

ROC Site Status & Enrollment as of 4/30/2007									
		IRB	Initial HS IRB Approval	IRB Approval to Start	TBI Cohort Enrolled	Shock Cohort Enrolled	Community Consultation Completed		
	Overarching IRB-U of Iowa				0	0	Oct-06		
	Iowa Hospitals								
	Des Moines								
	Iowa Methodist Hospital	Iowa Health Systems	pending						
	Mercy Med Center	Mercy Medical Center	pending						
	Iowa City								
	U of Iowa Hospitals/Clinics-Iowa City	U of Iowa	12/15/2006	3/7/2007					
	Cedar Rapids								
	Mercy Med Center-Cedar Rapids	Mercy Medical Center	pending						
	St. Luke's Methodist Hospital-Cedar Rapids	St. Luke's Hospital	pending						
	Davenport								
	Genesis Medical Ctr. East-Davenport	Genesis Health System	pending						
	Sioux City								
	Mercy Medical Center-Sioux City	Health, Inc.	pending						
	Waterloo/Cedar Falls								
	Allen Memorial Hospital-Waterloo	Joint IRB	pending						
	Covenant Medical Center-Waterloo	Joint IRB	pending						
	Mercy Hospital of Franciscan Sisters-Oelwein	Joint IRB	pending						
	Santor Memorial Hospital-Cedar Falls	Joint IRB	pending						
	Dubuque								
	Mercy Medical Center	Mercy Health Services	pending						
	The Finley Hospital-Dubuque	Finley Hospital	pending						
	Mt. Pleasant								
	Henry County Health Center/Mt Pleasant	Patient Advocacy Council, Inc.	pending						
	EMS Agencies								
	Des Moines								
	Dallas County EMS	Des Moines City	pending						
	Des Moines Fire EMS	Des Moines City	pending						
	West Des Moines EMS	Des Moines City	pending						
	Iowa City								
	Iowa City Fire								
	Iowa City/Johnson County EMS	U of Iowa	12/15/2006	3/7/2007					
	Cedar Rapids								
	Cedar Rapids Area Ambulance Authority	Mercy Medical Center	pending						
	Cedar Rapids Fire	Mercy Medical Center	pending						
	Davenport								
	Bettendorf Fire	Genesis Health System	pending						
	Davenport Fire	Trinity Medical Center	pending						



Human Subjects Office

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IRB ID #: 200507715
To: Richard Kerber
From: IRB-01, DHHS Registration # IRB00000099,
Univ of Iowa, DHHS Federalwide Assurance # FWA00003007
Re: ROC - The Iowa Resuscitation Network: A Rural Regional Clinical Center - Trauma Protocol #1 (HS/HSD)

Protocol Number: NA
Protocol Version: NA
Protocol Date: 11/08/05
Amendment Number/Date(s): None - null

Approval Date: 03/07/07

Next IRB Approval Due Before: 09/30/07

Type of Application: New Project
 Continuing Review
 Modification

Type of Application Review: Full Board: Meeting Date: 02/16/07
 Expedited
 Exempt

Approved for Populations: Children
 Prisoners
 Pregnant Women, Fetuses, Neonates

Source of Support: US Department of Health & Human Services, National Institutes of Health

Investigational New Drug/Biologic Name: HSD
Investigational New Drug/Biologic Number: TBI Cohort = BB-IND 12505, Hypotensive Cohort = BB-IND 12506
Name of Sponsor who holds IND: University of Washington

Investigational Device Name:
Investigational Device Number:
Sponsor who holds IDE:

This approval has been electronically signed by IRB Chair:
Herbert Berger, MD, MD
03/07/07 0924

IRB Approval: IRB approval indicates that this project meets the regulatory requirements for the protection of human subjects. IRB approval does not absolve the principal investigator from complying with other institutional, collegiate, or departmental policies or procedures.

Agency Notification: If this is a New Project or Continuing Review application and the project is funded by an external government or non-profit agency, the original HHS 310 form, "Protection of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption," has been forwarded to the UI Division of Sponsored Programs, 100 Gilmore Hall, for appropriate action. You will receive a signed copy from Sponsored Programs.

