indicate “yes” or “No”.

ii – *Was the patient able to shop without assistance prior to the injury?* Indicate “yes” or “No”. This information distinguishes between a pre-existing condition and a change due to injury.

Item 5b: Travel includes either driving or the use of public transit. Ability to use a taxi is sufficient, provided the person can call for the taxi and instruct the driver independently.

i - *Is the patient able to travel locally without assistance?* Indicate “Yes” or “No

ii – *Was the patient able to travel without assistance prior to the injury?* Indicate “yes” or “No”. This information distinguishes between a pre-existing condition and a change due to injury.

Item 5c: Work typically is defined as a job which earns a wage in a position that, at least theoretically, is open to others. (For retirees or full-time home makers, assess whether or not there has been a change in their ability to perform the same tasks as they did pre-injury.) If patients 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 chance 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. For students, differentiate between disruptions due to absence and reduced capacity for study: increased difficulties in studying, unaccustomed problems with progress e.g. failing grades; revised program of study because of problems.

i – *Is the patient working at his/her previous capacity?* Has there been a change in level of skill or responsibility required? E.g. a change from full-time to part-time working, special allowances (increased supervision), change from steady to casual employment (e.g. no longer able to hold steady job). Distinguish between changes in employment due to end of contract, retirement or redundancy. Indicate “Yes” or “No. If “yes” skip to question iii.

ii – *How restricted are they?* Indicate level of restriction choosing from the list provided.

iii – *Prior to injury was the patient?* Describe the patient’s level of pre-injury employment as indicated.

Item 6: Social and leisure activities can vary depending on the age and background of the patient and might range from actively participating in sport, attending sporting events as a spectator, walking, going to a club or pub or visiting friends. Remember that some activities are seasonal.

Item 6a – *Is the patient able to resume regular social and leisure activities outside the home?* Indicate “Yes” or “No. If “Yes” complete item C only.

Item 6b – *What is the extent of restriction on their social and leisure activities?* Ultimately for the sake of simplicity, the fact of participation post – injury as compared to pre- injury is rated.

Item 6c – *Did the patient engage in regular social and leisure activities outside the home before the injury?* Indicate “yes” or “No”. This information distinguishes between a pre-existing condition and a change due to injury.

Item 7: Family and friendships: Typical post-traumatic personality changes: quick temper, irritability, insensitivity to others, mood swings, depression and unreasonable childish behavior.

Item 7a – *Have there been psychological problems which have resulted in ongoing family disruption or disruption to friendships?* Indicate “yes” or “No”. If “No”, complete item C only.

Item 7b – *What has been the extent of the disruption or strain?* Indicate the extent of the disruption.

Item 7c - *Were there problems with family or friends before the injury?* Indicate “yes” or “No”. If there were some problems, but the problems have become markedly worse since the injury, then the answer should be “No”.

Item 8: Return to normal life. Other typical problems reported after head injury include: headaches, dizziness, tiredness, sensitivity to noise/light, slowness, memory failures and concentration problems

Item 8a – *Are there any other current problems relating to the injury that affect daily life?* Indicate “yes” or “No”.

Item 8b - *Were there similar problems present before the injury?* Indicate “Yes” or “No”. This information distinguishes between a pre-existing condition and a change due to injury.

Item 9 – *What do you feel has had the greatest impact on outcome following this injury?* Choose answer from the list provided

Item 10: Level of consciousness. This section is very similar to the Glasgow Coma Scale.

Item 10a – *Does the patient open eyes?* It may be best to read the choices to the respondent to get the most accurate answer.

- Spontaneous (eyes open with sleep/wake rhythms indicating active arousal mechanisms, does not assume awareness)
- To Speech (a response to any verbal approach, whether spoken or shouted, not necessarily the command to open the eyes. Also, response to touch, mild pressure.)
- To pain (tested by a painful stimulus.)
- None (no eye opening even to painful stimulation)

Item 10b – Communication ability? It may be best to read the choices to the respondent to get the most accurate answer.

- Oriented (implies awareness of self and the environment. Patient able to tell you a) who he is; b) where he is; c) why he is there; d) year; e) season; f) month; g) day ; h) time of day)
- Confused but conversant (attention can be held and patient responds to question but responses are delayed and/or indicate varying degrees of disorientation and confusion.)

- Inappropriate (intelligible articulation but speech is used only in an exclamatory or random way (such as shouting and swearing); no sustained communication exchange is possible.)
- Incomprehensible (moaning, groaning or sound without recognizable words; no consistent communication signs.)
- None (no sounds or communication signs from patient)

Item 10c - What is the patient's best motor response? It may be best to read the choices to the respondent to get the most accurate answer.

- Obeys commands (obeying command to move finger on best side. If no response or not suitable try another command such as "move lips", "blink eyes", etc. Do not include grasp or other reflex responses.)
- Localizes to pain (a painful stimulus at more than one site causes limb to move (even slightly) in an attempt to remove it. It is a deliberate motor act to move away from or remove the source of noxious stimulation. If there is doubt as to whether withdrawal or localization has occurred after 3 or 4 painful stimulations, rate as localization.)
- Withdraws from pain (any generalized movement away from a noxious stimulus that is more than a simple reflex response.)
- Flexor posturing (painful stimulation results in either flexion at the elbow, rapid withdrawal with abduction of the shoulder or a slow withdrawal with adduction of the shoulder. If there is confusion between flexing and withdrawing, then use pinprick on hands.)
- Extensor posturing (painful stimulation results in an extension of the limb.)
- None (no response can be elicited. Usually associated with hypotonia. Exclude spinal transaction as an explanation of lack of response; be satisfied that an adequate stimulus has been applied.)

Item 11: Cognition and independence. Items 11 a, 11b and 11c focus specifically on the cognitive ability, not the physical ability to perform these tasks. Assess if the patient shows awareness of when and how to perform each specified activity.

Item 11a - Does the patient have the cognitive ability to feed himself? E.g. how to use suitable utensils, how to bring food to his mouth, how to drink and swallow safely, how to open cans, cut meat, put straw in glass, scoop food, pour liquids, how to chew, when to eat. Select from the choices listed.

- Complete (continuously shows awareness that he knows how to feed and can convey unambiguous information about when this activity should occur.
- Partial: Intermittently shows awareness that he knows how to feed and/or can intermittently convey reasonably clearly information that he

*knows when this activity should occur. Subject may be able to eat with some supervision (e.g. due to eating too fast if not prompted) and asks for food at appropriate time*

- Minimal: Shows questionable or infrequent awareness that he knows in a primitive way how to feed and/or shows infrequently by certain signs, sounds or activities that he is vaguely aware when the activity should occur. Subject seems vaguely aware, once or twice per week asks for food. Can eat a modified diet because of choking due to gulping.
- None: (shows virtually no awareness at any time that he knows how to feed self and cannot convey information by signs, sounds; or activity that he knows when the activity should occur.

Item 11b – *Does the patient have the cognitive ability to use the toilet?* Select from the choices listed.

- Complete: (continuously shows awareness that he knows how to toilet and can convey unambiguous information that he knows when this activity should occur.)
- Partial: (Intermittently shows awareness that he knows how to toilet and/or shows infrequently by certain signs, sounds or activities that he is vaguely aware when the activity should occur.) Continent of bowel during the day, indicates need to void, but by the end of the day does not consistently show awareness of need (due to fatigue or confusion)
- Minimal: (shows questionable or infrequent awareness that he knows in a primitive way how to toilet and /or shows infrequently by certain signs, sounds or activities that he is vaguely aware when the activity should occur.) Indicates awareness for both bowel and bladder during the day but is incontinent at night. Subject rarely shows that he can help with toileting activities.
- None: (Shows virtually no awareness at any time that he knows how to toilet and cannot convey information by signs, sounds; or activity that he knows when the activity should occur.

Item 11c - *Does the patient have the cognitive ability to groom and dress?* (E.g. wash, brush teeth, comb or brush hair, bathe, dress, shave). Select from the choices listed.

- Complete: (continuously shows awareness that he knows how to groom self and can convey unambiguous information that he knows when this activity should occur.)
- Partial: (Intermittently shows awareness that he knows how to groom self and/or shows infrequently by certain signs, sounds or activities that he is vaguely aware when the activity should occur ) Caregiver sets up

*all the equipment for personal hygiene (toothbrush, comb, shaver) sets out clothes, then he can dress and complete tasks independently.*

- Minimal: (shows questionable or infrequent awareness that he knows in a primitive way how to groom self and/or shows infrequently by certain signs, sounds or activities that he is vaguely aware when the activity should occur.) Subject does not initiate any personal hygiene tasks, and will wear the same clothing for several days. He requires close supervision for some hygiene items due to safety.
- None: (Shows virtually no awareness at any time that he knows how to groom self and cannot convey information by signs, sounds; or activity that he knows when the activity should occur.

Item 12 – How would you describe the patient's current level of functioning (physical, mental, emotional, or social)? Indicate the patient's level of independence, selecting from choices listed.

- Completely independent: (able to live as he wishes, requiring no restriction due to physical, mental, emotional or social problems)
- Independent in a special environment (capable of functioning independently when needed requirements are met (mechanical aids such as crutches, cane or memory books)
- Mildly dependent-limited assistance (able to care for most of own needs but required limited assistance due to physical, cognitive and/or emotional problems (e.g., needs non-resident helper).)
- Moderately dependent-moderate assist (person in home) (able to care for self partially but needs another person at all times.)
- Markedly dependent-asst a; major activities all the time (needs help with all major activities and the assistance of another person at all time.)
- Totally dependent-24 hour nursing care (not able to assist in own care and requires 24-hour nursing.)

After web entry, print the form and verify it against the worksheet or source document. If it matches, date and sign the verified information and place in your site files.





## QUICK REFERENCE

### Adverse Events

**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 result 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 or 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.

**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 or severe head injury.

Adverse events will be considered to be study-related when the event follows a reasonable temporal sequence from administration of the study drug.

### REPORTING ADVERSE EVENTS

- 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.
- CTC should be alerted within 24 hours of the site being notified of an adverse event.

## **Potential Serious Adverse Events (SAEs) in the HS study**

### **Anaphylaxis**

A severe, whole body allergic reaction. Tissues in different parts of the body release histamine and other substances. This causes constriction of the airways, resulting in wheezing, difficulty breathing, and gastrointestinal symptoms such as abdominal pain, cramps, vomiting, and diarrhea. Histamine causes the blood vessels to dilate (which lowers blood pressure) and fluid to leak from the bloodstream into the tissues (which lowers the blood volume). These effects result in shock. Fluid can leak into the alveoli (air sacs) of the lungs, causing pulmonary edema.

Hives and angioedema (hives on the lips, eyelids, throat, and/or tongue) often occur. Angioedema may be severe enough to block the airway. Prolonged anaphylaxis can cause heart arrhythmias.

Anaphylaxis can occur in response to any allergen. Common causes include insect bites/stings, horse serum (used in some vaccines), food allergies and drug allergies. Some people have an anaphylactic reaction with no identifiable cause.

Anaphylaxis occurs infrequently. However, it is life-threatening and can occur at any time. Risks include prior history of any type of allergic reaction. This should be reported as a serious adverse event.

### **Evidence of increased intracranial hemorrhage on head CT scan**

For patients with > 1 head CT during the first 7 days following the injury episode date, the 2nd and 3rd CT's should be reviewed for evidence of increased intracranial hemorrhage on. If present, this should be reported as a serious adverse event.

### **Hypernatremia**

Sodium >160 mEq/L requiring therapeutic intervention should be reported as a serious adverse event.

### **Seizure**

The physical manifestations (as convulsions, sensory disturbances, or loss of consciousness) resulting from abnormal electrical discharges in the brain (as in epilepsy). This should be reported as a serious adverse event if associated with hypernatremia.

### **Death unexplained by injury severity**

Any death which is not explained by injury severity will be reported and reviewed. If it is not possible to exclude the possibility that the study protocol, in whole or in part, played a role in the death, then it will be reported as a serious adverse event.

## **ALI/ARDS definitions**

### **Acute Lung Injury (ALI):**

- (a) Hypoxia with a  $\text{PaO}_2/\text{FiO}_2$  ratio  $>200, \leq 300$  and
- (b) bilateral infiltrates on chest X-ray and
- (c) no clinical evidence of increased left atrial pressure or a pulmonary artery pressure of  $<18\text{mmHg}^*$

### **Acute Respiratory Distress Syndrome (ARDS):**

- (a) Hypoxia with a  $\text{PaO}_2/\text{FiO}_2$  ratio  $\leq 200$  and
- (b) bilateral infiltrates on chest X-ray and
- (c) no clinical evidence of increased left atrial pressure or a pulmonary artery pressure of  $<18\text{mmHg}^*$

*\*For those without pulmonary catheter, monitoring clinical evidence of left atrial hypertension includes:*

- a) Acute myocardial infarction or known cardiomyopathy or severely reduced ejection fraction ( $<30\%$ ) or critical valvular disease*
- b) Chronic or acute oliguric renal failure with fluid input that exceeds output by  $\geq 3$  liters in the previous 24 hours*

## **Predicted Body Weight (PBW) calculations**

To calculate predicted body weight (PBW):

**Males** =  $50 + 2.3 [\text{height (inches)} - 60]$

**Females** =  $45.5 + 2.3 [\text{height (inches)} - 60]$

## **Base Deficit Calculations**

The base excess is a calculated figure which provides an estimate of the metabolic component of the acid-base balance. Because the base excess is a calculated (not a measured) value, it may be inaccurate and misleading. Despite these problems, it is important to understand the concept.

