

ROC Site Status and Enrollment as of 4/30/2007							
Seattle/King County Overarching IRB-University of WA	IRB	IRB Approval to Start	FDA Amendment Approval	TBI Cohort Enrolled	Shock Cohort Enrolled	Community Consultation Completed	
Hospital							
Harborview Medical Center	Univ of WA	7/17/2006	11/29/2006	62	62	Jul-06	
EMS Agencies							
Airift Northwest	Univ of WA	7/17/2006	11/29/2006				
Belleuve Medic One	Univ of WA	7/17/2006	11/29/2006				
King County Medic One	Univ of WA	7/17/2006	11/29/2006				
Redmond Medic One	Univ of WA	7/17/2006	11/29/2006				
Seattle Medic One	Univ of WA	7/17/2006	11/29/2006				
Shoreline Fire Department	Univ of WA	7/17/2006	11/29/2006				
All agencies are enrolling subjects							

Shock Enrollment Breakdown as of 4/30/2007		Harborview Medical Center	Died in the field	Pre-hosp disposition unknown	Total
EMS Agencies/Hospitals					
Airlift Northwest		6	0	1	7
Bellevue Medic One		2	0	0	2
King County Medic One		17	3	0	20
Redmond Medic One		2	0	0	2
Seattle Medic One		29	0	0	29
Shoreline Fire Department		2	0	0	2
Total for Hospital		62	0	0	62

TBI Enrollment Breakdown as of 4/30/2007		Harborview Medical Center	Died in the field	Pre-hosp disposition unknown	Total
EMS Agencies/Hospitals					
Airlift Northwest		22	0	0	22
Bellevue Medic One		1	0	0	1
King County Medic One		18	0	0	18
Redmond Medic One		2	0	0	2
Seattle Medic One		20	0	0	20
Shoreline Fire Department		0	0	0	0
Total for Hospital		62	0	0	62

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Modification Form

This box is for Human Subjects Review Committee Use Only

HSRC signature: [Signature] Date approved/noted/denied: 11/29/06

Contingencies: _____

Master

Committee

Investigator

AE/Safety Report

PLEASE READ THIS FORM CAREFULLY, ADDRESS EACH APPLICABLE ITEM OF INFORMATION REQUESTED IN NUMBERS

1-8, AND SEND THE REQUESTED NUMBER OF COPIES.

PLEASE DO NOT submit double-sided forms or attached materials!

Unless otherwise stated, submit three (3) copies of this form collated with three (3) copies of revised or additional materials. We will not accept handwritten forms, incomplete forms, or forms printed on both sides of the paper. Use 10 point type or larger throughout modification form.

Modifications may not be implemented until you have received approval. The approval of this modification does not change the original period of approval of your Human Subjects Review Committee application.

If an adverse event occurs at a site covered in your approval for this study, submit a UW "Adverse Event Report Form." This form is available on the Human Subjects Division web site at <http://depts.washington.edu/hsd/formin.htm>

If you have any questions, please call our office at (206) 543-0098.

TITLE OF APPLICATION: "Hypertonic Resuscitation Following Traumatic Injury"

Principal Investigator: Eileen Bulger MD

Current HSRC approval no: 05-7193-A 01

Dept./Div.: Surgery/HMC Box/Mailstop: 359796 Phone: 731-3656 Fax: 731-3656 Email: ebulger@u.washington.edu

Contact person if not the PI: Sandy Hanson Phone: 731-4720 Email: sandyrh@u.washington.edu

1. ADDING A NEW FUNDING SOURCE. Complete the information in the box below. Briefly summarize the procedures involving Human Subjects in this new funding proposal and describe any differences between the approved application and the new proposal. If there are multiple aims in this grant, please specify which aim(s) pertain to this specific Human Subjects Application, and flag or indicate the page. If this grant will modify the population, purpose or procedures, outline these changes under the appropriate heading below. Submit 3 copies of this form and 1 copy of the grant proposal.

Funding Type: Research Grant Fellowship Training Grant Contract Other, specify: _____

Principal Investigator (on grant proposal): _____

Proposal Title: _____

Funding Agency: _____ Agency Number (if known): _____

Status: New Competing Renewal Non-competing Renewal

Start Date: _____ End Date: _____ Submitted through OSP? Yes No. If No, explain _____

2. CHANGE IN STUDY PURPOSE: Describe the change/revision to the purpose of the study, and explain the reason for this change.

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X 3. CHANGE IN PROCEDURES: Briefly summarize proposed changes below. Explain why the changes are being made. Describe any changes in risks, and an assessment of whether or not any changes should be made to the consent form(s). If you believe no changes are necessary, please state. Send 3 copies of this form along with 3 copies of the revised consent form(s). (See 4, below.)

Summary of Discussion with the FDA regarding Protocol Amendment for ROC Hypertonic Resuscitation Trial IND 12505 and 12506 November 2006

Several discussions were held with the FDA in early October regarding review of an SAE that occurred at one of the Canadian sites. This case involved a patient with severe traumatic brain injury who was appropriately enrolled in the HSD trial. The patient had a normal serum sodium value on admission to the hospital and again 4 hours later, but then when next measured 29 hours after injury, the serum sodium was 175mEq/L. The patient was diagnosed with central diabetes insipidus and managed appropriately and survived. This case was reviewed in detail by our DSMB chair, who sent a letter to the FDA summarizing his findings (see attached). Following this review the FDA indicated that they were concerned that there was not a standardized hospital monitoring plan for serum sodium during the first 24 hours after admission. This led to several telephone conferences in mid-October and the voluntary suspension of enrollment on October 26, 2006 until a plan could be fully developed. We initially proposed q8 hour monitoring of serum sodium for all patients during the first 24 hours and inclusion of an information sheet that would be placed in the patient's chart to remind care providers of the expected changes in serum sodium related to the study intervention. The FDA agreed with this approach but then requested that we add more intensive monitoring for patients receiving additional hypertonic saline (3%) or mannitol for management of intracranial hypertension. Although they acknowledged that these late changes in serum sodium are not related to the study intervention they wanted to be assured that we were monitoring these patients adequately and would report late elevations in serum sodium as SAEs. Thus, we agreed to q6 hour sodium monitoring for all patients who require 3% saline infusion or mannitol until 6 hrs beyond the discontinuation of therapy up to 5 days after injury. We also agreed to report any serum sodium value > 160mEq/L during this time period as an AE and kept our original definition for SAEs of: serum sodium > 160mEq/L requiring therapeutic intervention or associated with seizure activity. The final hospital protocol for sodium monitoring is outlined in the attached algorithm. There has been no communication from the FDA regarding their concerns and requests. All communication from the FDA has been via phone calls.