Recruitment/Consent: Your IRB application has been approved for recruitment of subjects not to exceed the number indicated on your application form. If you are using written informed consent, the IRB-approved and stamped Informed Consent Document(s) are attached. Please make copies from the attached "masters" for subjects to sign when agreeing to participate. The original signed Informed Consent Document should be placed in your research files. A copy of the Informed Consent Document should be given to the subject. (A copy of the *signed* Informed Consent Document should be given to the subject if your Consent contains a HIPAA authorization section.) If hospital/clinic patients are being enrolled, a copy of the signed Informed Consent Document should be placed in the subject's chart, unless a Record of Consent form was approved by the IRB.

Continuing Review: Federal regulations require that the IRB re-approve research projects at intervals appropriate to the degree of risk, but no less than once per year. This process is called "continuing review." Continuing review for non-exempt research is required to occur as long as the research remains active for long-term follow-up of research subjects, even when the research is permanently closed to enrollment of new subjects and all subjects have completed all research-related interventions and to occur when the remaining research activities are limited to collection of private identifiable information. Your project "expires" at 12:01 AM on the date indicated on the preceding page ("Next IRB Approval Due on or Before"). You must obtain your next IRB approval of this project on or before that expiration date. You are responsible for submitting a Continuing Review application in sufficient time for approval before the expiration date, however the HSO will send a reminder notice approximately 60 and 30 days prior to the expiration date.

Modifications: Any change in this research project or materials must be submitted on a Modification application to the IRB for prior review and approval, except when a change is necessary to eliminate apparent immediate hazards to subjects. The investigator is required to promptly notify the IRB of any changes made without IRB approval to eliminate apparent immediate hazards to subjects using the Modification/Update Form. Modifications requiring the prior review and approval of the IRB include but are not limited to: changing the protocol or study procedures, changing investigators or funding sources, changing the Informed Consent Document, increasing the anticipated total number of subjects from what was originally approved, or adding any new materials (e.g., letters to subjects, ads, questionnaires).

Unanticipated Problems Involving Risks: You must promptly report to the IRB any serious and/or unexpected adverse experience, as defined in the UI Investigator's Guide, and any other unanticipated problems involving risks to subjects or others. The Reportable Events Form (REF) should be used for reporting to the IRB.

Audits/Record-Keeping: Your research records may be audited at any time during or after the implementation of your project. Federal and University policies require that all research records be maintained for a period of three (3) years following the close of the research project. For research that involves drugs or devices seeking FDA approval, the research records must be kept for a period of three years after the FDA has taken final action on the marketing application.

Additional Information: Complete information regarding research involving human subjects at The University of Iowa is available in the "Investigator's Guide to Human Subjects Research." Research investigators are expected to comply with these policies and procedures, and to be familiar with the University's Federalwide Assurance, the Belmont Report, 45CFR46, and other applicable regulations prior to conducting the research. These documents and IRB application and related forms are available on the Human Subjects Office website or are available by calling 335-6564.

**Executive IRB-01 FULL BOARD MEETING MINUTES
New Project Review**

Meeting Date: 12/15/06 12:00 PM
Meeting Roster: Herbert Berger (Chair)
Bertolatus, J. Andrew (1); Weiner, George (2); Adams, Harold (3); Berger, Herbert (5); Somers, Douglas (6); Woodman, Catherine (7); Teresi (Milavetz), Mary (8); Jones, Martha (9); Wertz, Philip (10); Goldsmith, Nancy (14); Schuldt, David (15)

Non-Voting Attendees: Suzanne Bentler, Grainne Martin, Anne Alberhasky, Kelly O'Berry

Consultant to the IRB: Lauris Kaldjian, MD

Primary Reviewer: Herbert Berger

IRB #: 200507715
Principal Investigator: Richard Kerber
Title: ROC - The Iowa Resuscitation Network: A Rural Regional Clinical Center - Trauma Protocol #1 (HS/HSD)

IRB DECISION AND VOTE

A motion was made to **approve** the study *pending receipt of required actions*.

8 agree
J disagree
0 abstain

J. Andrew Bertolatus was recused and was not present for the discussion and vote on this agenda item as his immediate family member is a member of the research team.

Harold Adams and George Weiner were not present for the final discussion and vote on this item.

Lauris Kaldjian was not present for the final discussion and vote on this item as his role was that of an ethical consultant to the IRB.