Uncorrected hemorrhagic shock will lead into inadequate cellular perfusion, anaerobic metabolism and the production of lactic acid. This leads to profound metabolic acidosis which also interferes with blood clotting mechanisms and promotes coagulopathy and blood loss. As efficient tissue perfusion is restored, the lactate concentration will fall. Serial monitoring of base deficit can be an effective gauge of resuscitation efforts.

### Base Excess (Base deficit)

Definition: Base that must be added to restore a normal pH

Normal Range: -2 to +2 mEq/L

A base excess > +3 = metabolic alkalosis

a base excess < -3 = metabolic acidosis (Base deficit)

### Calculation

Base Excess = (Actual pH – Predicted pH) \* 67

Calculate predicted pH based on PaCO<sub>2</sub>

### Interpretation

Positive (Base Excess)

Metabolic Alkalosis

Negative (Base Deficit)

Metabolic Acidosis: This is characterized by a primary decrease in serum bicarbonate and a slight decrease in paCO<sub>2</sub>. Serum pH may be reduced or normal.)

Raised serum lactate and base deficit are indicators of tissue hypoxia associated with hypoperfusion that follows hypovolemia.

## **Infectious and non-infectious complications tracked in the data forms defined**

### **Definitions for Nosocomial Infections**

#### **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 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)

#### **Cholecystitis**

Acute inflammation of the gallbladder as diagnosed by ultrasound.

#### **Empyema**

Positive bacterial cultures from a tap of the pleural fluid.

#### **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.

#### **Line Infection**

This refers to a central line infection and is diagnosed by either a positive line tip culture *or* the presence of pus and erythema at the central line insertion site.

#### **Meningitis**

Inflammation of the meninges, as diagnosed by lumbar puncture with positive cultures.

#### **Pseudo-membranous colitis**

A form of gastroenteritis which occurs when there is an over-growth of *Clostridium difficile* bacteria in the intestine, as evidenced by a stool culture positive for *C. difficile* toxin.

#### **Pneumonia**

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

1. Radiological 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/mm<sup>3</sup> **or** 25% increase over last available value **or** bands > 10% of total WBC **or** new decrease in WBC to < 4000/mm<sup>3</sup>
3. Bacteriologic confirmation by **at least one of:**

- positive blood culture for bacterial pathogen also identified in sputum or pathogenic bacteria (if not quantitative, then must be moderate or heavy growth) 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 bacteria.

### **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  $< 4000/\text{mm}^3$

### **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

## **Definitions for Non-infectious complications**

### **Abdominal Compartment syndrome**

For the purposes of this study, a patient is considered to have abdominal compartment syndrome if they have a decompressive laparotomy.

### **Acute Lung Injury (ALI):**

- a) Hypoxia with a  $\text{PaO}_2/\text{FiO}_2$  ratio  $>200$ ,  $\leq 300$  *and*
- b) bilateral infiltrates on chest X-ray *and*
- c) no clinical evidence of increased left atrial pressure or a pulmonary artery pressure of  $<18\text{mmHg}^*$

### **Acute Respiratory Distress Syndrome (ARDS):**

- A) Hypoxia with a  $\text{PaO}_2/\text{FiO}_2$  ratio  $\leq 200$  *and*
- b) bilateral infiltrates on chest X-ray *and*
- c) no clinical evidence of increased left atrial pressure or a pulmonary artery pressure of  $<18\text{mmHg}^*$

*\*For those without pulmonary catheter monitoring clinical evidence of left atrial hypertension includes:*

- a) Acute myocardial infarction **or** known cardiomyopathy **or** severely reduced ejection fraction (<30%) **or** critical valvular disease*
- b) chronic or acute oliguric renal failure with fluid input that exceeds output by  $\geq 3$  liters in the previous 24 hours*

### **Cardiac arrest**

The complete cessation of cardiac activity (heart beat) as documented in the chart.

### **Cerebral infarction**

Infarction of brain tissue as documented by CT or MRI findings.

### **Deep venous thrombosis (DVT)**

A blood clot that forms in a vein resulting in obstruction of venous flow, as documented by venous duplex testing.

### **Extremity compartment syndrome**

Swelling of tissue within its anatomical enclosure (e.g. a leg or arm muscle within its muscular sheath) producing pressure that interferes with circulation and adversely affects the function and health of the tissue itself. For the purposes of this study a patient is considered to have extremity compartment syndrome if they have surgical decompression of the fascial compartments.

### **Fat embolism syndrome**

Ultimately fat embolism syndrome is a clinical diagnosis of exclusion made by an attending or consulting physician and documented in the chart. This syndrome may include multiple signs and symptoms of varying subtlety (e.g. unexplained petechiae, unexplained hypoxia or difficulty ventilating, etc. usually occurring in the presence of a long bone fracture.)

### **Myocardial infarction**

To diagnose myocardial infarction, criteria one and two OR three must be satisfied:  
1) A typical rise and fall of biochemical indicators of myocardial necrosis. (Defined by the Joint European Society of Cardiology/ACC as "maximal concentration of troponin T or I exceeding the decision limit (99th percentile of the values for a reference control group) on at least one occasion during the first 24 hours after the index clinical event; or maximum value of CK-MB (preferably CK-MB mass) exceeding the 99th percentile of the values for a reference control group on 2 successive samples, or the maximal value exceeding twice the upper limit of normal for the specific institution on one occasion during the first hours after the index clinical event.")

**AND** at least one of the following:

- 2)
  - a) Ischemic symptoms
  - b) Development of pathologic Q's on ECG
  - c) ECG changes indicative of ischemia (ST elevation or depression)



d) Coronary intervention.

**OR**

3) For the purpose of this study, a patient with non-specific ECG changes and elevated troponin (for whom the differential diagnoses include acute coronary syndrome and blunt chest trauma) will be classified as MI to ensure adequate review of potential complications.

**Pulmonary embolus**

A blood clot lodged in the lumen of a pulmonary artery as diagnosed by CT angiogram, pulmonary angiogram or ventilation perfusion scan.

**Injury scoring systems: AIS, NISS and TRISS**

**Abbreviated Injury Scale AIS and Injury Severity Score (ISS)**

The Abbreviated Injury Scale assigns a unique seven digit numerical identifier to describe diagnosed injuries and their severity. The first six digits describe and classify injuries by anatomical region; the 7<sup>th</sup> digit (to the right of the decimal point) is the severity scale. The 6 point ordinal severity scale ranges from AIS 1 (minor) to AIS 6 (currently untreatable).

<u>AIS code</u>	<u>Description</u>
1	Minor
2	Moderate
3	Serious
4	Severe
5	Critical
6	Maximum

The AIS is the foundation for the Injury Severity which is the sum of the squares of the highest AIS code in each of the three most severely injured ISS body regions. The six body regions of injuries used in calculating the ISS are:

Head/ neck: Includes injury to the brain or cervical spine, and skull or cervical spine fractures.

Face: includes injuries to the mouth, ears, eyes, nose and facial bones.

Chest: Includes injuries to the chest and the contents of the chest cavity, and also injuries to the diaphragm, rib cage and thoracic spine.

Abdominal or pelvic contents: Includes injuries to organs in these cavities, including lumbar spine lesions.

Extremities or pelvic girdle: Includes injuries to the extremities or to the pelvic or shoulder girdle including sprains, fractures, dislocation and amputations, except for the spinal column, skull and rib cage. Included here are injuries to the femoral artery and veins.

External: Includes lacerations, contusions, abrasions and burns independent of their location on the body surface.

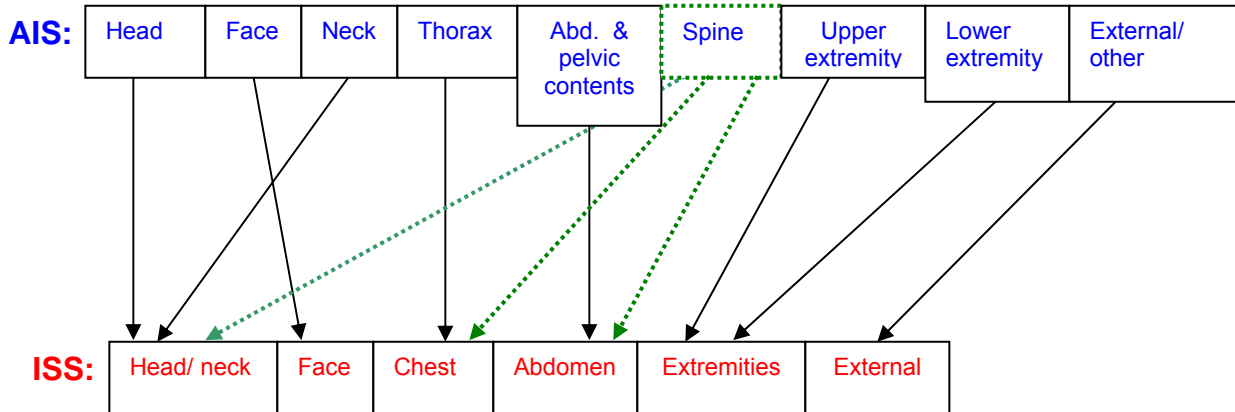
ISS scores range from 1 to 75. A score of 75 results in one of two ways, either with three AIS 5 injuries, or with at least one AIS 6 injury. Any injury coded AIS 6 is automatically assigned an ISS of 75. If there is any doubt about the severity of an injury, code conservatively.

**New injury Severity Score (NISS)**

The NISS is calculated from the three worst injuries suffered **regardless** of anatomical region. This allows for a higher severity score even if all injuries are limited to one area of body – some argue this is a more accurate mortality predictor.

**AIS 98 cheat sheet**

The AIS dictionary divides the body into 9 regions for describing assigned injury severity, then these 9 regions are compressed into 6 for the purposes of computing the ISS score:



**HINT #1 Spinal injuries** are coded in the region that contains the level of injury, i.e. cervical injuries are coded in the Head/Neck region; thoracic spine injuries into the Chest region; Lumbar spine injuries into Abdomen.

**Hint #2** Abrasions, contusions, hematomas, lacerations, avulsions and burns are coded in the **EXTERNAL** region

ISS region	Includes AIS areas	Except for
<b>Head/Neck</b>	<b>Head</b> 11300.6 – 16100.2 <b>Neck</b> 31100.6 – 350200.2 <b>Cervical spine</b>	<i>Head 110099.1 through 110808.3 code External</i> <i>Neck 310099.1 through 310806.3 code External</i>
<b>Face</b>	<b>Face</b> 21600.1 – 251800.2	<i>Face 210099.1 through 210806.3 code External</i>
<b>Chest</b>	<b>Thorax</b> 411000.2 – 450804.2 <b>Thoracic spine</b>	<i>Thorax 410099.1 through 410806.3 code External</i>
<b>Abdomen</b>	<b>Abd and pelvic contents</b> 516000.1 – 545626.3 <b>Lumbar spine</b>	<i>Abd/ pelvic 510099.1 through 510806.3 code External</i>
<b>Extremities</b>	<b>Upper extremity</b> 711000.3 – 753206.3 <b>Lower extremity</b> 811000.3 - 853606.1	<i>Upper ext. 710099.1 through 710806.3 code External</i> <i>Lower ext. 810099.1 through 810806.3 code External</i>
<b>External</b>	<b>External/Other</b> 910200.1- 912032.6 <b>AND</b> includes AIS scores for abrasions, contusions, lacerations, avulsions, burns from all regions of the body: see list of AIS scores in right hand column	

**Revised Trauma Score (RTS)\***

The Revised Trauma Score is a physiological scoring system, with high inter-rater reliability and demonstrated accuracy in predicting death. It is scored from the first set of data obtained on the patient, and consists of the Glasgow Coma Scale, Systolic Blood Pressure and Respiratory Rate.