An additional concern was raised, by the FDA, during these discussions, regarding patient monitoring and investigator involvement at sites with multiple hospitals receiving study patients. The FDA requested that each hospital have a named local investigator who would sign the 1572 form and thus take responsibility for over site of patients received by that hospital. In conjunction with this request they asked for a summary of our monitoring plan for hospitalized patients to ensure that patients were carefully followed by study coordinators after admission. These issues are not as relevant to the Seattle/King County site as all patients enrolled in our region are treated at a single hospital, Harborview Medical Center. Our original 1572 was signed by Dr. Peter Kudenchuk who is the primary PI for ROC and in response to this request we did send an additional 1572 naming Dr. Eileen Bulger as the responsible physician for Harborview patients.

The final FDA approved protocol change results in the following changes in procedures:

- prehospital providers will give the health care providers in the ER an information sheet stating that the patient has been enrolled in the Hypertonic Saline study and what to expect regarding Na levels in the first 24 hours. Please see attached form
- serum sodium will be drawn from subjects every 8 hours for the first 24 hours. The first sodium will be drawn in the ER upon admission and then there will be one drawn 8 hours later, 16 hours after ER admit and the final sodium draw will be at 24 hours after the patient arrived in the ER.
 - o We will coordinate the serum blood draws with the sodium draws that occur with the patient's clinical care.
- for Traumatic Brain Injured patients who receive either 3% Na IV drip and/or Mannitol : serum sodium's will be drawn every six hours for the duration of the therapy until 6 hours beyond discontinuation of therapy up to 5 days after injury
 - o we will again coordinated the sodium blood draws with the standard of care. For all patients who are placed on a 3% Na IV drip a sodium level is drawn every 4 hours. There is no standard of care in regards to Na levels for patients who receive Mannitol

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- all serum sodium levels >160 will be collect and reported (in de-identified form) to the Clinical Trials Center, so the cases can be tracked and reviewed by the DSMB

The following changes are in the new protocol, however our site has these in place prior to starting the trial here in Seattle/King County.

1. A study coordinator or investigator will be on call 24 hours a day, 7 days a week
2. Each hospital accepting patients enrolled in the trial will have a named physician on the medical staff responsible for facilitation communication with study personnel and addressing any concerns regarding patient management. At Harborview Medical Center, Dr Eileen Bulger is this physician.
3. Investigative personnel (research nurses and/or Dr Bulger) will assess the subject'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

4. **CHANGE IN POPULATION and/or RECRUITMENT:** Briefly describe proposed changes in subject population or recruitment, including the reasons for this change. Include the following for each new population, if relevant: inclusion criteria, exclusion criteria, age range, number of subjects (cases and controls), approach and recruitment methods. **Submit 3 copies of this form and 3 copies of all revised or new recruitment materials.**

5. **SITE:** Submit three copies of this form and one copy of a letter of cooperation from each non-UW site. The letter should acknowledge that the agency is familiar with the study purpose and procedures, and with the investigator and their affiliation with the University of Washington.

X 5 REVISIONS TO CONSENT DOCUMENTS: Submit 3 copies of this form and 3 copies of each revised consent/assent form or oral consent script, incorporating changes in purpose, procedures, population, investigators and risks as described elsewhere on this form. **Highlight changes on one copy.** Please check the sample consent form and the consent form checklist on the HSD web site at <http://depts.washington.edu/hsd/FORMS> for current requirements. Please also refer to Clinical Trials Handbook, at <http://www.hsccr.washington.edu/clinicaltrials/handbook/4Consent.html>, for other sample consent form language.

State the total number of approved consent forms in current use for this study. State if this consent form replaces a current version (and specify the approval date), or is an additional consent form.

The submitted consent form (version 5) is to replace the currently approved consent form (version 4, approved July 20, 2006). Version 5 of the consent form reflect the procedure changes, that is the increased in blood draws for the purpose of monitoring serum sodium levels. As each subject will have a different number of blood draws based on their clinical treatment, we are unable to specifically state how many extra blood draws will be performed, and how much blood will be obtained overall. It is our goal to coordinate the standard of care blood draws with the research driven Na blood draws, so that the subject does not have excessive blood draws.

In addition, as the serum sodium monitoring is being mandated by the FDA for safety purposes, we do not believe that we can give the subject the option of not having blood drawn for sodium levels. Thus there is no place for the patient to agree/disagree for those blood draws on the consent. We have submitted an waiver of consent to cover this issue.

X 7. CHANGE IN INVESTIGATORS: Provide information requested below for each new investigator; also indicate if an investigator is no longer associated with this research. **If the Principal Investigator is appointing a new PI, both the current PI and new PI should sign this form.**

Name and Title	University Position	Dept./Div.	Phone	Box
Jeanne O'Brien RN	Research Nurse	UWMC Cardiology	521-1221	

8. **OFF SITE ADVERSE EVENTS and SAFETY REPORTS:** If an event occurs at a site covered in your approval for study that is unexpected or more severe than anticipated, submit the UW "Adverse Event Report Form" available at

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<http://depts.washington.edu/hsd/FORMS/aereport.doc>. If an adverse event occurs that is anticipated or no more severe than expected, it must be reported on the Status Report at annual renewal or when closing the study. Otherwise, state how many events are being reported here, list the dates of occurrence and provide a brief description of each event. Also, inform us whether these adverse events are new or follow-ups of events that were already reported to us, then include the date the event was originally reported. Assess whether or not changes are required to the consent form. If you believe no changes are required, please state. Also state whether enrollment is still open for this study and whether subjects are still undergoing study procedures. **Submit 2 copies of this form and 1 copy of each adverse event/safety report.**

X 9 PROTOCOL AMENDMENTS and INVESTIGATOR DRUG BROCHURES (for FDA regulated studies only): Describe what changes are being made if not described above, and assess any changes in risks to subjects. If you believe there are no changes in risks, please state. If submitting a protocol amendment, **submit 3 copies of this form, 3 copies of the amendment and 1 copy of the revised protocol.** If submitting an updated Investigator Drug Brochure, **submit 3 copies of this memo and 1 copy of the brochure.**

A brief outline of the protocol amendment is provided below. The full amendment is attached and there is a flow diagram to aid in the understanding of the changes that are occurring as a result of monitoring serum sodium's.