Regulatory Determinations

- Because this study is being conducted under the exception from informed consent requirements for emergency research, the IRB determined that the continuing review of this study should occur more frequently than annually. The expiration date for this study will be set for May 1, 2007. With the continuing review application, the research team should include a description of the response to the spring 2007 mass e-mail and continuing public notification in addition to a study progress report.
- The IRB determined that this project meets the criteria for an exception from informed consent requirements for emergency research as described in 21CFR50.24:

(a)(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence is necessary to determine the safety and effectiveness of this intervention. The subjects will be involved in serious trauma or brain injury. Despite current efforts, trauma is the leading cause of death among North Americans between the ages of one and forty four years. Preliminary studies on Hypertonic

fluids have revealed some possible specific advantages in brain injury and severe trauma.

(a)(2)(i) Obtaining informed consent is not feasible because the subjects will not be able to give their informed consent as a result of their medical condition which is severe trauma and / or brain injury.

(a)(2)(ii) Obtaining informed consent is not feasible because the intervention under investigation must be administered before consent from the subjects' legally authorized representative is feasible. A field script will be read to the legally authorized representative or a family member who is eighteen years of age or older. The therapeutic window is essentially when EMS arrive to the completion of infusion of the 250 cc's of the study fluid.

(a)(2)(iii) Obtaining informed consent is not feasible because there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation. There is no way to prospectively identify who will be a trauma victim.

(a)(3)(i) Participation in the research holds out the prospect of direct benefit to the subjects because subjects are facing a life-threatening situation that necessitates intervention; subjects have severe head injury or hypovolemic shock.

(a)(3)(ii) Participation in the research holds out the prospect of direct benefit to the subjects because 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. Prior animal and human studies have suggested alternative resuscitation may reduce mortality and have advantages in brain injured patients.

(a)(3)(iii) Participation in the research holds out the prospect of direct benefit to the subjects because risks associated with the investigation are reasonable in relation to what is known about the medical condition of this 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. Trauma victims need appropriate resuscitation. Standard therapy may be inadequate to resuscitate trauma victims and may lead to further injury in those with brain injury. In eight previous trials there have been no risks reported for the use of the study fluids. However, high salt levels may potentially cause encephalopathy and seizure. Dextran may result in an allergic reaction in one out of a hundred thousand.

(a)(4) The clinical investigation could not practicably be carried out without the waiver. The therapeutic window is short i.e. from when EMS arrive to the completion of infusion of the 250 cc's of the study fluid. A field script will be read to the legally authorized representative or a family member (who is eighteen years of age or older) if present in the field. This will give an opportunity for the LAR or a non minor family member to object to a subject's participation in the clinical investigation.

(a)(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 research team is directed to summarize efforts to contact the LAR or family member (who is eighteen years of age or older) and make this information available to the IRB at each continuing review.

(a)(6) The IRB has reviewed and approved the consent procedures and an informed consent document consistent with 21CFR50.25. These procedures/documents are to be used with

subjects or the LARs when 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. At the scene of the accident/trauma either a legally authorized representative or a family member (who is eighteen years of age or older) will have the opportunity to object to the subjects participation in the clinical investigation.

Additional protections of the rights and welfare of the subjects was provided, including:
(a)(7)(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 was provided. The IRB reviewed the community consultation and disclosure information. The IRB also closely reviewed the communities' opinions and concerns when deciding the investigation should be approved.

(a)(7)(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 was provided. The public disclosure has occurred in conjunction with the community consultation. In addition, there is a plan outlined in the application. The plan for continuing disclosure throughout the year was reviewed and approved by the IRB contingent upon the receipt of required actions by the investigators..

(a)(7)(iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including demographic characteristics of the research population, and its results are to be assessed at the completion of the clinical investigation.

(a)(7)(iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation was done in the following manner. The data safety and monitoring board will consist of individuals outlined in the application who have extensive experience and are part of NIH and the IRB determined that this was adequate.

(a)(7)(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 an LAR and asking whether he or she objects to the subject's participation in the clinical investigation. The research team will be required to read the field script to a family member (who is eighteen years of age or older) or a legal authorized representative and allow for the opportunity to opt out of this study.

(b) The IRB has ensured that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, an LAR of the subject, or if such a representative is not reasonably available, a family member (who is eighteen years of age or older), of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB determined that the research team must inform as soon as possible (and no later than 24 hours after admission) the participation of the subject in this research study. If the subject is no longer incapacitated, this information should first be given to the subject. If this is not possible, the information will be given to the legally authorized representative and if they are not available, a family member (who is eighteen years of age or older).