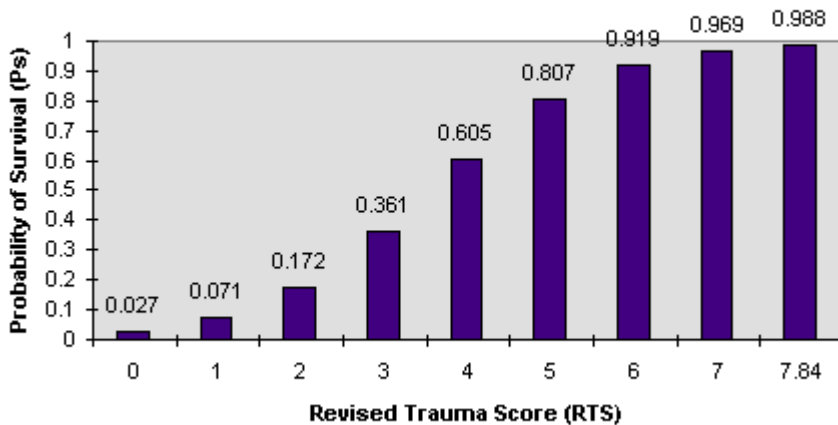
Glasgow Coma Scale (GCS)	Systolic Blood Pressure (SBP)	Respiratory Rate (RR)	Coded Value
13-15	>89	10-29	4
9-12	76-89	>29	3
6-8	50-75	6-9	2
4-5	1-49	1-5	1
3	0	0	0

$$RTS = 0.9368 \text{ GCS} + 0.7326 \text{ SBP} + 0.2908 \text{ RR}$$

Values for the RTS are in the range 0 to 7.8408. The RTS is heavily weighted towards the Glasgow Coma Scale to compensate for major head injury without multi-system injury or major physiological changes. A threshold of RTS < 4 has been proposed to identify those patients who should be treated in a trauma center, although this value may be somewhat low.

The RTS correlates well with the probability of survival.

**Survival Probability by Revised Trauma Score**



\*From Trauma.org website

**Trauma Score - Injury Severity Score: TRISS \***

TRISS determines the probability of survival (Ps) of a patient from the ISS and RTS using the following formulae:

$$Ps = 1 / (1 + e^{-b})$$

Where 'b' is calculated from:

$$b = b0 + b1(RTS) + b2(ISS) + b3(AgeIndex)$$

The coefficients b0 - b3 are derived from multiple regression analysis of the Major Trauma Outcome Study (MTOS) database. Age Index is 0 if the patient is below 54 years of age or 1 if 55 years and over. b0 to b3 are coefficients which are different for blunt and penetrating trauma. If the patient is less than 15, the blunt coefficients are used regardless of mechanism.

	<b>Blunt</b>	<b>Penetrating</b>
<b>b0</b>	-0.4499	-2.5355
<b>b1</b>	0.8085	0.9934
<b>b2</b>	-0.0835	-0.0651
<b>b3</b>	-1.7430	-1.1360

The TRISS calculator determines the probability of survival from the ISS, RTS and patient's age. ISS and RTS scores can be inputted independently or calculated from their base parameters.

\*From the TRAUMA.ORG web site

### **Normal Lab Values**

Bilirubin (total)	0 -1.4 mg/dL 0 - 22 $\mu$ mmol/L
Chloride	95-112 mEq/L 96-112mmol/L
Creatinine	0.6-1.5 mg/dL $\leq$ 106 $\mu$ mmol/L
Glucose	70-125 mg/dL 3.9 – 6.9 mmol/L
Lactate	0.3 - 2.3 mEq/L 0.3 -2.3 mmol/L
Potassium	4.5-19.8 mg/dL 3.5-5.3 mEq/lL 3.5- 5.3 mmol/L
Sodium	135-145 mEq/L 135-145 mmol/L
Osmolality	275-300 mOsm/kg 275-300 mmol/kg

### **Arterial Blood Gasses**

pH	7.35-7.45
pCO <sub>2</sub>	35-45 mmHg
pO <sub>2</sub>	80-100 mmHg
HCO <sub>3</sub>	21-27 mEq/L
O <sub>2</sub> sat	95-100%
Base deficit	-2.0 – 2.0

### **Hematology**

Fibrinogen	160-450 mg/dL 1.6-4.5 g/L
Hct	35-49 %
Hgb	11-18 g/dL 110-180g/L
Plt	150-450 $\times 10^3$ $\mu$ L ( $\times 10^3/\mu$ L = $\times 10^9/L$ )
INR	0.9 – 1.2 seconds
PT	10-14 seconds
PTT	25– 43 seconds



## Care Guidelines

### Summary of HS Care Guidelines, March 7, 2006

**Preface:** The trauma group has recognized and discussed the limitations of implementing care guidelines. The original recommendation for the use of the Glue Grant Guidelines has been relaxed to allow for the use of existing care guidelines that have the same intent, if not the same exact management. Where no pre-existing guidelines exist in an institution it is still expected that the Glue Grant Guidelines will serve as examples of good clinical practice and will be encouraged at ROC hospitals.

**1.) Trauma resuscitation protocol:** Tiered resuscitation efforts should include ATLS protocols and guide use of crystalloid administration and blood transfusion. Volume repletion efforts and restoration of hemodynamic stability may be guided by the use of CVP and/or PA catheters. The ultimate goal of resuscitation is restoration of oxygen delivery.

Monitored in CRF on the Care Guideline Form: Assessment of the presence of either CVP or PA catheters in the first 48 hours of hospitalization.

*Data is also collected regarding fluid totals every 12 hours for the first 24 hours after enrollment, including RBC use; 1<sup>st</sup>/worst ABGs, 1<sup>st</sup>/worst base deficit; 1<sup>st</sup> Lactate, 1<sup>st</sup> HGB and 1<sup>st</sup> coags are also monitored during the first four hours following ED admit.*

**2.) Mechanical Ventilation Protocol:** Goals include the use of a low tidal volume, lung-protective strategy is for patients meeting the criteria for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) and the discontinuation of mechanical ventilation and/or extubation as early as possible based on frequent assessments of the patient's readiness to wean.

The widely accepted clinical criteria for ARDS is based on the American-European Consensus Conference on ARDS published in 1994.

**Acute Lung Injury (ALI):**

- a) Hypoxia with a  $\text{PaO}_2/\text{FiO}_2$  ratio  $>200, \leq 300$  and
- b) Bilateral infiltrates on chest X-ray and
- c) No clinical evidence of increased left atrial pressure or a pulmonary artery pressure of  $<18\text{mmHg}^*$

**Acute Respiratory Distress Syndrome (ARDS):**

- a) Hypoxia with a  $\text{PaO}_2/\text{FiO}_2$  ratio  $\leq 200$  and
- b) Bilateral infiltrates on chest X-ray and
- c) No clinical evidence of increased left atrial pressure or a pulmonary artery pressure of  $<18\text{mmHg}^*$

*\*For those without pulmonary catheter, monitoring clinical evidence of left atrial hypertension includes:*



- a *Acute myocardial infarction or known cardiomyopathy or severely reduced ejection fraction (<30%) or critical valvular disease*
- b *Chronic or acute oliguric renal failure with fluid input that exceeds output by ≥3 liters in the previous 24 hours.*

**3.) Ventilator Associated Pneumonia, diagnosis and treatment:** It is expected that each ICU will have a consistent definition of VAP. Various clinical criteria can be used to make the diagnosis, but utilizing quantitative lab values is encouraged when possible. Each ICU is expected to have guidelines regarding how to institute, contract and conclude antibiotic therapy.

**4.) Guidelines for Glucose Control in the ICU:** For critically ill patients with persistent blood glucose >110mg/dL, there should be standardized insulin infusion orders that target a defined level of glucose control.

**5) Transfusion Guidelines:** (Excluding of immediate resuscitation) it is recommended to limit transfusions for Hgb >7. NOTE: A higher transfusion trigger may be appropriate for patients with acute coronary syndrome and traumatic brain injury.

**6.) Guidelines for sedation/analgesia of the mechanically ventilated patient.** Recommend daily wake-up (sedation vacation) to limit ventilator day due to over sedation. An objective scoring instrument is also recommended to monitor sedation levels.

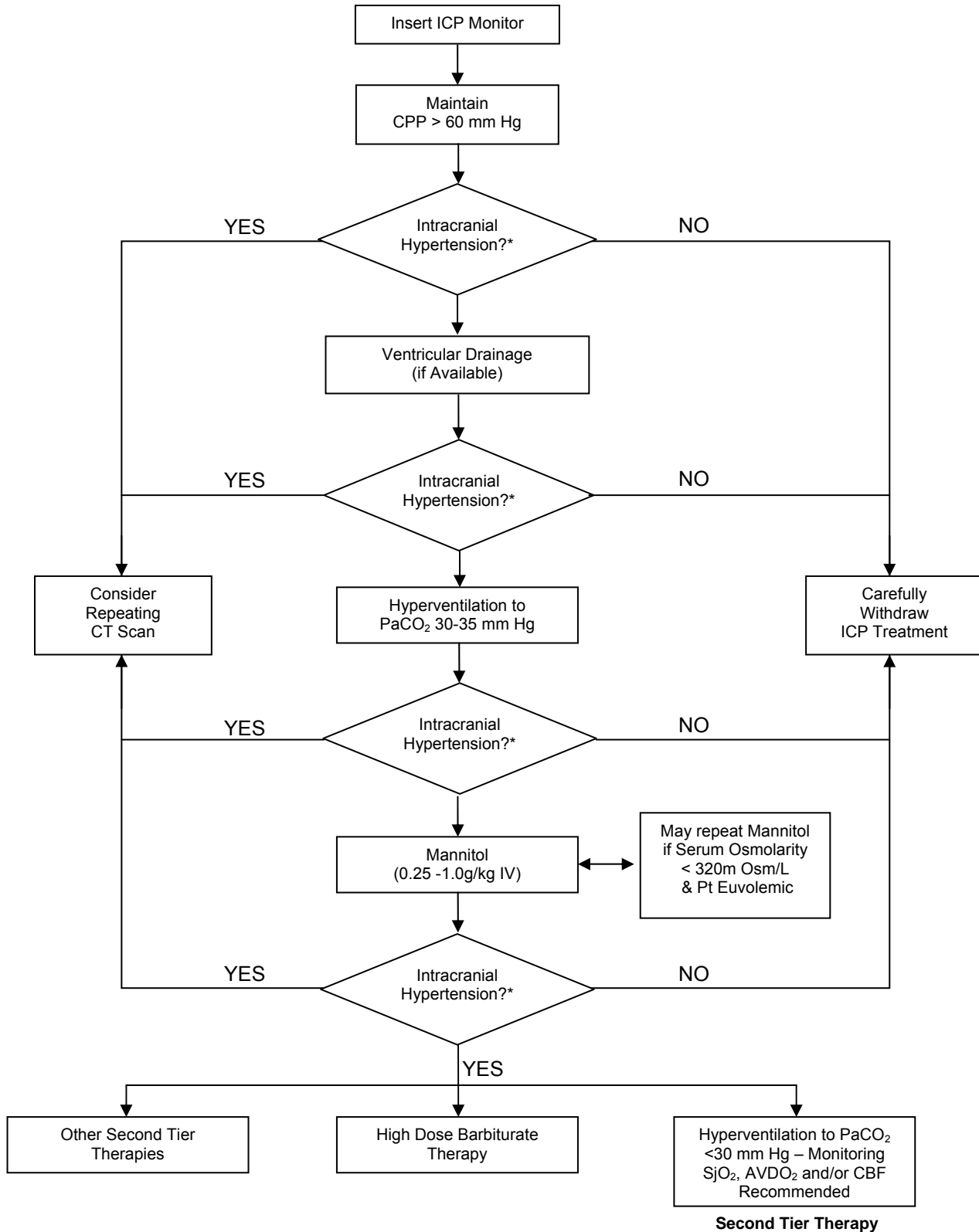
**7.) Nutrition guidelines:** Recommend early enteral nutrition to promote restoration of positive nitrogen balance.

**8.) Management of Traumatic Brain Injury: (UNCHANGED)**

All patients meeting the criteria for severe traumatic brain injury (persistent GCS <9) should have an intracranial pressure monitor placed. Patients with a sustained ICP >25mmHg should have intervention aimed at lowering ICP. This intervention is at the discretion of the treating physician but guided by the Brain Trauma Foundation Guidelines. Excess hyperventilation should be avoided unless the patient is showing signs of acute herniation. Patients should be resuscitated to avoid episodes of hypotension (SBP <90mmHg.)

There is also critical pathway for the treatment of established intra-cranial hypertension. It should be viewed as a framework that may be useful in guiding an approach to treating intra-cranial hypertension. It can and should be modified in an individual case by any circumstances unique to the patient as well as by the response of the ICP to individual treatment steps. SEE NEXT PAGE:

**Critical Pathway for the Treatment of Intracranial Hypertension**



\*Threshold of 20-25 mm Hg may be used. Other variable may be substituted in individual conditions.



## **Glue Grant Guidelines:**

### **TR1: Clinical Protocol for Trauma Resuscitation**

*The contents of this protocol were developed by the Inflammation and the Host Response to Injury Large-Scale Collaborative Research Program under a grant from the National Institute of General Medical Sciences. If any material from this protocol is used, proper credit to the Program and the NIGMS must be given.*

#### **Summary**

The goal of this protocol is to guide consisted resuscitation efforts. Developed by expert consensus, this protocol progresses through a tiered approach to resuscitation, beginning with the widely accepted Advanced Trauma Life Support protocol. Since the majority of severe trauma patients present in shock due to excessive hemorrhaging, these patients require crystalloid administration and blood transfusion. The protocol aims for an optimal hematocrit of 30 during the acute resuscitation phase. If volume repletion efforts are inadequate to restore hemodynamic stability and hypovolemia is considered unlikely, a pulmonary artery catheter and/or echocardiogram may help rule out cardiac dysfunction as the etiology. Data from the pulmonary artery catheter are used to maintain an adequate, but not supranormal, cardiac index and oxygen delivery.