The protocol amendment has three components:

1. Monitoring plan for serum sodium after study drug administration

- a. Prehospital providers will deliver an information sheet for the receiving health providers to notify them of the patients enrollment in the study and details the expected rise in serum sodium that may be related to the study fluid.
- b. Monitor all subjects serum sodium's for the first 24 hours and then as needed, based on treatment with a 3% sodium IV drip or the IV drug mannitol.
- c. The Clinical Trial Center (here in Seattle) will track compliance
- d. All serum sodium's >160 will be reported to the CTC and the DSMB. Sodium's > 160 requiring therapeutic intervention and associated with seizure activity will be reported as SAE's, as per the original protocol.

2. Study patient oversight during hospitalization

- a. A study coordinator or investigator will be on call 24/7
- b. Each hospital (only participating hospital at the Seattle/King County site is Harborview Medical Center) will have a named physician on the medical staff for facilitation communication with study personnel and addressing any concerns regarding patient management. Dr Eileen Bulger has and will continue in this role.
- c. Investigative personnel will assess the patient's clinical status daily after ICU admission for the first 5 days and then every other day for the remainder of the ICU stay.

3. Management of variations in hospital care

- a. A formal declaration and the rationale of why the ROC will not attempt to protocolize trauma and or traumatic brain injury care.

There is a minimal change in risk related to the addition of serum sodium blood draws. Although the vast majority of the patients in the ICU have IV's that are used for blood draws, there might be the rare occurrence where a needle stick is necessary to obtain the serum Na value.

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10. **CONFLICT OF INTEREST:** If there has been a change in the financial interest for any members of the research team, provide a copy of the letter you received from the Office of Research about how this conflict of interest should be managed.

11. **OTHER** (protocol violations, relevant compliance approvals, and data monitoring, etc.):

Typed name and original inked signature of P.I.



Date: 11/22/06

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Current HS study procedures for monitoring serum sodium after study drug administration:

1. Review all sodium levels drawn for standard of care for a level greater than 160.
 2. Assess all patients with hypernatremia ($\text{Na} > 160$) for therapeutic intervention
 3. Assess all study patients for seizure activity associated with hypernatremia.
- No serum sodium is drawn for research purposes.

Standard of Care:

- Sodium level drawn on admission to ER
- At a minimum, a Na level is drawn once a day, in the morning
- When the patient is placed on a 3% Na drip (for treatment of increased brain swelling), sodium levels are drawn before the IV drip is started and then every 4 hours as long as the patient is receiving the 3% IV.
- Typically patients do not have Na levels drawn as part of the treatment with Mannitol (another drug given IV to reduce brain swelling by drawing off fluid)

New HS protocol changes:

1. Notify Health Care Providers of patient's enrollment in the HS study and details the expected rise in serum sodium that may be related to the study fluid.

This will be done via an information sheet placed in the study bag kits (which contain the study drug) and the prehospital providers will hand the sheet to the ER MDs.

2. Monitor Serum Sodium:

- All study patients: Na level on admission to ER
- All study patients admitted to the ICU: Na level every 8 hours for first 24 hours.
 - Thus all critically injured patients will have a Na level drawn 4 times in the first 24 hours
- All study patients with a traumatic brain injury who require either a 3% Na IV drip or a administration of the drug Mannitol
 - Every 6 hour Na levels (until 6 hours beyond discontinuation of therapy and or 5 days which ever comes first)

When Na levels are not considered standard of care by the hospital provider, the HS study will pay for the laboratory studies.

3. Continued monitoring of Serious Adverse Event:
 - any Na level > 160 requiring therapeutic intervention
 - any seizure activity associated with hypernatremia

In addition to: all patients with a Na > 160 regardless of treatment will be reported to the CTC so these cases can be tracked.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Heart, Lung, and
Blood Institute
Bethesda, Maryland 20892

October 4, 2006

Laurence Landow, M.D.
Medical Officer
FDA
Division of Blood Applications
1401 Rockville Pike
Suite 425N, HFM-392
Rockville, Maryland 20852-1448

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Dear Dr. Landow:

As Chair of the Data Safety Monitoring Board (DSMB) for the Resuscitation Outcomes Consortium (ROC) clinical trials, I receive copies of all reported SAEs within 15 days of their being reported by the clinical sites. When indicated, I communicate with members of the ROC Data Coordinating Center and/or investigators at the clinical sites to resolve any questions I might have about the report. For an SAE of particular concern, the case is discussed by the entire DSMB in an expedited fashion. Otherwise, all SAEs are reviewed by the entire DSMB at our regularly scheduled, at least semiannual, meetings. As you requested, I am enclosing a detailed review of the hypertonic saline/dextran (HSD) case, and my judgment regarding the HS protocol safety, and protocol continuation.

Review of the QTT 00070 HS-1 case:

Briefly, this patient was involved in car accident sustaining head injury (GCS of 4) and was enrolled into the HS study on August 25 and received study allocated fluid at 1:44 am and transported to local medical center ED for further care. Serum sodium levels, measured at 1:54 am (139 mEq/L) and on August 26 at 1:55 am (143 mEq/L) were within normal limits. Subsequent serum sodium level (177 mEq/L) was measured at 7:05 am that day. Observed hyponatremia occurred approximately 29 hours after receiving the study treatment (HS, HSD or NS). Patient status was unblinded and the result was provided to the local treating critical care physician. Subsequent serum sodium levels were checked 6 times a day thereafter. Patient received standard therapy with serum sodium levels returning to normal level by August 28, 2006.