The IRB has ensured that there is a procedure to inform the subject, or if the subjects remains incapacitated, an LAR of the subject, or if such a representative is not reasonably available, a family member (who is eighteen years of age or older), that he or she may discontinue the

subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. This would pertain to the outcome followup study; however, hospital data will be collected to report on safety as required by the FDA.

If an LAR or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is enrolled with waived consent and dies before an LAR or family member can be contacted, information about the clinical investigation is to be provided to the subject's LAR or family member, if feasible. The IRB reviewed, modified, and approved a letter to be sent to the LAR or family of a deceased subject.

(d) This protocol is being performed under a separate investigational new drug application (IND) that clearly identifies this protocol as a protocol that may include subjects who are unable to provide consent. The University of Washington holds the IND. They have been in contact with the FDA about this study including the recent hold and restart of enrollment of subjects except at sites where the centers are geographically dispersed.

- The project has funding from DHHS and as such, must be considered under the waiver of informed consent requirements in certain emergency research as provided in the federal register (61 FR 51531-51533). Under this waiver, the IRB is responsible for the review, approval and continuing review of this activity and has approved both the activity and the waiver of informed consent and has found and documented that 1) the research activity is subject to the regulations codified by the FDA and 2) that the requirements for exception from informed consent for emergency research as detailed above from 21CFR50.24 have been met.
- Overall project determination for children:
The IRB determined that the classification for this study with regard to the enrollment of children (ages 15-18) is **45CFR 46.405 and 21CFR50.52** because the study involves greater than minimal risk due to intravenous fluids being tested for resuscitation in a life threatening situation. This study does present the prospect of direct benefit to individual subjects due to the potential advantages of some of the study fluids. **No signatures and no assent required as detailed above for adult subjects.**

Determination for children involved in the follow-up phase of this research:

The IRB determined that the classification for this study with regard to the enrollment of children (ages 15-18) is **45CFR 46.404 and 21CFR50.51**. because this part of the study involves answering questions and involves no greater than minimal risk. The IRB determined that the permission of **one parent or legal guardian is sufficient.**

The IRB determined that there **should** be an assent process since children of 15 years of age or older will have an understanding that they will be answering questions at a later date. The assent form was reviewed and approved by the IRB.

- Overall, the IRB determined that the criteria for approval as described in 45 CFR 46.111 and 21 CFR 56.111 have been met.

Required Actions

1. The IRB requires that Dr. Kerber obtain documentation from the ROC center that the FDA release to continue and begin enrollment of subjects includes the center at The University of Iowa. In reference to the FDA letter stating "may restart of enrollment of subjects except at sites where the centers are geographically dispersed," the IRB requires the principal investigator to provide documentation that The University of Iowa is not part of the geographically dispersed centers, or if it is, what measures have been taken to fulfill FDA requirements for the geographically dispersed sites.

2. In reference to the single sheet "information for care providers/hypertonic resuscitation trial: resuscitation outcomes consortium" that will be given to the hospital on subjects who have been enrolled in the study, the IRB required the following changes.
 - a. The last sentence of the first paragraph should read: "No further study intervention is required in the hospital, but we want you to be aware of the following issues:"
 - b. The second paragraph should be broken into two. The break should occur after the sentence that begins with "we do not recommend that you intervene for the small initial rise in serum sodium..."
 - c. The next paragraph should begin and be modified with the following "the study requires that you monitor the serum sodium every 8 hours over the first 24 hours. The research team will ensure that this is performed."
 - d. At the bottom of this sheet the local contact information should be placed in order to contact those individuals on the research team whom will ensure that the serum sodium is monitored.

3. The IRB has reviewed the application and requires the following:
 - a. Section IV, question 4: The last sentence that currently reads "there are no protocol mandated requirements for blood or radiographic studies other than as part of the standard of medical care" should be removed. It should be replaced with "The study requires the monitoring of the serum sodium every 8 hours over the first 24 hours. The research team will ensure that this is performed."