#### **Protocol Goals**

- Early recognition of the shock state for prompt initiation of resuscitation
- Ensure acute resuscitation of the trauma patient is conducted in a consistent manner
- Provide guidelines for the use of a pulmonary artery catheter (PAC) in the resuscitation of the major trauma patient.

#### **Protocol Rationale**

The primary objective of this protocol is to guide consistent resuscitation efforts for all eligible patients.<sup>1,2</sup> There is no level I research evidence on how to best resuscitate the severely injured trauma patient nor are there resuscitation parameters whose close monitoring (to guide intervention) clearly impact on patient outcome.<sup>3-5</sup> Further, the proof of benefit of a pulmonary artery catheter to guide resuscitation in a population of young, previously healthy subjects is limited.<sup>3</sup> Given the lack of available evidence, this protocol has been developed by expert consensus to promote a tiered approach to trauma resuscitation. The protocol begins with the widely accepted Advanced Trauma Life Support (ATLS) protocol and continues with the ATLS protocol until it becomes evident the patient is at high risk for post-traumatic organ failure, by virtue of an anticipated need for blood transfusion in the clinical context of either ongoing shock or evidence of impaired tissue perfusion (base deficit >6).<sup>6</sup>

Once a high-risk patient is identified, the patient should have a central venous pressure monitor placed in the subclavian or internal jugular position. If the central venous

pressure (CVP) is high (CVP>15) an echocardiogram and early insertion of a pulmonary artery catheter should be considered to rule tamponade or cardiac dysfunction and to better guide resuscitation.

While the majority of severe trauma patients present in shock due to excessive hemorrhaging, the optimal hematocrit required to lower the risk of organ failure in patients with hemorrhagic shock is unknown, yet the risks of inadequate blood transfusion given the potential for ongoing blood loss are significant. As a result of compromise, the protocol aims for a minimum hematocrit of 30 during the acute resuscitation phase.

The protocol calls for volume repletion to a central venous pressure of 10-15 in the presence of sustained tachycardia and/or hypotension. If intravascular volume has been appropriately increased to this level and the patient remains unstable or has a persistent base deficit, there exists a component of cardiac dysfunction. At this point, a pulmonary artery catheter may be helpful to evaluate cardiac dysfunction.

Once data from the pulmonary artery catheter are available, the principal objective is to maintain an adequate (not supranormal) cardiac index (CI) if  $3.8 \text{ l/min/m}^2$ . There is little evidence to support supranormal resuscitation goals in this cohort of patients. Given a hemoglobin (Hgb) of 10g/dl and a reasonable oxygen saturation ( $\text{SaO}_2 > 90\%$ ), this should provide an oxygen delivery of over  $450 \text{ ml/min/m}^2$ . Cardiac index is supported first through an increase in preload to a pulmonary capillary wedge pressure (PCWP) of at least 15, with an incremental increase to a PCWP no higher than 25 through repeated administration of intravascular volume boluses to achieve this endpoint (Starling curve). If there is no further increase in CI with repeated administration of fluid, then further administration of fluid to increase the PCWP is unwarranted. If the goal CI has not been attained, inotropic support should be strongly considered. In the presence of hypotension, consider the use of dopamine, norepinephrine, or epinephrine and continually re-assess for ongoing bleeding or hypovolemia. Without hypotension, dobutamine (or Milrinone) should be selected at the discretion of the attending physician.

Occasionally, there are circumstances where there is persistent hypotension despite an adequate cardiac output. Continued re-evaluation for bleeding and/or hypovolemia is indicated. Once addressed, an agent with vasopressin properties should be considered. The specific choice of agent (norepinephrine, vasopressin, or dopamine) is at the discretion of the attending physician.

### **Protocol details**

1. Begin resuscitation using the standard ATLS protocol.
2. Identify the high risk patient:
  - Anticipated need for blood transfusion AND
  - Continued base deficit  $>6$  OR systolic blood pressure  $<90$  mm Hg
3. Insert central venous pressure monitor in the subclavian or internal jugular vein.
4. If sustained heart rate (HR)  $>120$  or systolic blood pressure (SBP)  $<90$ , administer blood and crystalloid to Hgb of 10 and CVP of 15 until HR  $<120$  or SBP  $>90$ .

5. If sustained HR > 120 or SBP < 90 and CVP ≥ 15, consider cardiac dysfunction or tamponade and insert a pulmonary artery catheter (PAC) and consider pericardial ultrasound or echocardiogram.
6. Insert a PAC if there is no improvement in base deficit despite administration of blood and crystalloid to Hgb of 10 and CVP of 10-15.
7. Once a PAC is inserted, aim for CI 3.8
  - If CI < 3.8 and PCWP < 15, administer crystalloid to PCWP = 15
  - If CI < 3.8 and PCWP > 15 and PCWP < 25, administer 500cc crystalloid (or blood as appropriate) boluses with repeat measurement of CI and PCWP within 5 minutes after each bolus (Starling curve)
  - If CI drops by 0.3, record prior PCWP as “optimal” and maintain this PCWP with crystalloid (and/or blood to maintain HGB 10)
  - If CI < 3.8 and optimal PDWP has been attained (or PCWP 25), begin inotrope of choice to achieve CI > 3.8; consider echocardiogram
  - If CI < 3.8 with MAP < 60, re-evaluate for bleeding and/or hypovolemia, then treat with an inotrope with vasopressor effects (e.g. dopamine, levophed or epinephrine)
  - If CI < 3.8 with MAP < 60, then treat with a vasopressor (e.g. levophed or vasopressin)

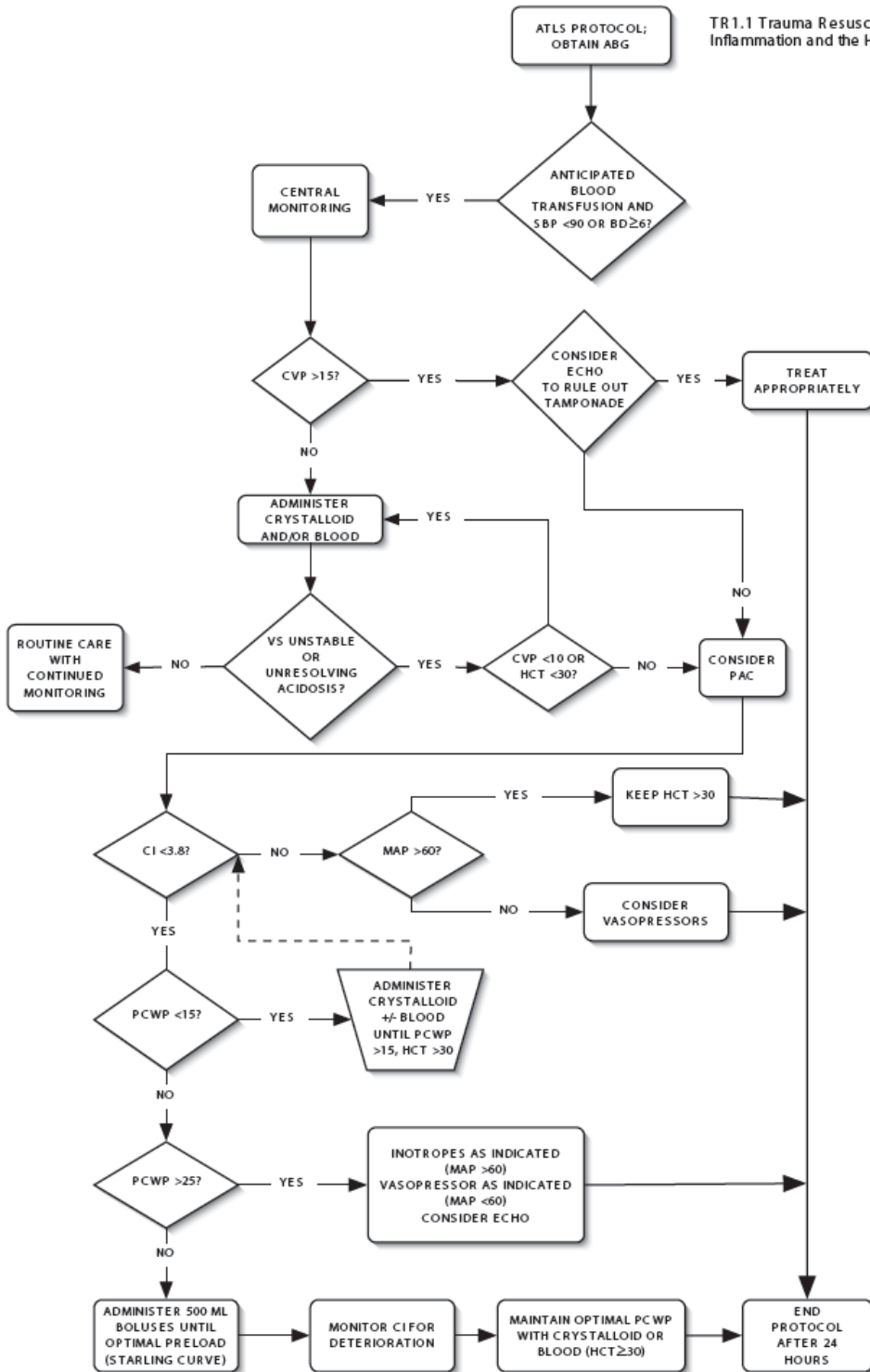
## References

1. Sauaia A, Moore FA, Moore EE, Lezotte DC. Early risk factors for post-injury multiple organ failure. *World J Surg.* 1996; 20:392-400.
2. Moore FA, Moore EE, Sauaia A. Blood transfusion: an independent risk factor for post-injury multiple organ failure. *Arch Surg.* 1997; 132:620-625.
3. Velmahos GC, Demetriades D, Shoemaker WC, Chan LS, Tatevossian R, Wo CC et al. Endpoints of resuscitation of critically injured patients: normal or supranormal? A prospective randomized trial. *Ann Surg.* 2000; 232(3):409-418.
4. Porter JM, Victory RR. In search of the optimal end points of resuscitation in trauma patients: a review. *J Trauma.* 1998; 44(5):908-914.
5. McKinley BA, Kumar RA, Coca our CS, Maldivian A, Sailors RM, Ware DN et al. Normal versus supranormal oxygen deliver goals in shock resuscitation: the response is the same. *J Trauma.* 2002; 53(5):825-832.
6. American College of Surgeons. Shock. *Advanced Trauma Life Support Manual.* Chicago: American College of Surgeons: 1997:87-107

## Accompanying Document

TR1.1 Trauma Resuscitation Flowchart

*Published on [www.gluegrant.org](http://www.gluegrant.org) in May 2004 by the Inflammation and the Host response to Injury Investigators. Supported by a large-Scale Collaborative Project Award (U54-GM62119) from The National Institute of General Medical Sciences.*



## TR2: Clinical Protocol for Mechanical Ventilation

*The contents of this protocol were developed by the Inflammation and the Host Response to Injury Large-Scale Collaborative Research Program under a grant from the National Institute of General Medical Sciences. If any material from this protocol is used, proper credit to the Program and the NIGMS must be given.*

### Summary

This protocol promotes a low tidal volume, lung-protective strategy for ventilating patients meeting the criteria for acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). To achieve adequate oxygenation, variable positive end-expiratory pressure (PEEP) and inspired oxygen (FiO<sub>2</sub>) is left to physician discretion, but the FiO<sub>2</sub> to PEEP ratio should be less than or equal to 5. If arterial oxygenation is not within the target range, then either fiO<sub>2</sub> or PEEP should be adjusted within 30 minutes, after which oxygenation should be reassessed within 15 minutes and subsequent adjustments made if necessary. The mode of mechanical ventilation is left to physician discretion; however, once patients are ready to wean, a daily trial of spontaneous breathing offers the best chances for early extubation. If the patient cannot be weaned from mechanical ventilation, the protocol recommends gradual reduction in breathing support, at the physician's discretion. In these patients, subsequent cycles of spontaneous breathing, weaning, and breathing support overnight for rest should be continued daily until the patient is breathing independently.