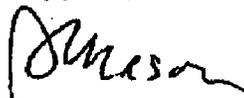
The site investigator completed an SAE report, concluding that the hyponatremia was probably not related to the study infusion. The SAE report was mailed to me on September 7. I noted the hyponatremia and contacted Judy Powell, Project Director at the Clinical Trial Center, by email on September 13 requesting an explanation from the site investigator for classifying the hyponatremia as not study treatment-related. His judgment was based on the observation that serum sodium was within normal limits one hour and five hours after fluid administration. The hyponatremia was detected 29 hours after the infusion. There were no additional serum sodium determinations between 5 hours and 29 hours after study drug infusion. The case was also reviewed, according to the study procedures, by Bert Bardarson, Trauma Project Manager at the Clinical Trial Center, and Dr. Eileen Bulger, HS study Co-Principal Investigator and in a meeting of the Principal Investigators.

With respect to the diagnosis of hypernatremia, my review supports the site investigator's conclusion as the correct one. Had the subject received hypertonic saline, its effect on serum sodium would have been noted in the first two measurements done within 1 and 5 hours after fluid administration, and any effect would have dissipated before hour 20. A possible cause of hypernatremia in this subject is trauma-related central diabetes insipidus (CDI). In my own experience managing cardiac transplant donors with unrecoverable brain injury, CDI often leads to hypernatremia if it is not anticipated. In managing these donors I saw serum sodium levels exceeding 175 mEq/L frequently when DI was not proactively diagnosed and treated. Parenthetically, we did not observe fatalities in our donors due to severe hypernatremia because the usual causes of death from hypernatremia, coma and respiratory arrest, are managed in the ICU setting.

In summary, my opinion is that this SAE certainly does not require an interruption or major change in the HS protocol. I reviewed this case with the Principal investigators before this writing. I asked the them to review the patient management information and recommendations that are provided currently to all participating physicians and to consider if more information should be provided regarding the extent and time course of hypertonic saline-induced hypernatremia and that of CDI in the first hours and days after head trauma. A potential vehicle for this information is the written material that is inserted into each enrolled subject's medical record that announces the patient's involvement, describes the trial and makes general recommendations concerning patient management.

This case will be reviewed by the full DSMB at its next meeting on January 25, 2007. At that meeting the ROC Principal investigators will present their proposed advice to participating physicians on how to assess hypernatremia and to differentiate between the expected and desired elevation resulting from hypertonic saline and hypernatremia secondary to CDI. At present I believe that observation by the site investigators of existing standards of care for patients with severe head-trauma is sufficient to deal with hypernatremia, but the committee will also consider whether a change in protocol is needed to manage this problem

Sincerely yours,



Jay W. Mason, MD
 Chairman, ROC DSMB
 Adjunct Professor of Medicine
 University of Utah
 Medical Director and Director of Research and Development
 Covance Cardiac Safety Services

Protocol Amendment IND 12505 & 12506

11/21/06

PROTOCOL AMENDMENT

IND 12505 & 12506

Hypertonic Resuscitation after Trauma: Resuscitation Outcomes Consortium
October 28, 2006

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This protocol amendment seeks to address three issues recently raised by the FDA relative to IND 12505 & 12506. These include:

1. Monitoring plan for serum sodium after study drug administration
2. Study patient oversight during hospitalization
3. Management of variations in hospital care

This amendment has been approved by all study investigators and will take effect immediately upon resumption of patient enrollment. This amendment will be submitted to all IRBs (U.S.) and REBs (Canada) that provide local oversight for this trial.

1. Monitoring Plan for Serum Sodium

A. Background

1. Summary of Expected Changes in Serum Sodium related to Study Solution Infusion

Based upon previous trials of 7.5% saline administration in trauma patients, the serum sodium is expected to rise immediately after infusion and normalize by 12 hours after study fluid administration. The table below shows the mean serum sodium on admission to the hospital or shortly after drug infusion in 11 prior studies. These elevations in serum sodium have not been associated with adverse events in previous trials and there have been no reports of seizure activity. In the study by Bulger et al, at the request of the FDA, investigators and care providers were blinded to the serum sodium and chloride for the first 12 hours after admission to avoid the possibility that a physician would elect to treat the patient differently based upon an early elevation in these electrolytes. Any persistent elevation in serum sodium after 12 hours or a subsequent rise in serum sodium after admission must be presumed to be due to another etiology and should not be attributed to the study intervention solution.

Serum Sodium Levels in Previous trials

Study	N	Mean Serum Na ± SD (mEq/L) Admission	Mean Na post infusion
Maningas et al. 1989	48	151 ± 7 Tx group	145 ± 5 Tx group 4 hrs post
Holcroft et al., 1987	49	153 ± 4	N/A
Holcroft et al., 1989	32	148 ± 10	N/A
Vassar et al., 1991	166	154 ± ?	N/A
Mattox et al. 1991	359	151 ± 9	N/A
Vassar et al., 1993 J Trauma	258	152 ± 6	N/A
Vassar et al., 1993 Arch Surg	194	148 ± 7	N/A

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Younes et al., 1992	155	155 ± 4 (15 min after infusion)	N/A
Cooper et al, 2005	229	149 ± 4	147 ± 4
Rizoli et al, 2006	27	147 ± 3 (1hr after infusion)	146 ± 4 3 hrs post
Bulger et al, 2006	209	147 ± 6	N/A
Topher Hit study (unpublished data, Univ Toronto), 2006	64	147 ± 2 (1hr after infusion)	145 ± 3 3 hrs post

2. Late rise in Serum Sodium after Hospital Admission

The two primary reasons for the subsequent development of hypernatremia following hospital admission are the administration of 3% saline infusion or mannitol for control of intracranial pressure (ICP) and the development of central diabetes insipidus (DI) in patients with severe traumatic brain injury (TBI). 3% saline infusion is an accepted approach to ICP management, but is not used universally in all centers. Centers using this therapy routinely couple it with frequent monitoring of serum electrolytes.

Hypernatremia can also be associated with the use of mannitol, due to development of dehydration. This treatment is accompanied by frequent osmolality and electrolyte monitoring to avoid this complication. Central DI is not uncommon after severe TBI with recent studies reporting severe DI in 2.9% of patients and more mild forms of DI in up to 22%. Development of DI is accompanied by increased urine output, which will be evident in these cases and drives the more frequent monitoring of serum electrolytes and pharmacological treatment. All trauma centers involved in this trial have experience in caring for severe TBI patients and thus will be aware of these clinical scenarios and appropriate management. A patient could also have isolated elevated sodium due to laboratory error or withdrawal of blood from a saline intravenous line. In this circumstance sodium values before and after that value would be normal.