 - b. Section VI, question 5.1: "Describe how capacity to consent will be assessed." The last two sentences in the first paragraph should be reworded to state: "If a LAR or a non minor family member is present at the scene and uninjured, the field script for consent will be read to them. This will give the opportunity for the LAR or non minor family member to object to enrollment in the study. If, however, the LAR or non minor family member is not available, the study will be begun with the exception to informed consent."
 1. A second paragraph should be added to state: "The subject, LAR, or non minor family member will be informed as soon as possible (but no later than 24 hours after being admitted) that the subject was in a research study."
 2. The last paragraph in the current section should have the following change. The word "patients" should be changed to "subject". In addition, a sentence should state the following: "If the subject remains incapacitated to consent for the followup outcome measures, the LAR will be approached prior to hospital discharge to obtain informed consent for the purpose of obtaining outcome followup information via a phone interview. The consent process will take place either in the ICU or step down area."

 - c. Section VII, question 14 should have the following changes:
 1. The sentence beginning: "If the patient has a legally authorized representative..." should be changed to the following: "If the patient has a legally authorized representative or a family member (who is eighteen years of age or older) present in the field at the time of the injury, a script will be read to inform them of the study and give them a chance to opt out of the study."

 2. The second bullet item should be divided into two bullet items.
 - o one bullet item should state: "the subject, Legally authorized representative, or a family member (who is eighteen years of age or older) will be informed as soon as possible (but no later than 24 hours after being admitted) that the subject has been enrolled in a research study".

 - o A second bullet item should state: "In reference to obtaining informed consent for the purpose of obtaining followup outcome information via phone interview,

informed consent will be obtained in person with either the subject (if no longer incapacitated), or the legally authorized representative. They will be approached prior to hospital discharge and will take place either in the ICU or step down area to obtain informed consent for the purpose of obtaining outcome followup information via a phone interview.

- d. In reference to the "Continuing disclosure-ROC trauma study number 1" continuing public disclosure plans, the IRB requires the research team to modify the UI mass e-mail distribution plan to the following: "We will propose a twice a year mass e-mail to UI faculty, staff, and student population to occur 4 weeks after the beginning of the spring and fall semester (essentially occurring twice a year)." This should be changed in the document attachment and should also be included in the HawkIRB application under Section VII, Question 22.
4. Make the following changes to the informed consent document:
- a. Under the section "What is the Purpose of this Study?",
 - Place a paragraph space between the first and second paragraph.
 - The second paragraph should be changed to read "The purpose of this research study is to decide if concentrated salt solutions can improve a person's health after severe injury."
 - The paragraph beginning with the sentence "Because treatment was needed immediately, we were unable to talk to you about volunteering for this study" should be moved to the end of this section and all remaining sentences except for the first sentence, should be removed from this paragraph.
 - The paragraph beginning with "Besides normal saline there are different types of salt solutions..." the last sentence should read: "The concentrated salt solutions are considered experimental therapies and are not FDA approved for general use."
 - b. Under the section, "How Long will I be in this Study?", the end of the first paragraph should read "...we would like to obtain follow-up information about you at six months."
 - c. Under the section, "What will Happen During this Study?", after the sentence "We will ask you if you have experienced any problems since leaving the hospital," there should be another sentence describing the type of information obtained during the phone interview. A sentence should be added stating "Some of the questions will deal with topics such as ability to follow simple commands and communication, independence inside and outside of the home, ability to participate in work, social and leisure activities, and interaction with family and friends."
 - d. The entire section "What Other Treatment Options Are There?" needs to be removed from the consent since this part of the research study only involves outcome follow up and does not involve treatment.
 - e. Under the section, "Will I Be Paid for Participating" the IRB determined the original language should be maintained in this section. Include the sentence "You will receive \$25 for completing the 28-day phone or hospital follow-up and you will receive another \$25 after completing the 6-month phone call interview (if you had a head injury)." The sentence stating "Those patients requiring a 6-month phone call interview will be compensated \$50 for completing the interview" should be removed. The final two sentences in this section should remain as is.
 - f. The entire section "What If I Am Injured as a Result of This Study?" needs to be removed from the consent since this part of the research study only involves outcome follow up and

does not involve treatment.

g. Under the section, "What if I Have Questions?", after the sentence "If you have any questions about the research study itself, please contact..." put the names with the title and phone number in a bulleted format so that they are in a column and easy to read with a phone number adjacent to each name. The sentence "If it is an emergency during the evenings, nights, weekends or holidays, you can reach Dr. Kerber or the ROC coordinator by leaving a voice message at this phone number. The messages are checked daily" should be removed.

h. The IRB also requires the research team to put the consent document in a larger type font (as least 12 point.)