### Protocol Goals

- Ensure that a low tidal volume, lung protective strategy is used for the ventilation of subjects who meet criteria for acute lung injury (ALI) or acute respiratory distress syndrome (ARDS)
- Provide guidelines for the use of PEEP inpatients with ALI or ARDS
- Ensure discontinuation of mechanical ventilation and/or extubation occur at the earliest possible time

### Protocol Rationale

There exists Level 1 research evidence supporting a lung protective strategy using low-tidal volume (V<sub>t</sub>) ventilation in patients meeting criteria for ALI or ARDS. Described in detail at <http://hedwig.mgh.harvard.edu/ardsnet/studies.html> , this strategy demonstrated a 23% reduction in mortality in patients treated with a protocol designed to limit alveolar stretch using a tidal volume of 6 ml/kg compared to subjects ventilated at a tidal volume of 12 mL/kg.<sup>1</sup>

It remains unknown if there exists any benefit to higher levels of PEEP compared with higher levels of FiO<sub>2</sub> in patients with ALI or ARDS. The only available Level 1 evidence comparing higher levels of PEEP to higher inspired oxygen concentrations with lower levels of PEEP suggests there is no benefit to one strategy or the other. This



randomized controlled trial was stopped due to lack of efficacy after enrollment of 550 patients and has not yet been published (<http://hedwig.mgh.harvard.edu/ardsnet/ards04.html> ).

In patients without ALI or ARDS, no specific mode of mechanical ventilation is known to offer any advantage. As such, the decision about the mechanical ventilation mode is left to physician discretion. Once a patient is ready to wean, it appears that a daily trial of spontaneous ventilation offers the greatest potential for early extubation. This approach is superior to gradual withdrawal of ventilation using pressure support or intermittent mandatory ventilation.<sup>2-5</sup> In patients requiring prolonged ventilation, there is no conclusive evidence that airway management (intubation versus “early” tracheotomy) has an impact on outcome.

### Protocol Summary

- Patients with ALI or ARDS as defined by a  $\text{PaO}_2/\text{FiO}_2 \leq 300$  and bilateral pulmonary infiltrates are managed by following a low tidal volume, lung protective mechanical ventilation strategy with the expectation this lung protective strategy is achieved (i.e.  $V_t \leq 6$  ml/kg) within 24 hours of meeting ALI criteria.
- Patients without ALI are managed by conventional mechanical ventilation. The specific mode of mechanical ventilation is left to physician discretion. Should ALI criteria be met subsequently, the patient is managed utilizing the low tidal volume strategy.
- Once the patient meets readiness to wean criteria, a daily trial of spontaneous breathing is performed. If this trial is successful, it is expected that the patient is extubated or otherwise liberated from mechanical ventilation.
- If readiness to wean criteria are met, but the patient is not likely to be successfully liberated from mechanical ventilation or does not demonstrate the ability to protect the airway, a procedure for gradual reduction in ventilatory support is instituted consistent with patient tolerance. The specific mode of weaning is left to physician discretion.
- All patients who meet readiness to wean criteria, but are not successfully liberated from mechanical ventilation after the weaning process receive sufficient mechanical ventilatory support overnight to rest and prevent occult fatigue.
- The cycle of spontaneous trial of breathing, weaning and rest are continued daily until the patient is liberated from mechanical ventilation.
- Airway management strategies (continued end tracheal intubation versus tracheotomy) are left to the treating physician’s discretion.

### Protocol Details

#### Initial Ventilator Settings

- Tidal Volume ( $V_t$ )
- $V_t$  calculations are based on predicted body weight (PBW) as follows:
- For males:  $\text{PBW} = 50 + 2.3 [\text{height (inches)} - 60]$
- For females:  $\text{PBW} = 45.5 + 2.3 [\text{height (inches)} - 60]$

- Initial Vt is set at 8mL/kg PBW. This setting is reduced by 1 mls/kg PBW at intervals of <2 hours until Vt = 6 mls/kg PBW.

#### Ventilator rate

- Initial ventilator rate is set at 12 -20 breaths per minute if possible. Maximum rate setting is 35 breaths/minute.

#### **Subsequent Ventilator Adjustments**

Ventilator rate and tidal volume are adjusted to achieve arterial pH and end-expiratory plateau pressure goals, respectively.

#### Arterial pH

- The goal is to maintain the arterial pH between 7.25 and 7.45 Arterial pH is measured upon admission to the ICU and then every morning as well as 15 minutes after every change in tidal volume or respiratory rate. The clinical setting and physician discretion dictate additional measurement. Suggested management of alkaloid and acidemia is as follows;
- Alkaloid (pH >7.45) Decrease ventilator rate
- Mild acidemia (7.15 ≥pH <7.25) Increase ventilator rate up to maximum of 35 or until pH>7.25 or PaCO<sub>2</sub> <25mm Hg. If ventilator rate = 35 or paCO<sub>2</sub> <25, then bicarbonate infusion may be administered.
- Severe acidemia (pH <7.15) increase ventilator rate to 35. If ventilator rate = 35 and pH <7.15 and bicarbonate has been considered or infused, then tidal volume may be increased by 1 ml/kg until pH >7.15. Under these conditions, the target plateau pressure described below may be exceeded.

#### End-inspiratory plateau pressure goals: ≤ 30 cm H<sub>2</sub>O

- Plateau pressures are measured and recorded every eight hours and 1-5 minutes after each change in PEEP or tidal volume. For each measurement, patients must be relaxed, not coughing or moving. The pressure corresponding to the first plateau that occurs after initiating a 0.5 second pause is recorded. The pause is removed for at least 6 breaths, and repeated at least twice. The mean of at least 3 replicates represents the plateau pressure.
- If plateau pressures cannot be measured because of air leaks, then peak inspiratory pressures are substituted.
- Tidal volumes are reduced by 1 ml/kg PBW q2 hours if necessary to maintain plateau pressures less than or equal to 30 cm H<sub>2</sub>O (if arterial pH <7.15, tidal volume needs not be reduced; see “suggested management of severe acidemia”). Measure arterial pH 15 minutes following every change in tidal volume.
- The minimum tidal volume is 4 mL/kg PBW. If the tidal volume is less than 6 mL/kg and plateau pressure is <25 cm H<sub>2</sub>O then Vt is increased in 1mL/kg PBW increments until plateau pressure is 25-30 cm H<sub>2</sub>O or Vt = 6 mL/kg PBW.

### Oxygenation

Target ranges for oxygenation are 55 mm Hg is less than or equal to PaO<sub>2</sub> is less than or equal to 80 mm Hg, or 88% is less than or equal to SpO<sub>2</sub> is less than or equal to 95%. When PaO<sub>2</sub> and SpO<sub>2</sub> measurements are available simultaneously, the PaO<sub>2</sub> measurement takes precedence. When oxygenation goals are achieved, the FiO<sub>2</sub> should be weaned down to <0.67 at the earliest possible time. The PEEP and the FiO<sub>2</sub> combinations used to achieve the goals above are left to physician discretion, but as a general rule the FiO<sub>2</sub> (as a percentage) to PEEP ratio should be less or equal to 5.

When increasing PEEP above 10 cm H<sub>2</sub>O, do so by 2-5 cm H<sub>2</sub>O increments to a maximum of 35 cm H<sub>2</sub>O or until PaO<sub>2</sub> = 55-80 mm Hg or SpO<sub>2</sub> = 88-95%. If the PEEP increase does not lead to an increase in PaO<sub>2</sub> of >5 mm Hg within 4 hours, PEEP is set to the last level that achieved a response.

Arterial oxygenation can be assessed by either SpO<sub>2</sub> or PaO<sub>2</sub> at a minimum of every 4 hours.

If arterial oxygenation is not within the target range, then either FiO<sub>2</sub> or PEEP should be adjusted within 30 minutes. Following adjustments, oxygenation is reassessed within 15 minutes and subsequent adjustments are made if necessary.

If PaO<sub>2</sub> <55 mm Hg or SpO<sub>2</sub> <88% and tidal volume = 4mL/kg PBW (or the minimum tidal volume necessary for pH control) and plateau pressure > 30 cm H<sub>2</sub>O then FiO<sub>2</sub> is raised until PaO<sub>2</sub> = 55-80 mm Hg or SpO<sub>2</sub> = 88-95% or FiO<sub>2</sub> = 1.0. If PaO<sub>2</sub> <55 mm Hg or SpO<sub>2</sub> <88% and FiO<sub>2</sub> = 1.0, PEEP is raised to achieve adequate oxygenation. In these circumstances, plateau pressure may exceed 30 cm H<sub>2</sub>O. Brief periods (5-10minutes) of SpO<sub>2</sub> <88% or >95% may be tolerated without making changes in PEEP or FiO<sub>2</sub>. FiO<sub>2</sub> = 1.0 may be used for brief intervals (10 minutes) of transient desaturation or to prevent desaturation during treatments such as tracheo-bronchial suctioning or position changes.

Changes in more than one ventilator setting driven by measurement of PO<sub>2</sub>, pH and plateau pressure may be performed simultaneously if necessary.

### **Assessment of readiness to wean**

Patient assessment of the following criteria should be performed each day between the hours of 0400 and 0800. If the assessment is precluded by procedures or other extenuating circumstances, the assessment and initiation of weaning procedures may occur later in the day, but should not be held off to the next day.

- A. Resolution or stabilization of the underlying disease process leading or contributing to the requirement for mechanical ventilation
- B. Not receiving neuromuscular blocking agents and without residual effects of neuromuscular blockade
- C. Exhibiting respiratory efforts
- D. Hemodynamically stable with no inotropic or vasopressor support (less than or equal to 5µg/kg/min of dopamine or dobutamine will not exclude patients from consideration for liberation).
- E. FiO<sub>2</sub> less than or equal to 0.5 and PEEP less than or equal to 10 CM H<sub>2</sub>O
- F. PaO<sub>2</sub> > 75mmHg

- G.  $V_e < 15\text{L/min}$
- H.  $V_e > 80\%$  of  $V_e$  mechanical
- I. pH between 7.30 and 7.50

### **Trial of spontaneous breathing protocol**

All patients receiving mechanical ventilation who are considered ready to wean are evaluated on a daily basis for the ability to tolerate unassisted ventilation by means of a 30-90 minute trial of spontaneous breathing between the hours of 0500 and 0900. If circumstances preclude the conduct of the trial at this time of the day, the assessment and trial can be performed later in the day, but should not necessarily be held off to the next day. A trial is attempted unless there is a physician order to delay the trial.

- A 30-90 minute trial of spontaneous breathing is performed with the continuous positive airway pressure (CPAP) setting set to the current PEEP setting, no greater than an inspiratory pressure support of 8 cm H<sub>2</sub>O and FiO<sub>2</sub> equal to current FiO<sub>2</sub>. (FiO<sub>2</sub> at the initiation of the trial may be increased by 0.1 above previous FiO<sub>2</sub> at the discretion of the physician.)
- If the patient meets any one of the criterion below, the trial is terminated and the patient is returned to the previous ventilator settings:
  - Respiratory rate > 35 for ≥ 5 minutes
  - SpO<sub>2</sub> < 90% for ≥ 30 seconds
  - Heart rate > 140 beats/minute or sustained heart rate increase or decrease of 20% from baseline; systolic BP > 180 mm Hg or < 90 mm Hg
  - Sustained increase in anxiety, diaphoresis, or other signs of respiratory distress
  - Cardiac instability or dysrhythmias
  - pH less than or equal to 7.32
- The patient should be evaluated for transient issues that may negatively influence a trial of spontaneous breathing (that is, excess sedation, agitation, acidemia, etc.). In these cases, another assessment should be made later in the day when the issue has been resolved. Otherwise, the patient should be returned to the previous mechanical ventilator settings and weaning commenced as ordered by the attending physician.

### **Assessment of readiness for extubation**

If the patient successfully completes a trial of spontaneous breathing, the following criteria should be assessed to determine readiness for extubation:

- Does not require suctioning more than every 4 hours
- Anticipated good spontaneous cough
- Endotracheal tube cuff leak with less than or equal to 30 cm H<sub>2</sub>O positive pressure
- No known history of upper airway obstruction or stridor within the prior 48 hours
- No known history of reintubation for bronchial hygiene within the prior 48 hours

The therapist should notify the primary physician team of the protocol success and discuss readiness for extubation criteria. If the physician decides not to extubate, the

patient may be placed on a T-piece, with CPAP equal to the PEEP setting on the ventilator or on a low level of pressure support (PS <8).

For the purposes of this protocol, all of the following are considered unassisted breathing

- Extubated with face mask, nasal prong oxygen, or room air OR
- T-tube breathing OR
- Tracheostomy mask breathing, OR
- CPAP=5 without PS (PS >8) or intermittent mandatory ventilation (IMV) assistance

If the patient fails the trial of spontaneous breathing, the patient may be weaned using a mode of ventilation prescribed by the treating physician. The patient must rest overnight and another assessment of readiness to wean and a trial of spontaneous breathing (if ready to wean) should be conducted the following morning.