3. Experience with Serum Sodium in HSD Trial to Date

At the time of voluntarily ceasing enrollment, 140 patients had been enrolled in the clinical trial. We have reviewed the serum sodium measurements made during the first 24 hours post ED admission and recorded in the trial database. The following table presents aggregate data across both cohorts (TBI and hypovolemic shock) for all three treatment arms. According to the current study protocol, data is collected on the first measured sodium post ED admission, as well as for the highest recorded serum sodium for each patient during time intervals corresponding to 0-4 hours post ED admission, 4-12 hours post ED admission, and 12-24 hours post ED admission. Descriptive statistics on these measurements are provided in the table below. Due to patterns of additional mortality (e.g., a total of 20 subjects died at some time during the first 24 hours), sodium measurements not available (e.g., 20 subjects did not have sodium measurements between 12 and 24 hours post admission), or data not yet entered into the database, there are fewer measurements for later time intervals.

Time Interval	n	Mean	SD	Median	Min	Max	Percent >160
First recorded value	106	142.8	5.46	142	129	156	0.0%
Highest value 0-4 hours	103	144.7	6.99	144	129	175	2.9%
Highest value 4-12 hours	80	143.7	5.73	142	135	180	1.3%
Highest value 12-24 hours	68	144.0	6.59	143	132	176	1.5%

During the first 4 hours post ED admission, 3 patients experienced a single, isolated serum sodium measurement greater than 160 meq/L. In each of these 3 cases, the elevated sodium was preceded by a normal serum sodium level measured less than 15 minutes prior and was followed by a normal serum sodium level within 25 minutes. The clinical impression from our medical monitor, Dr. Eileen Bulger, is that these 3 elevated serum sodiums are spurious values due to errors in sample collection or measurement. A single patient had consistently elevated serum sodium starting between 4 and 12 hours post ED admission and persisting through the second day. This patient was reported as an SAE. The clinical impression was that this finding was consistent with the development of central diabetes insipidus and related to the use of 3% saline to control intracranial hypertension. The SAE data have been reviewed by the Chair of the Data and Safety Monitoring Board (DSMB). These and other SAE and AE data will be also reviewed by the full Data and Safety Monitoring Board at its next review in January 2007.

B. Notification of Care Providers regarding Expected Changes in Serum Sodium

Prior to the start of enrollment, care providers of trauma patients at the study hospitals were notified of the study and the expected changes in serum sodium. To reinforce this education, an information sheet will now be added to all packets of study fluid and will be delivered to the hospital based providers by the prehospital providers at the time that they transfer care of the patient to hospital-based providers in the emergency department. This document notifies the care providers of the patient's enrollment in the study and details the expected rise in serum sodium that may be related to the study fluid. In addition, we remind the care provider that an excessive initial rise in serum sodium or any rise in serum sodium after 12 hours should not be attributed to the study intervention. This should trigger a search for other etiologies such as 3% saline infusion, mannitol induced dehydration, or the development of central DI. In addition, we remind the care

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provider about the risk of diabetes insipidus in patients with severe TBI and reinforce the importance of sodium monitoring as described in the monitoring protocol below. We also provide a local contact number to call for any questions related to the study. (see attached form)

C. Monitoring of Serum Sodium

All hospitals will now be 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. We maintain that q8hour monitoring will be sufficient for the detection of a subsequent rise in sodium after admission and thus alert the care provider to investigate the etiologies described above. In addition, this monitoring system will capture patients with significant medical co-morbidities that may influence serum electrolytes. Patients with minor injuries that do not require ICU admission will not be subject to q8hour monitoring. To ensure that these levels are drawn there will be a study coordinator on call 24hrs a day/7 days a week for each site. This coordinator will be notified of patient enrollment by the EMS providers immediately after arrival at the hospital. The coordinator will be responsible for communicating with hospital providers to ensure that the q8hour sodium values are ordered and will follow up to ensure that they have been drawn and record the results. This interaction will allow the coordinator to further address any concerns by the care provider relative to the development of hypernatremia. When q8hour sodium values are not considered standard of care by the hospital provider, the ROC will incur the cost of these laboratory studies. Current data collection forms will be modified to reflect this monitoring frequency.

D. Central tracking of compliance with new sodium monitoring system

The CTC will closely track the compliance with this monitoring plan, and deviations from the presumed standard of care at each hospital will be reviewed at regular intervals by the study "sodium/protocol monitoring/compliance committee" (CTC staff, Trauma co-chair, and Trauma Co-PIs) and the DSMB. Should any hospital show a consistent pattern of failure in adequately monitoring serum sodium in these patients, the local PI will review the study protocol and our recommendations with attending ED and ICU physicians at that hospital. If the DSMB finds that the standard of care at any hospital is not in keeping with that required for the safety of patients in this trial despite timely efforts at remediation, then all future patients to be transported to that hospital will be judged ineligible for the clinical trial and EMS providers will be instructed not to administer the study fluids to those patients

E. Reporting of SAEs and AEs related to hypernatremia.

The prior protocol described two SAEs related to hypernatremia. These included any sodium value $>160\text{mEq/L}$ requiring therapeutic intervention and any seizure activity associated with hypernatremia. We will continue reporting these events as SAEs, but will also now report to the CTC any patient with a sodium values reported to be $>160\text{mEq/L}$, even if therapeutic intervention is not required, so that these cases can be

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tracked and reviewed by the DSMB. This will apply to the first 5 days after injury. We anticipate that this will include patients treated with a 3% saline infusion or mannitol osmotic therapy who may have a transient elevation >160 which resolves by simply discontinuing the infusion and patients with potentially spurious values due to laboratory error or a sample obtained from an intravenous line with saline infusion. These cases will be reviewed in detail by CTC staff and reported to the DSMB to track the overall incidence of hypernatremia in the study population.

2. 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 we have devised the following patient oversight requirements, which must be met at every hospital before patient enrollment can begin at that hospital. The components of this plan are as follows:

- a. 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.
- b. 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.
- c. 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 attached for detailed forms and 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. The CTC guided training of study coordinators will ensure consistency across sites in compliance with these oversight parameters.