See the Consent Document attached to the HawkIRB electronic application. Review the modifications to the Consent Document and submit the revised Consent Document for IRB review. DO NOT accept the tracked changes. If you are requested to add or delete information, use the "EDIT" function to the right of the document name on the Form Attachments tab in HawkIRB and carefully follow the directions provided in the yellow box. DO NOT attach your revisions as a new consent document.

5. Make the following changes to the document titled "ROC Trauma Study Notification / Information Sheet-For Patients and / or Families":
 - a. Change the listing of the names of the investigators, titles, and phone numbers to a bulleted format for easy reading.
 - b. Under the section "Consent for Participation," the sentence "You needed Fluid resuscitation emergently" should be changed to "You needed fluid resuscitation urgently." The IRB determined that this might be easier for subjects to understand.
6. Make the following changes to the document titled "Item33bROCbExpiredPtLtrwStamp." The IRB had extensive discussion that this letter as currently written was much too long and complex and rather it should be very brief and concise and should convey sincere sorrow for the passing of a family member with contact information available. In particular, the main body of the letter should read "We sincerely express our sorrow for the loss of your (fill in appropriate individual). On the way to the hospital and prior to his/her arrival, s/he was involved in a research study to decide what type of fluids can help a person after severe injury. The research team is available to talk to you over the phone. Please call us if you would like to talk about this study further. We understand that you may not want to talk about this now, but call us if you do have questions and when you feel ready. We have also enclosed a postcard if you find it would be easier to let us know your wishes by mailing the postcard back to us.

Please feel free to contact us with any questions or concerns that you have. Again, we are sorry for your loss. Sincerely,... " Put the research team as you have on the letter. In addition, the IRB requires the PI to sign this type of letter which would go to a family or LAR.

The accompanying postcard should have three choices that the family member/LAR could check off: a) I would like to be contacted, b) I will contact you, c) Please do not contact me any further.

7. ***A response to the above Required Actions is required on or before 2/17/2007.***

Trauma is the leading cause of death among North Americans between the ages of 1-44 years. The majority of these deaths result from hypovolemic shock or severe brain injury. Conventional resuscitation involves the intravenous (IV) administration of a large volume of isotonic (normal saline) or slightly hypotonic solution beginning in the pre-hospital setting. Hypertonic fluids may have specific advantages in brain injured patients as they may aid in the rapid restoration of cerebral perfusion and prevent extra vascular fluid sequestration. In addition, recent studies have demonstrated hypertonicity significantly alters the activation of inflammatory cells. This study seeks to address the impact of hypertonic resuscitation on two injured patient populations, those with hypovolemic shock and those with severe traumatic brain injuries. A primary outcome for the hypovolemic shock group will be a 28 day survival and a primary outcome for the traumatic brain injury group will be neurological outcome six months after injury based on extended Glasgow outcomes score. There have been eight clinical trials for acute resuscitation of hypovolemic patients. The six pre-hospital trials all demonstrated a survival benefit for patients treated with hypertonic saline and dextran vs. conventional resuscitation. The two emergency room trials showed no difference in survival, suggesting that administration of fluid at the time of initial reperfusion may be critical. Overall, this study will use either hypertonic saline alone vs hypertonic saline plus dextran vs. normal saline (conventional intervention). Outcome measures are mentioned above.

Because of the nature of the study population and intervention, the investigators seek approval to conduct this study under the regulations governing the exception from informed consent (EIC) for emergency research.

SUMMARY OF BOARD DISCUSSION

- The IRB reviewed prior board discussion from the meeting of 10/20/2006. Materials available for review prior to this meeting are noted in the HawkIRB application. Essentially, a 510 page document was distributed prior to this meeting for the IRB members to review and allow comment during this meeting.
- After reviewing prior board discussion and the federal regulations, Dr. Lauris Kaldjian, MD, PhD, was invited as a consultant on discussion of the biomedical ethics of performing emergency research without informed consent. He had a very concise one-page sheet that he handed out which included several references in the literature to this topic and he reviewed each of them with the IRB. He reviewed the Final Rule and commented that community consultation is a two-way process that is designed to take into account community attitudes and cultural beliefs regarding the research. He pointed out that this community consultation should be looked upon by the IRB as "the community acts as an advisory board to the IRB."