## References

1. ARDS Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N.Engl.J.Med. 2000;342:1301-8
2. Ely EW, Baker AM, Dunagan DP, Burke HL, Smith AD, Kelly PT et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. N.Engl.J.Med. 1966; 335(25):1864-9.
3. Esteban A, Frutos F, Tobin MJ, Alia I, Solsona JF, Valverdu I et al. A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. N.Engl.J.Med. 1995; 332(6):345-50.
4. Esteban A, Alia I, Tobin MJ, Gil A, Gordo F, Vallverdu I et al. Effect of spontaneous breathing trial duration on outcome of attempts to discontinue mechanical ventilation. Spanish Lung Failure Collaborative Group. Am.J.Respir.Crit Care Med. 199; 159(2):512-8.
5. MacIntyre NR, Cook DJ, Ely EW, Jr., Epstein SK, Fink JB, Heffner JE et al. Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory care ; and the American College of Critical Care Medicine. Chest 2001; 120(6 Suppl):375S-95S.

## Accompanying documents

- TR2.1 Mechanical Ventilation Protocol Pocket Card 3x5 Inch Side 1
- TR2.1 Mechanical Ventilation Protocol Pocket Card 3x5 Inch Side 2

*Published on [www.gluegrant.org](http://www.gluegrant.org) in May 2004 by the Inflammation and the Host response to Injury Investigators.*

*Supported by a large-Scale Collaborative Project Award (U54-GM62119) from The National Institute of General Medical Sciences.*

### **TR2.1 Mechanical Ventilation protocol 3x5 Inch Pocket Card**

#### **Inflammation and the Host Response to Injury**

Patients with ALI Or established ARDS ( $\text{PaO}_2/\text{FiO}_2 \leq 300$ , bilateral pulmonary infiltrates) aim for the following within 24 hrs of meeting criteria:

- Initial tidal volumes may be set at 8 mL/kg predicted body weight (PBW); tidal volumes should be reduced by 1 ml/kg at intervals of < 2 hours until the tidal volume = 6mL/kg. Tidal volume calculations are based on predicted body weight as follows:  
For males:  $\text{PBW} = 50 + 2.3 [\text{height (inches)} - 60]$   
For females:  $\text{PBW} = 45.5 + 2.3 [\text{height (inches)} - 60]$
- $\text{PaO}_2 \geq 55$  mm Hg or  $\text{PaO}_2$  88%-95%.  $\text{FiO}_2/\text{PEEP}$  ratio should be  $\leq 5$  and PEEP must be  $\leq 35$  cm H<sub>2</sub>O  
pH 7.25-7.45 with RR < 35 and  $\text{PaCO}_2 \geq 24$ .  $\text{HCO}_3^-$  infusion may be given if necessary. If pH < 7.25 then Vt may be increased by 1 mL/kg to pH  $\geq 7.25$  and target plateau pressures (see below) may be exceeded
- Plateau pressures (PP)  $\leq 30$  cm H<sub>2</sub>O. Reduce Vt to no less than 4 mL/kg. If Vt < 4 mL/kg and PP < 25 then increase Vt until PP = 25-30 of Vt + 6 mL/kg

**Patients not meeting ALI/ARDS criteria** can be ventilated using the mode, rate and tidal volume chosen at the treating physician's discretion.

**Patients should undergo a daily assessment of readiness to wean:** (a) resolution or stabilization of the underlying disease process; (b) no residual effects of neuromuscular blockade; (c) exhibiting respiratory efforts; (d) hemodynamically stable; (e)  $\text{FiO}_2 \leq 0.5$  and PEEP  $\leq 8$  cm H<sub>2</sub>O; (f)  $\text{PaO}_2 > 75$  mm Hg; (g)  $\text{Ve} < 15$  L/min; (h)  $\text{Ve}$  spontaneous  $\geq 80\%$  of  $\text{Ve}$  mechanical; (i) pH between 7.30 - 7.50. If not ready to wean, then return to previous mode of ventilator support and reassess daily.

If ready to wean, then the patient should receive **a trial of spontaneous breathing (SBT) for 30-90 minutes:** otherwise continue weaning using a mode of ventilation selected at the discretion of the treating physician.

Criteria for **failure of a SBT:** (a) RR > 35 for  $\geq 5$  minutes; (b)  $\text{SpO}_2 < 90\%$  for  $\geq 30$  seconds; (c) HR > 140 or increase or decrease of 20% from baseline; (d) SBP > 180 mm Hg or < 90 mm Hg; (e) Sustained evidence of respiratory distress; (f) cardiac instability or dysrhythmias; (g) pH  $\leq 7.32$ . If any criteria are met, the CPAP trial is terminated and patient returned to previous ventilator settings and rested overnight. Repeat CPAP trial in the morning.

If patient completes a CPAP trial, the following criteria should be assessed to determine **readiness for extubation** and patient extubated if possible: (a) Does not require suctioning more than Q4 hours; (b) good spontaneous cough; (c) endotracheal tube cuff leak; (d) no recent upper airway obstruction or stridor; (e) no recent reintubation for bronchial hygiene.



### **TR3: Clinical Protocol for the Prevention, Diagnosis and Treatment of Ventilator-Associated Pneumonia**

*The contents of this protocol were developed by the Inflammation and the Host Response to Injury Large-Scale Collaborative Research Program under a grant from the National Institute of General Medical Sciences. If any material from this protocol is used, proper credit to the Program and the NIGMS must be given.*

#### **Summary**

This protocol addresses ventilator-associated pneumonia (VAP). Prevention of VAP is best accomplished through adequate hand washing, inclining the patient 30 degrees or more, avoiding gastric over distention, and maintaining the patient's oral hygiene. Various clinical criteria can be used to diagnose VAP. Patients with a threshold clinical pulmonary infection score (CPIS) greater than 6 should be evaluated for pneumonia. Quantitative protected sampling of the lower respiratory tract can help distinguish between colonization and infection. In contrast, quantitative Endotracheal aspiration cannot be considered sensitive or specific enough to accurately diagnose VAP. Quantitative protected-specimen brush obtained via bronchoscopy may be useful, but both the sensitivity and specificity of this analysis varies considerably among patients. It is critical that treatment of suspected VAP should begin with early, empiric therapy titrated to common organisms, as defined by the local antibioticogram for the unit in question. Inadequate antibiotic coverage significantly increases mortality in these patients. On the other hand, if no sign of infection is found, antibiotic therapy should be halted so as to prevent superinfection and secondary pneumonia from resistant organisms.

#### **Protocol Goals**

- Describe techniques utilized to minimize the incidence of VAP
- Define the minimal criteria to meet the diagnosis of VAP
- Describe the general regimens used in the treatment of VAP

#### **Protocol Rationale**

This protocol is based on available published literature recognizing the criteria that define VAP are not clearly standardized. It should be recognized that even when there are "good" data to support guidelines for the management of VAP, the patient populations studied in the literature were seldom severely injured patients for the most part.

#### **Prevention of VAP**

The following recommendations, published by the Centers for Disease Control and Prevention (CDC) and available at <http://www.cdc.gov/>, are supported by at least one randomized, controlled trial.

- Adequate hand washing between patients.
- Semi-recumbent positioning of the patient to > 30 degrees.
- Avoidance of gastric over-distention.
- Routine oral hygiene as part of daily care.



## Diagnosis of VAP

There is no “gold standard” criteria that define VAP. Initial calculation of a CPIS is used to screen patients for presumed VAP<sup>1</sup>. Use of this score allows comparison of patients treated for pneumonia across study sites. Patients with a CPIS of <6 have little chance of having pneumonia in a group of hospitalized medical patients. Patients with a CPIS>6 are evaluated for pneumonia. The rationale is that there is no microbiological diagnostic test that is 100% specific for VAP and use of this score threshold minimizes the risk that patients with few clinical signs and symptoms of VAP will have false-positive culture results with subsequent administration of antibiotics.<sup>2</sup>

Recent studies to evaluate criteria for treatment with antibiotics for a presumed diagnosis of VAP have utilized data from quantitative protected sampling of the lower respiratory tract. Quantitative cultures, while not 100% sensitive and specific, can help distinguish between colonization and infection. Identification of the most likely organism can lead to antibiotic de-escalation once sensitivities are known. These studies suggest that clinical management strategies based on an invasive diagnostic procedure (bronchoalveolar lavage (BAL) or protected specimen brush (PSB) leads to improved survival and decreased antibiotic complications compared with strategy based on clinical guidelines without protected lower respiratory tract sampling.<sup>3</sup>

There are a number of techniques that can be utilized for quantitative evaluation. Quantitative endotracheal aspiration cannot be considered sensitive or specific enough to accurately diagnose VAP. The sensitivity of quantitative BAL obtained via bronchoscopy ranges from 42 to 93% (mean, 73%) and the specificity ranges from 45 to 100% (mean, 82%). The sensitivity of quantitative PSB obtained via bronchoscopy ranges from 33 to 100% (mean 67%) and the specificity ranges from 50 to 100% (mean, 95%). Finally, blinded specimen collection techniques demonstrated sensitivity that ranges from 60 to 100% and specificity that ranges from 70 to 100%.

The threshold values used for a positive quantitative culture are those values presently used by the CD and generally accepted in the medical literature (available at <http://www.cdc.gov/ncidod/hip/nnis/members/members.html>).

## Treatment of VAP

Treatment of suspected VAP should begin early with empiric therapy directed at the typical antibiogram for the given unit location. At least 4 studies have shown if the initial antibiotic therapy is inadequate to cover the organisms that are ultimately isolated, then mortality is significantly increased.<sup>4</sup> Further, if antibiotic selection is either withheld or escalated once the culture results are known, mortality is still greater than if the correct antibiotic selection had been made empirically at the start of treatment.

Discontinuation of antibiotics if BAL cultures are negative is supported in the literature. It has also been shown that unnecessary use of antibiotics for VAP increases the likelihood of superinfection with multi-resistant organisms. Recent data suggest that antibiotics can be stopped once clinical signs of infections have resolved rather than fixed duration of antibiotic therapy. Discontinuation of antibiotics may also decrease the incidence of secondary pneumonias with multi-resistant organisms.<sup>5</sup>

## References

2. Singh N., Rogers, P., Atwood, S.W., et al. Short course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. *Am J Respir Crit Care Med.* 2000; 162:505.
3. Rodriguez de Castro, F., Solé, J., Elcuaz, R. Quantitative cultures of protected brush specimens and bronchoalveolar lavage in ventilated patients without suspected pneumonia. *Am J Respir Crit Care Med.* 1994; 149: 320.
4. Fagon, J.Y., Chastre, J., Wolff, M., et al. Invasive and non-invasive strategies for the management of suspected ventilator-associated pneumonia: a randomized trial. *Ann Intern Med.* 132:621, 2000.
5. Rello, J., Gallego, M., Mariscal, D., et al. the value of routine microbial investigation in ventilator-associated pneumonia. *Am J Respir Crit Care Med.* 1997; 156: 196.
6. Ibrahim, E.H., Ward, S., Sherman, G., et al. Experience with a clinical guideline for the treatment of ventilator-associated pneumonia. *Cri Care Med.* 2001; 29: 1109.

## Unnumbered Reference

Hubmayr, R.D. Statement of the 4<sup>th</sup> international consensus conference in critical care on ICU-acquired pneumonia – Chicago, Illinois, May 2002. *Int Care Med.* 2002; 28: 1521.