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Summary of Hospital Data Collection

Admission & Emergency Department Care	Initial Resuscitation 0-24 hours (Data collected for both 0-12hr and 12-24hr)	Intensive Care & TBI Management 1-5 days	Subsequent ICU Care 5-28 days	Outcome 28d to 6mon
<ul style="list-style-type: none"> ◆ Vital signs ◆ Temperature ◆ GCS score ◆ Electrolytes ◆ Osmolarity ◆ Arterial Blood Gas ± lactate ◆ Hemoglobin ◆ Coagulation studies ◆ Ventricular arrhythmias ◆ Intubation status ◆ ED procedures ◆ Angiography ◆ Adverse Events ◆ Disposition 	<ul style="list-style-type: none"> ◆ Type and Quantity of IV fluids ◆ Blood products transfused ◆ Highest lactate or worst base deficit ◆ Q8 hr sodium values ◆ ICP monitor placement ◆ Highest ICP, #hrs ICP>25, #hrs CPP<60 ◆ Total gm mannitol ◆ GCS score ◆ Interventions for elevated ICP ◆ Any seizure activity ◆ Adverse Events 	<ul style="list-style-type: none"> ◆ ARDS/ALI ◆ MODS score* ◆ Highest ICP, #hrs ICP>25, #hrs CPP<60 ◆ Total gm mannitol ◆ GCS score ◆ Interventions for elevated ICP ◆ Any seizure activity ◆ Results of first 3 head CT scans with Marshall score ◆ All Infections & Non-infectious complications ◆ All operative procedures ◆ Compliance with guidelines d3-5: <ul style="list-style-type: none"> Glucose levels and insulin use Lowest Hgb & transfusion rate Sedation used for mechanical ventilation Type of nutrition ◆ Adverse Events 	<ul style="list-style-type: none"> ◆ MODS score QOD ◆ ARDS/ALI ◆ All Infections & Non-infectious complications ◆ All operative procedures ◆ Duration of ventilation and ICU stay ◆ Adverse Events 	<ul style="list-style-type: none"> ◆ TBI outcome interview prior to discharge & 6 months after injury ◆ Survival follow-up to 28 days after injury

*MODS score includes QOD review of platelet ct, creatinine, bilirubin, GCS score, CVP, use of pressors, vital signs, oxygenation
See data collection forms for additional detail

3. Management of Variations in Hospital Care

This study was designed as a pre-hospital intervention effectiveness trial in accordance with the regulations describing trials to be conducted under the Emergency Medicine Waiver of Informed Consent (50.24). Integral part of the study design is anticipated variation in the usual care provided to trauma patients in the hospital. This reflects the lack of adequate scientific evidence to protocolize all aspects of patient care. The study design employs randomization in the prehospital setting, multiple centers, and a large sample size, all of which should eliminate or minimize any confounding related to variability in care. All hospitals receiving patients in this trial are designated as Level I, II, or III trauma centers through an intensive site review process by organizations such as the American College of Surgeons or governmental agencies. Selection of these trauma specialized centers ensures the availability of the infrastructure and surgical and subspecialty expertise to care for critically ill trauma patients 24 hours a day/7 days a week. This specifically ensures timely involvement of neurosurgeons in the care of patients with severe traumatic brain injury. A recent study (MacKenzie, et al., *NEJM*, 354:366-78, 2006) shows that treatment at a trauma center vs. a nontrauma center improves survival. Trauma systems have been established so that patients with severe injuries are triaged to these centers from the field to optimize their outcome and the ROC uses this structure to ensure that patients receive timely and appropriate care. Level III trauma centers tend to be lower volume than level I or II centers, so we have planned an observational analysis to compare outcome for patients in the trial managed at Level I & II centers vs. Level III centers. If a ROC patient is not being transported to one of these centers they are not eligible for enrollment in the trial.

We have chosen not to protocolize the care received by patients, as this would interfere with the standard of care, which is not consistent with an effectiveness trial. Furthermore, should we mandate a management strategy that is not clearly supported as superior in the scientific literature, we might exclude the patient from other beneficial therapies. For example, there is no Class I evidence to define the appropriate management strategy for intracranial hypertension following TBI. There are several accepted approaches including the use of mannitol, 3% saline, or both. To mandate a uniform approach in this circumstance, and thus eliminate clinical judgment of the neurosurgeon, could be harmful to the individual patient. The randomization stratified within EMS agencies should eliminate any overall confounding due to variation in the usual clinical practices across providers, hospitals, and/or sites, as well as with respect to other pre-randomization variables. Our data collection will also allow us to evaluate the impact of ICP management strategies on outcome related to the study intervention. However, because these are post-randomization variables, all such analyses must be interpreted cautiously. In fact, a beneficial effect of treatment could be associated with higher use of specific treatments, if the patients saved by the therapy are more prone to have more serious injuries than those who would have survived without the treatment.

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There are some aspects of ICU care following injury for which evidence based guidelines have been developed. Many of these were developed by the NIH (NIGMS) sponsored multi-center network studying the inflammatory response after injury (GLUE grant). These are implemented as care guidelines instead of protocols, as there are always some patients who are not appropriate for this approach. These guidelines have been reviewed and accepted as care guidelines in all the ICUs where patients in the study will be treated. We have built into our patient monitoring data collection variables which allow us to track compliance with these guidelines at the individual hospitals. We believe that it is critical that these remain as guidelines and not study protocols, however, given the importance of including clinical judgment in decisions regarding an individual patient. These guidelines may also need to be revised as new evidence becomes available and thus they will be reviewed at each steering committee meeting by the ROC clinical care guideline committee. Compliance with the guidelines will be tracked through the data collection process (see table) and the onsite clinical monitoring by the study coordinator and local investigator. Site visits are held by the CTC as well to evaluate compliance and this data will be reviewed by the DMC. Should any hospital show a consistent inability to adhere to these guidelines then the DMC will have the authority to request that they no longer receive patients enrolled in the trial.

Enc: Information Sheet for Care Providers
Copy of Data Collection forms for Hospital Care

Protocol Amendment IND 12505 & 12506

11/21/06

November 7, 2006

Office of Blood Research and Review
Center for Biologics Evaluation and Research
1401 Rockville Place
Rockville, MD 20852-1448

RE: IND 12505 and IND 12506

Dear Drs. Golding and Landow,

As requested we are writing with an addendum to our protocol modification dated October 28, 2006 for INDs 12505 and 12506. We would like to add the following to the plan for monitoring of serum sodium: For those patients with traumatic brain injury who are receiving 3% saline infusion or mannitol boluses for management of intracranial pressure we will require, at a minimum, q6hr monitoring of serum sodium for the duration of that therapy.