Dr. Kaldjian pointed out an article from Dr. Ernst (Academy of Emergency Medicine, 2005;12:1050-1055) that included the following statement "During community consultation, the communities cannot prevent or halt the research: However, IRB's should be present during community consultation and should document how community concerns were addressed. In addition, IRB's must take community issues and concerns into account during their deliberations."

Dr. Kaldjian also pointed out a keynote address published in the Academy of Emergency Medicine, 2005;12:1019-1021 by Dr. McGee that stated "the FDA does not empower the community to reverse an IRB decision that a study should proceed." In addition to reviewing several of these articles, Dr. Kaldjian pointed out that the research team must make a good faith effort to get community feedback and have a chance for the community to respond. Overall the IRB determined that this had occurred.

Dr. Kaldjian also pointed out that community consultation should not be thought of as the community giving consent for the study to occur. Rather, the community consultation should be looked upon as feedback and advice to the research team as well as to the IRB.

Finally, Dr. Kaldjian discussed that when emergency research is conducted with a waiver of consent, although there are opportunities to opt out, individual autonomy is more difficult to address in this type of research study. However, beneficence and justice can prevail. Dr. Kaldjian then was excused from the rest of the IRB meeting. The IRB members took a vote and with unanimous agreement concurred that the research team has fulfilled the community consultation with adequate feedback that has been taken into account to allow the study to move on for further review.

- The IRB reviewed the continuing public disclosure plans. There was discussion about when the next mass e-mail distribution should occur. It will be left up to the research team to formulate the e-mail for these future distributions. The content of the e-mail will need to be reviewed by the IRB before distribution, however this e-mail should be submitted at a later date as a modification in order for the research team to first complete the current required action to obtain approval for this research study. The IRB had a discussion about when the mass e-mail should occur. The IRB concurred that this should occur four weeks after the beginning of the spring and fall semester. This would allow students and faculty to settle into the semester before receiving yet another e-mail. Review of the study should occur after this mass e-mail is distributed. The study expiration date will be set accordingly. **See Required Action # 3d.**
- The IRB reviewed the protocol amendment pertaining to high levels of sodium identified in the blood stream after infusion of the study fluids. Changes in the information sheet for care providers are outlined in the required actions. In particular, the IRB requires the research team to closely follow these subjects and assure that the Q8 Hour serum sodium monitoring be performed in the first 24 hours and to assure that this order has been written. **See Required Action # 2.**
- The IRB also requires the PI obtain documentation from the ROC coordinating center that the FDA has released the UI site to begin enrollment of subjects. Also, the FDA stated "you may re-start enrollment of subjects except at sites where the centers were geographically dispersed." The PI is required to obtain documentation that the UI is not part of the "geographically dispersed" centers or, if the UI is a "geographically dispersed" center, that the research team has fulfilled the FDA requirements with regard to "geographically dispersed" sites. In reference to this addendum, the IRB also required the research team to update the application with regard to the monitoring of blood sodium levels during the first 24 hours. **See Required Actions # 1 & # 3a.**
- The IRB discussed the field script that would be read at the scene of the trauma. The IRB determined that the field script should be read to either a legally authorized representative or a family member who was 18 years of age or older. This would provide the LAR or the non-minor family member to object to participation and enrollment in the study for the subject. **See Required Actions # 3b & 3c1.**
- The IRB discussed and determined that notification that the subject was in a research study prior to arrival at the hospital should occur as soon as possible and no later than 24 hours after subject is admitted. The subject should be notified if his/her condition improves, or if it does not improve, the LAR or family member should be notified. **See Required Actions # 3b & 3c2 & 5.**
- In terms of the informed consent for obtaining follow-up outcome measures, this document was reviewed and changes are outlined in the Required Actions. The IRB determined that obtaining the informed consent for the follow-up outcomes could be obtained at any time prior to discharge and should first seek the subject's consent, if having the capacity to do so. Otherwise, the consent from the LAR should be obtained. **See Required Actions #3c2 & #4.**

The letter that would be sent to a family member or LAR of a subject who had died, informing the LAR/family member that the subject was involved in a research study prior to arrival at the