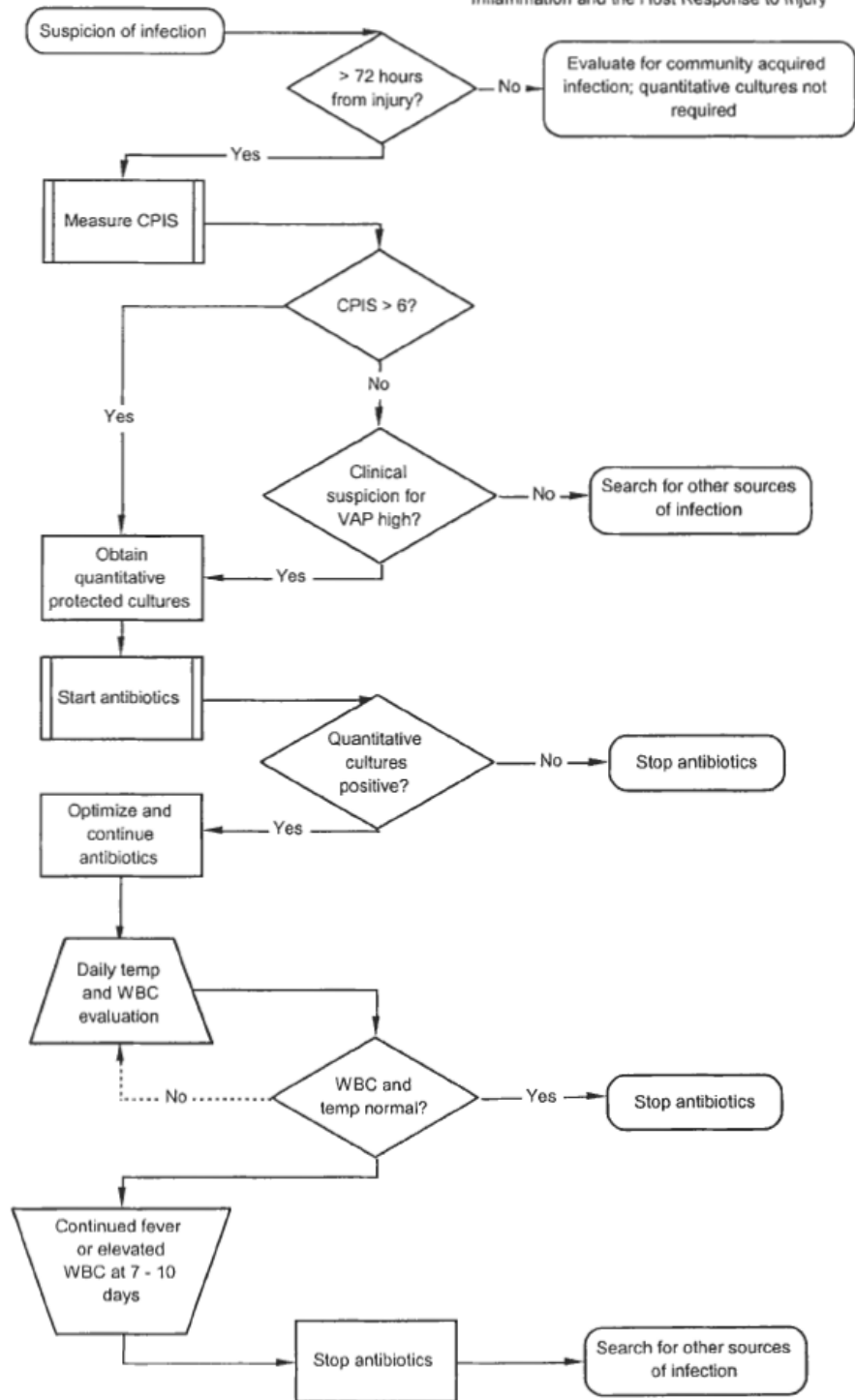
## ACCOMPANYING Document

Tr3.1 Ventilator-Associated Pneumonia Flowchart

*Published on [www.gluegrant.org](http://www.gluegrant.org) in May 2004 by the Inflammation and the Host response to Injury Investigators.*

*Supported by a large-Scale Collaborative Project Award (U54-GM62119) from The National Institute of General Medical Sciences.*

TR3.1 Ventilator-Associated Pneumonia Flowchart  
Inflammation and the Host Response to Injury



**TR4: Insulin Infusion Orders**

*The contents of this protocol were developed by the Inflammation and the Host Response to Injury Large-Scale Collaborative Research Program under a grant from the National Institute of General Medical Sciences. If any material from this protocol is used, proper credit to the Program and the NIGMS must be given.*

**Goal: Blood Glucose 80-110mg/dL**

1. Indication : Critically ill patients with persistent blood glucose >110mg/dL
2. Monitoring:
  - Check blood glucose 2 2 hrs and q 1 hr prn
  - If tube feed, TPN or fluids with D5W are stopped; decrease insulin infusion rate by 50 and check blood glucose q 1 r
  - **If blood glucose decreases by >50mg/dL and is still elevated** keep infusion at current rate and recheck blood glucose in 1 hour
  - Do NOT bolus for Serum Creatinine (SCr) >2

## 3. Initiation

Blood Glucose (mg/dL)	Bolus IV Push (units)	Infusion Rate (unit per hour)
111-150	2	1
151-200	2	2
201-250	4	2
251-300	6	4
301-350	8	4
>350	10	4

## 4. Continuation of insulin infusion:

Blood Glucose (mg/dL)	Bolus IV Push (units)	Infusion Rate (unit per hour)
< 60	0	d/c infusion; give ½ ampoule D50 IV push; recheck blood glucose in 30 minutes NAD if blood glucose >80 resume insulin infusion at 50 % of previous rate
60-79	0	d/c infusion; recheck blood glucose in 30 minutes AND if blood glucose >80, resume insulin infusion at 50% of previous rate
80-110	0	No change; if blood glucose continues to decrease within desired range over 4 hour; decrease rate by 20%**
111-150	0	Increase rate by 20%**
151-200	2	Increase rate by 20%**
201-250	4	Increase rate by 20%**
251-300	6	Increase rate by 20%**
301-350	8	Increase rate by 20%**
>350	10	Increase rate by 20%**

\*\* See below for rounded rate adjustment of 20 % (increase or decrease)

5. If infusion rate = 30 units /hour; notify H.O and continue to bolus per protocol as indicated by blood glucose. Do not increase infusion rate. Check blood glucose q 1 hr

** 20% adjustments (in u/hr)		
Current rate	Increase rate	Decrease rate
.05	1	0
1	1.5	0.5
1.5	2	1
2	2.5	1.5
2.5	3	2
3	3.5	2.5
3.5	4	3
4	4.5	3
4.5	5	3.5
5	5.5	1
5.5	6	1.5
6	6.5	2
6.5	7	2
7	8	2.5
7.5	8.5	6
8	9	6.5
8.5	10	7
9	11	7
9.5	11.05	7.5
10	12	8
10.5	12.05	8.5
11	13	9
11.5	14	9
12	14.5	9.5
12.5	15	10
13	15.5	10.5
13.5	16	11
14	17	11
14.5	17.5	11.5
15	18	12

** 20% adjustments (in u/hr) cont'd		
Current rate	Increase rate	Decrease rate
15.5	18.5	12.5
16	19	13
16.5	20	13
17	20.5	13.5
17.5	21	14
18	21.5	14.5
18.5	22	15
19	23	15
19.5	23.5	15.5
20	24	16
21	25	17
21.5	26	17
22	26.5	17.5
22.5	27	18
23	27.5	18.5
23.5	28	19
24	29	19
24.5	30	19.5
25	30	20
25.5	30	20.5
26	30	21
26.5	30	21
27	30	21.5
27.5	30	22
28	30	22.5
28.5	30	23
29	30	23
29.8	30	23.5
30	30	24

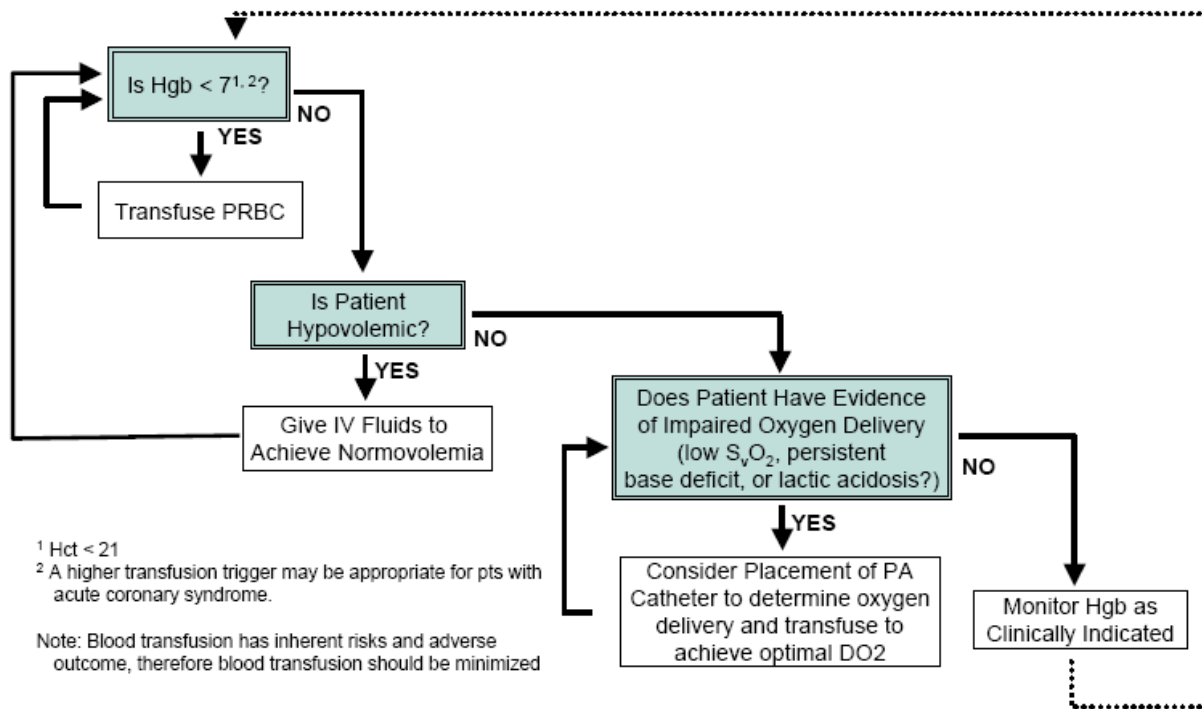
Published on [www.gluegrant.org](http://www.gluegrant.org) in May 2004 by the Inflammation and the Host response to Injury Investigators.  
 Supported by a large-Scale Collaborative Project Award (U54-GM62119) from The National Institute of General Medical Sciences.

## TR5: Transfusion Guidelines for Trauma Patient

The contents of this protocol were developed by the Inflammation and the Host Response to Injury Large-Scale Collaborative Research Program under a grant from the National Institute of General Medical Sciences. If any material from this protocol is used, proper credit to the Program and the NIGMS must be given.

### TR5 Transfusion Guidelines for Trauma Patient

(excludes immediate resuscitation)



Rev 07/12/04

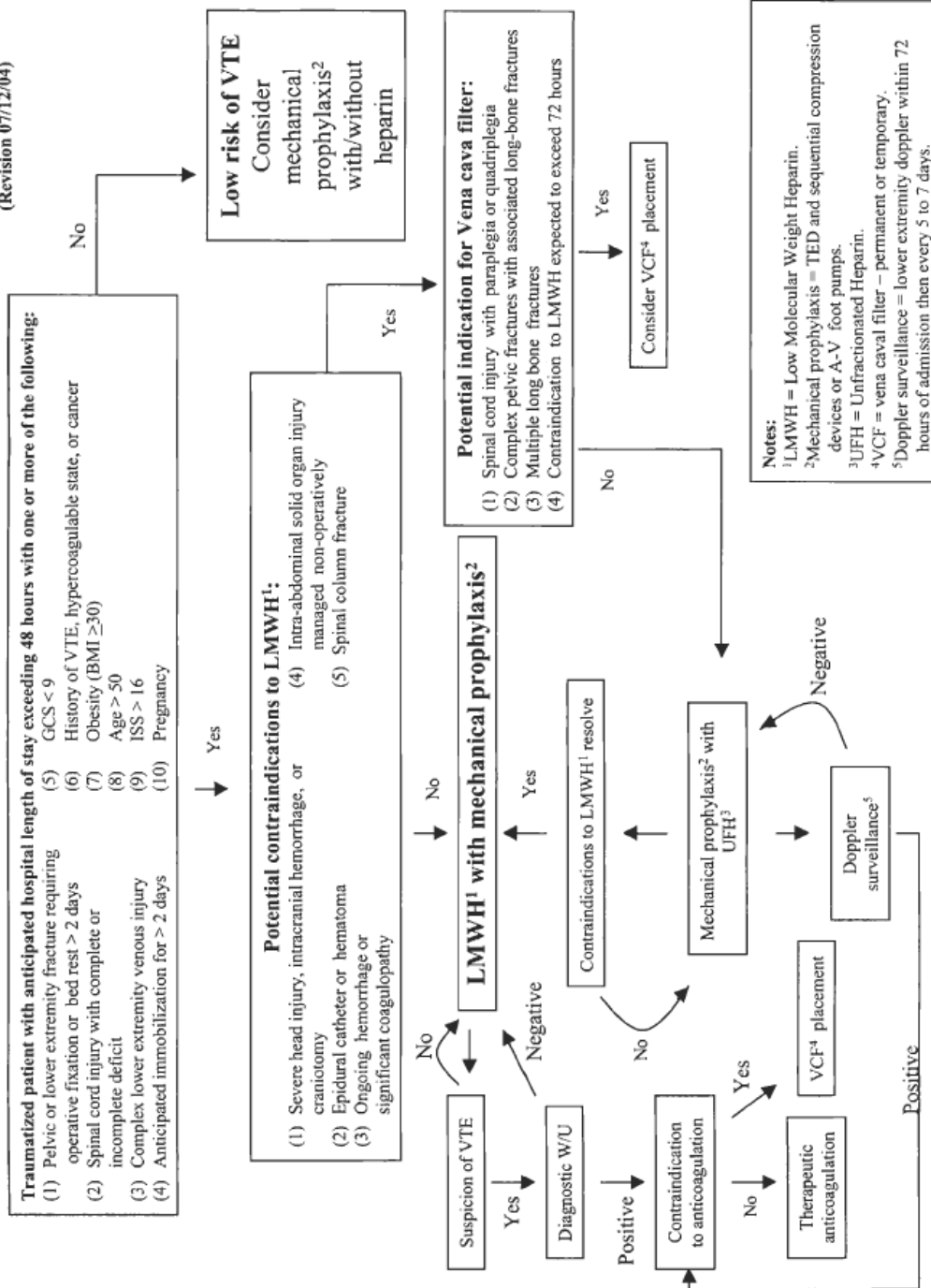
Published on [www.gluegrant.org](http://www.gluegrant.org) by the Inflammation and the Host response to Injury Investigators.