Based upon our discussion today we would also like to confirm that once this protocol amendment is approved we will resume enrollment only at those hospitals for whom an investigator agreement is already in place and will not resume enrollment at the more remote hospitals until the 1572 forms are complete along with an oversight plan for that site. These will be submitted to the FDA prior to enrollment.

We request that you send us in writing as soon as possible a statement that approves the protocol amendment as that is required by our Institutional Review Boards who must review the amendment as well before we can resume enrollment. Thank you for your time and attention.

Sincerely,

Eileen Bulger, MD
Co-Principal Investigator
ROC Clinical Trial Center

Cc: George Sopko, MD, NHLBI
David Lathrop, PhD, NHLBI

**Hospital Protocol for Sodium Monitoring
Resuscitation Outcomes Consortium: Hypertonic Resuscitation Trial**

Patient enrolled and prehospital study fluid administration by EMS Providers

Hospital arrival
Information Sheet re: hypernatremia given to hospital personnel
admission serum sodium drawn
Study Coordinator notified of patient enrollment

All patients require, at a minimum, q8hr serum sodium 1st 24 hrs (8, 16, 24 hrs)
If patient requires mannitol or additional non-study hypertonic saline infusion in 1st 24hrs
then serum sodium required, at a minimum, q6hrs (6, 12, 18, 24hrs)

Any patient requiring hypertonic saline infusion or mannitol boluses beyond
24 hrs will have q6hr sodium monitoring until 6 hrs beyond
discontinuation of therapy up to 5 days after injury

Serious Adverse Event Reporting

All sodium values obtained within the first 24 hours of injury will be collected and reviewed and any value > 160mEq/L will be reported. In addition, any patient requiring hypertonic saline infusion or mannitol boluses will have q6hr sodium collected and reviewed (until 6 hrs beyond discontinuation of therapy up to 5 days after injury) and any value > 160mEq/L will be reported.

Serious Adverse Events will include:

1. Any sodium value > 160mEq/L requiring therapeutic intervention
2. Seizure activity associated with a sodium value > 160mEq/L

11/21/06

INFORMATION FOR CARE PROVIDERS

HYPERTONIC RESUSCITATION TRIAL: RESUSCITATION OUTCOMES CONSORTIUM

This patient has been enrolled in a prehospital hypertonic fluid resuscitation trial sponsored by the Resuscitation Outcomes Consortium. He/She has received 250cc of either 7.5% saline/6% dextran, 7.5% saline w/o dextran, or normal saline administered by the prehospital provider. Administration of the blinded study intervention was completed before the patient was transferred to the care of hospital staff in the emergency department of your hospital. No further intervention is required in the hospital but we want you to be aware of the following issue:

As a result of this treatment, the patient could have a transient rise in serum sodium. Previous studies suggest that the average sodium on admission to the hospital ranges from 147 to 155mEq/L and these values should normalize by 12 hours. We do not recommend that you intervene for this small initial rise in serum sodium as this is expected and required for the study intervention to be effective. The study requires that you monitor the serum sodium every 8 hours over the first 24 hours. An initial rise in serum sodium beyond 160mEq/L over the first 12 hours, a persistently elevated serum sodium beyond 12 hours, or a subsequent rise in serum sodium after admission should *not* be presumed to be due to the study intervention and another etiology should be sought and appropriate treatment instituted.

Patients with severe traumatic brain injury are at risk for the development of central diabetes insipidus early after injury, and thus this diagnosis should be considered in this patient cohort.

Should you have any questions regarding this study, please do not hesitate to contact your local ROC investigator or coordinator.

PI: Dr Eileen Bulger

Questions : call the research nurses at 1-800-607-1879

APPROVED

NOV 29 2006

UM Human Subjects
Review Committee

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Human Subjects Division

NOV 22 2006

UW

**CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION
OFFICE OF BLOOD RESEARCH AND REVIEW
DIVISION OF BLOOD APPLICATIONS**

Woodmont Office Complex, 400N
1401 Rockville Pike
1401 Rockville, Maryland 20852-1448

FACSIMILE TRANSMISSION RECORD

TOTAL NUMBER OF PAGES: 2 (Including Cover Page)

FAX TO: Scott Emerson, MD, PhD, Principle Investigator

Facsimile Telephone No.: 206.543.0131 Voice Telephone No. 1.800.332-0586

FROM: Cecelia R. Watson, Regulatory Project Manager

Facsimile Telephone No. 301.827.2857 Voice Telephone No. Phone: 301.827.6164

DATE: Tuesday, 14 November 2006 TIME: 1413

MESSAGE:

Cecelia R. Watson, MS, SBB(ASCP)
Regulatory Project Manager, CSO
Division of Blood Applications
CBER, FDA, HFM-380
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Phone: (301) 827 6164
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E-mail: Cecelia.watson@fda.hhs.gov

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

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NOV 22 2006

UW

BB-IND 12505

Scott Emerson MD, PhD
Principal Investigator
Clinical Trial Center
University of Washington
Box 354806
1107 N.E. 45th Street, Suite 505
Seattle WA 98105-4689

Dear Dr. Emerson,

We have reviewed your email communication dated 11/13/06 to **Investigational New Drug Application (IND 12505) "Hypertonic Resuscitation Following Traumatic Brain Injury"**, which includes provision for **Exception from Informed Consent (21CFR 50.24)**, which contains an algorithm for serum sodium measurements.

According to the algorithm, all subjects will require at a minimum, q8h serum sodium measurements for the first 24 hours. If a subject requires mannitol or additional non-study hypertonic saline infusion within the first 24 hours, serum sodium will be captured, at a minimum, every 6 hours.

FDA finds this algorithm acceptable. As discussed during our telecon of 7 NOV 2006, you may restart enrollment of subjects except at sites where the centers are geographically dispersed.

If you have any questions, contact Cecelia Watson at (301) 827-6164.

Sincerely,

Bashl Golding, M.D.
Director
Division of Hematology
Office of Blood Research and Review
Center for Biologics
Evaluation and Research

UNIVERSITY OF WASHINGTON

NOV 22 2006

Confidentiality Agreement



Purpose(s): check as appropriate:

X Screening records to identify potential research subjects without their authorization

Retrospective record review without subjects' written authorization or consent

X Prospective record review without subjects' written authorization or consent

Retrospective review and/or abstraction of data from University of Washington non-medical records, such as academic or personnel records

for study entitled

HYPERTONIC RESUSCITATION FOLLOWING TRAUMATIC INJURY

{November 7, 2006}

This is an agreement between the following researchers and research staff members who will have access to original records (electronic or paper) without subjects' written consent or authorization:

<u>Researcher's name</u>	<u>Title</u>	<u>Position</u>	<u>Departmental affiliation</u>
Jeanne O'Brien	RN	Research Nurse	Cardiology

and the: **University of Washington Human Subjects Review Committee** for use of records maintained by (check, as appropriate):

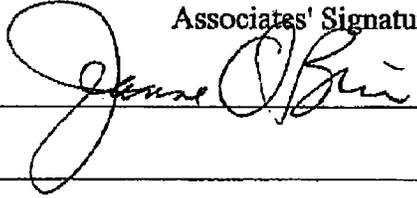
- University of Washington Medical Center
- Harborview Medical Center
- Veterans Affairs Puget Sound Health Care System
- Seattle Cancer Care Alliance
- Puget Sound Blood Center
- UW Registrar's Office
- Other UW unit (specify:)

A. The above-named researchers and associates have submitted an application identified by the above title and assigned application # 05-7193-A01 by the reviewing committee). The application describes the study, including its purpose and the information to be collected. It also describes the provisions for confidentiality and for the security of individually-identifiable records and record information as approved by the above-named committee on JUL 17, 2006.

B. The above-named researchers and associates will report and publish research findings and conclusions in a manner that does not permit identification of subjects of the records. Research reports and publications will not include photographs or visual representations contained in the personal records.

- C. The above-named researchers and associates will destroy the individual identities associated with the records or record information as soon as the purposes of the research project have been accomplished and will notify the agency to this effect in writing. These actions will be taken no later than 2015.
- D. The above-named researchers and associates will not disclose the records or record information in individually-identifiable form except (1) to the research professionals indicated on page one of this confidentiality agreement; (2) under the terms of the provisions indicated in RCW 42,48.040; (3) to representatives of the review committee that has the responsibility for monitoring, auditing, and reviewing the activities and methods of the research professionals engaged in this study. It is also understood that the Attorney General's Division and the Human Subjects Division will be notified of all requests for disclosure of information.
- E. A violation of any disclosure restrictions is a gross misdemeanor and may result in a civil penalty of not more than ten thousand dollars (\$10,000) for each violation, under the provisions of RCW 42.48.050.
- F. This study design shall not be altered in any form without the written approval of the review committee and the negotiation of a new, legally-binding confidentiality agreement.
- G. In the event the researchers or associates fail to comply with any terms of the agreement, the review committee has the right to take such action as it deems appropriate, including termination of this agreement. If the agreement is terminated, the researchers and/or associates will immediately relinquish all information to the review committee, including materials derived from this information.

The commitments made in the foregoing statements are hereby acknowledged and accepted:

Researchers and Associates' Names	Researchers' and Associates' Signatures	Date
Jeanne O'Brien		11-7-06
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Accepted on behalf of the University of Washington:

Name and Signature of Human Subjects Division authorized official	Date
---	------

UNIVERSITY OF WASHINGTON

Human Subjects Division
Office of Sponsored Programs Box 355752

HUMAN SUBJECTS REVIEW COMMITTEE APPLICATION

BOX FOR COMMITTEE USE ONLY		
MASTER <input type="checkbox"/>	COMM. <input type="checkbox"/>	INVESTIGATOR <input type="checkbox"/>
APPLICATION NO.		
05-7193-A01		

send nine one-sided copies of this form (including one copy with original inked signatures) and nine one-sided copies of all relevant materials (consent forms, questionnaires, instruments, drug information summary, data collection forms, debriefing statement, advertisements, etc.) to the Human Subjects Division, Box 355752. Do not leave blanks. Attach one one-sided copy of each research proposal, grant or contract, and/or one one-sided copy of the protocol and investigator's brochure for clinical trials. Students should attach one one-sided copy of thesis or dissertation proposals. For information and assistance, visit our web site at <http://depts.washington.edu/hsd> or call (206) 543-0098. We will not accept handwritten forms, incomplete forms, or forms printed on both sides of the paper. Use 10 point type or larger throughout application. The contents of this application and attachments will be kept confidential within the limits of the law.

Check this box if your project falls into one or more of the minimal risk ("expedited") categories of research (see web site for listing of categories) and send us only two copies of all your materials.

I. PRINCIPAL INVESTIGATOR (Provide all the information requested. Correspondence will be directed to this person. You may designate a contact person other than yourself in section II., below.)

Name Eileen Bulger Title M.D. Position Associate Professor
 Department Surgery Division HMC
 Mail box or address Box 359796
 Telephone 731-3696 Fax 206-616-1022 e-mail ebulger@u.washington.edu

II. CONTACT PERSON (Provide all the information requested. This person does NOT have signatory authority with regard to this application.)

Name Sandy Hanson Title R.N. Position Research Nurse
 Mail box or address Box 359796
 Telephone 341-4720 Fax 206-731-3727 e-mail sandyrh@u.washington.edu

RECEIVED
Human Subjects Division

III. TITLE OF PROJECT: Hypertonic Resuscitation following Traumatic Injury

FEB 08 2006

IV. SIGNATURES: The undersigned acknowledge that: 1. this application represents an accurate and complete description of the proposed research; 2. the research will be conducted in compliance with the recommendations of and only after approval has been received from the Human Subjects Review Committee (HSRC). The principal investigator is responsible for reporting any serious adverse events or problems to the HSRC, for requesting prior HSRC approval for modifications, and for requesting continuing review and approval.

A. Investigator:

Eileen M. Bulger, MD 1/24/06
 TYPED NAME PLUS SIGNATURE DATE

B. Faculty sponsor (for student):

TYPED NAME PLUS SIGNATURE DATE

C. The Chair, Dean, or Director signing below acknowledges that this proposed activity has received intra-mural review and approval of scientific merit and investigator qualification.

[Signature] 1/26/06
 TYPED NAME PLUS SIGNATURE DATE