Supported by a large-Scale Collaborative Project Award (U54-GM62119) from The National Institute of General Medical Sciences.



**TR6: VTE prophylaxis Algorithm  
(Revision 07/12/04)**

TR6 VTE Prophylaxis Algorithm  
(Revision 07/12/04)







## **TR7: Sedation Protocol     Draft (07/12/04)**

*The contents of this protocol were developed by the Inflammation and the Host Response to Injury Large-Scale Collaborative Research Program under a grant from the National Institute of General Medical Sciences. If any material from this protocol is used, proper credit to the Program and the NIGMS must be given.*

### **Sedation/Analgesia Protocol for Mechanical Ventilation**

**Purpose:** To provide a strategy for physician and nursing staffs to manage issues of sedation and analgesia in mechanically ventilated patients. These guidelines should direct the care of routine patients. They should be modified on the basis of clinical indication.

**Goals:** 1) Sedation level should be recorded using an objective scoring instrument (e.g. Ramsey, Riker, Richmond scales). 2.) Unless medically contraindicated, the optimal target level of sedation is that at which the patient is alert, not agitated, and able to maintain brief eye contact an/or follow simple instructions.

**Indications:** All ICU patients who are mechanically ventilated.

**Monitor:** Assess pain and sedation every 15 minutes until patient reaches desired level of sedation. Thereafter assess every 4 hours unless otherwise indicated.

**Exceptions:** Patients who are allergic to any of the following agents.

**Sedation Vacation:** Unless medically contraindicated, sedation should be interrupted daily until the patient is awake (establish eye contact and/or follow simple instructions), or until the patient becomes agitated or uncomfortable.

#### **Analgesia for PAIN:**

Fentanyl: bolus 25-200mcg IV q 5 min to achieve specified goal. If goal met, continue bolus doses q 30-60 min. If goal not met after 3 hours begin infusion at 50 mcg/hr. If goal not met in 1 hr, bolus with amount of current rate and increase infusion by 25 mcg/hr.

#### **Sedation for ANXIETY: (choose one)**

Lorazepam: Bolus 1-2 mg IV q 15 min prn. If goal met, continue bolus doses q 2-4hr prn. If goal not met within 3 hours begin scheduled doses at 4 mg IV q 6 hours and continue bolus doses. If goal not met in 24 hours, begin infusion at 2 mg/hr and continue bolus doses prn. If goal not met after 1 hour increase infusion rate by 1 mg/hr and continue boluses prn. Consider contribution of pain and delirium to agitation.

Propofol: (Consider use if expected duration of mechanical ventilation <48 hours, or for Neurosurgical patients). Bolus 0.5 mg/kg IV, then infuse 20 mcg/kg/min. If goal not met in 15 minutes rebolus with 0.5 mg/kg over 2 minutes and increase infusion by 10 mcg/kg/min q 15 min to maximum 100 mcg/kg/min. Consider contribution of pain and delirium to agitation.

#### **Antipsychotic for DELIRIUM:**

Haloperidol: 2-10 mg IV q 1 hr prn. If goal not met in 6 hours begin scheduled doses at 5 mg IV q 6 hrs and continue bolus doses.

#### **References:**

1. Brook, Alan D et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. Crit Care Med 1999 Vol 27: 2609-2615.
2. Jacobi, Judith, et al. Clinical practice guidelines for the sustained use of sedative and analgesics in the critically ill adult. Crit Care Med 2002 Vol. 30, No. 1: 119-141.
3. Kress, John P, et al. Daily Interruption of Sedative Infusions in Critically Ill Patients Undergoing Mechanical Ventilation. NEJM 2000 Vol.342:1471- 1477



## **Guidelines for Management of Traumatic Brain Injury** (Resuscitation Outcomes consortium)

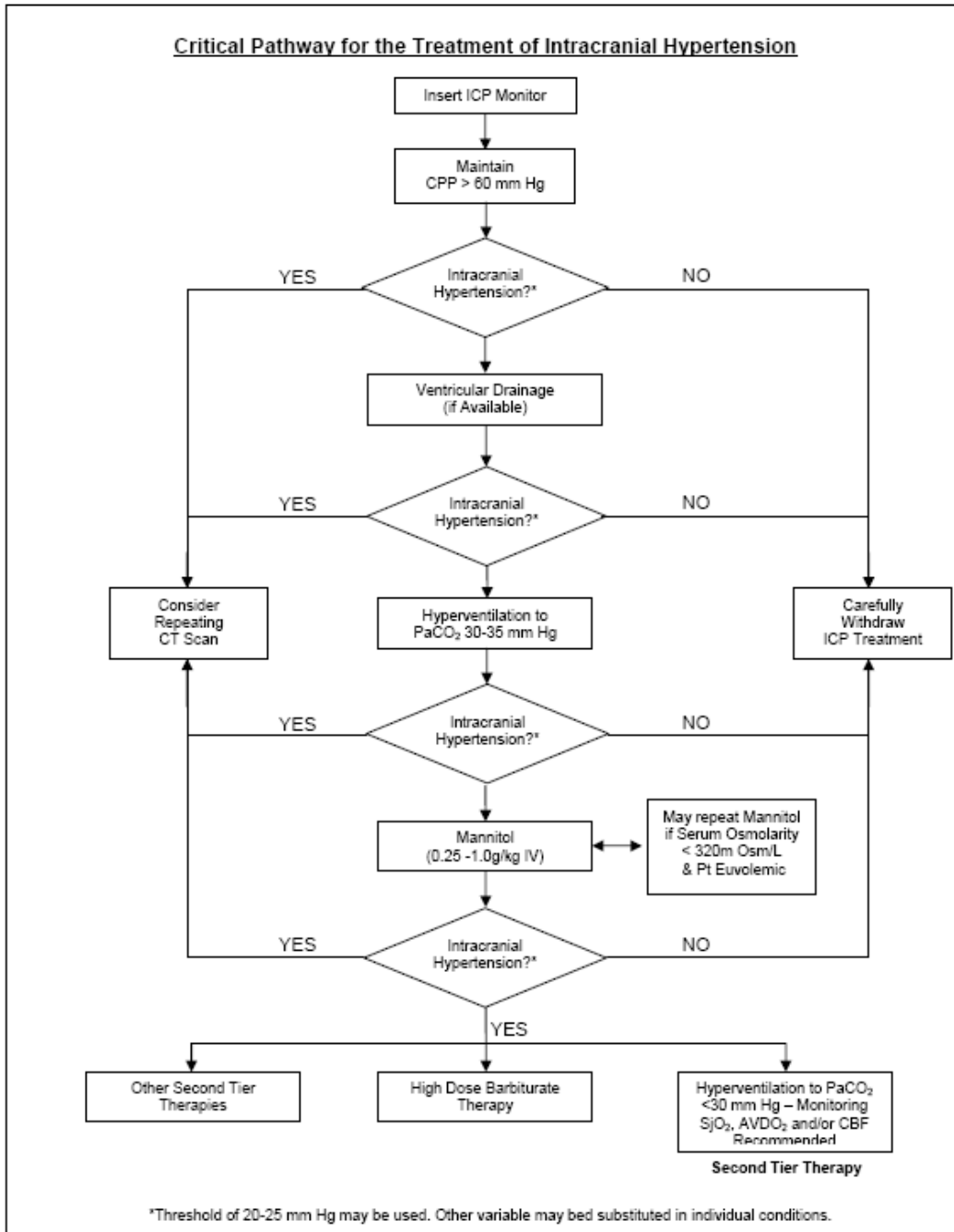
### *Monitoring & Management of Intracranial Pressure*

All patients meeting the criteria for severe traumatic brain injury (persistent GCS <9) should have an intracranial pressure monitor placed.

Patients with a sustained ICP>25mmHG should have intervention aimed at lowering ICP. This intervention is at the discretion of the treating physician but guided by the Brain Trauma Foundation Guidelines (See below). Excess hyperventilation should be avoided unless the patient is showing signs of acute herniation. Patients should be resuscitated to avoid episodes of hypotension (SBP<90 mmHg).

### *Brain Trauma Foundation Guidelines*

The Brain Trauma Foundation, by consensus, has developed a critical pathway for the treatment of established intra-cranial hypertension, which is printed on the following page. It should be viewed as a framework that may be useful in guiding an approach to treating intracranial hypertension. It can and should be modified in an individual case by any circumstances unique to the patient as well as by the response of the ICP to individual treatment steps.



Critical Pathway for the Treatment of Established Intracranial Hypertension in the severe head injury patient. Adapted from the Brain Trauma Foundation, Inc.

## Attachment A

### Exemption from informed consent, FDA regulation 21CFR50.24

#### 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.

(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.

(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.

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

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

(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.

## Attachment B

### Resource Document to Aid Institutional Review Boards with Development of Community Consultation and Public Notification Plans for the Resuscitation Outcomes Consortium

#### General Elements

1. Key speaking points for each ROC study.
2. Information regarding mechanisms to opt out, if required by the local IRB.
3. Translate into common languages based upon the target population as directed by the local IRB.

#### Options for Community Consultation

1. Consult with the public either by public meetings or random digit dialing surveys
  - a. Public meetings (focus groups or “town hall”)
    - i. Well publicized
    - ii. Track number of attendees, zip codes
    - iii. PowerPoint or other presentations shared with the CTC.
    - iv. Comments by attendees documented.
    - v. Representatives of the IRB invited to attend these events.
    - vi. Examples of focused events include religious or civic groups.
  - b. Meet with public officials
  - c. Dialing surveys document a summary of results, including all comments by participants.
    - i. Number and location (by zip code or phone number) of respondents.
2. Website includes information for the public to comment via e-mail, regular mail, phone, fax
  - a. Public comments logged.
  - b. Advertisements and press releases refer the public to the website.
  - c. Content of the website available to the CTC
    - i. Include information regarding exception from informed consent
    - ii. Include speaking points about each study.

#### Options for Public Notification

1. Press releases to newspapers, TV, and/or radio.
2. Advertising to target the community.
  - a. Articles placed in newspapers
  - b. Radio spots
  - c. Signage in public places, such as on busses.
3. Specific choices regarding media are up to the local investigators, based on the expected target population and the local IRB requirements.





## Attachment C

### ELECTRONIC SIGNATURE AGREEMENT

This Agreement is between you and the Resuscitation Outcomes Consortium (ROC) Clinical Trial Center (CTC), and provides for your informed consent to the use of your designated user name and password as an “Electronic Signature”. You have registered as a member with the CTC for the purpose of participating as a coordinator or investigator in clinical trials under the ROC. The ROC CTC has created an electronic data transmission system for all clinical forms and requires the use of Electronic Signatures. The CTC believes that this system reduces the time and expense of data submission and facilitates efficient and accurate data transmission from a clinical trial site to the CTC, without compromising data integrity, or the rights of the parties. Therefore:

1. You agree that the use of your user name and password constitutes your Electronic Signature when submitting or transmitting documents or data via the internet ROC CTC website.
2. Your Electronic Signature shall be considered for all such purposes as equivalent to your handwritten signature, provided below.
3. Your Electronic Signature, used in accordance with this Agreement, shall have the same legal weight associated with that of an original signature.
4. You agree not to raise the use of an Electronic Signature as a defense in connection with an internet ROC CTC website transmission, if your Electronic Signature is used in accordance with this Agreement.
5. Because the combination of your user name and password constitutes your Electronic Signature and bears the same legal weight associated an original signature when engaged in transmissions via the ROC CTC website, you understand that you are entirely responsible for maintaining user name and password confidentiality. You are accountable for any and all activities that occur using your user name and password. You agree to notify the CTC immediately of any unauthorized use of your user name or password, or any other breach of security known to you.
6. You agree to notify the CTC when you leave your position as a ROC member in order for the CTC to deactivate your Electronic Signature.

YOU REPRESENT THAT YOU HAVE READ THIS AGREEMENT. YOU UNDERSTAND THAT YOU ARE AUTHORIZING ALL FUTURE DATA TRANSMISSIONS BY YOU TO BE MADE ELECTRONICALLY VIA THE INTERNET ROC CTC WEBSITE AND THAT SUCH ELECTRONIC SUBMISSION CONSTITUTES YOUR ORIGINAL SIGNATURE. YOU AGREE THAT YOUR FACSIMILE SIGNATURE ON THIS DOCUMENT, SHALL BE DEEMED TO BE, AND MAY BE RELIED UPON BY THE CTC AS, AN ORIGINAL SIGNATURE.

Please print this Agreement. Sign and date where indicated below.

Return your signed Agreement to the ROC CTC, at the following facsimile number **(206) 543-0131**.

\_\_\_\_\_  
Your signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Your name (printed)

\_\_\_\_\_  
Your ROC user name

\_\_\_\_\_  
Principal Investigator signature (witness)