TRAUMATIC BRAIN INJURY IN LATIN AMERICA:
LIFESPAN ANALYSIS

MANUAL OF PROCEDURE (MOP)
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Traumatic Brain Injury in Latin America: Lifespan Research
A randomized, outcome masked, clinical trial of management of severe traumatic brain injury with or without monitoring of intracranial pressure in 324 participants with severe traumatic brain injury in Bolivia and Ecuador

Study Chair:
Randall Chesnut, M.D,  Professor, University of Washington

Supported by:
The National Institute of Neurological Disorders and Stroke (NINDS)
1R01NS058302-01

Study Intervention Provided by:
Integra Lifesciences Corporation or Integra Foundation

(Any modification to the protocol should be annotated on the coversheet or in an appendix. The annotation should note the exact words that are changed, the location in the protocol, the date the modification was approved by the Executive Committee, and the date it became effective.)

Version 6
February 11, 2010
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CLINICAL SITES PARTICIPATING IN THE STUDY

University of Washington
Randall Chesnutt, M.D.
Principal Investigator
Address: Harborview Medical Center Box 359924, 325 9th Avenue, Seattle, WA 98104-2499
Phone: 206-390-4548
Fax: 206-744-9944
Pager: 206-559-1485
Email: chesnutr@u.washington.edu

Fundacion ALAS
Carlos Rondina, MD
Principal Investigator
Felipe More 1284
Rosario (2000), Santa Fe, Argentina
Phone: 549-341-589-7908
Fax: 54-341-485-5074
Email: rondinac@arnet.com.ar

Latin American Brain Injury Consortium (LABIC)
Walter Videtta, MD
President, LABIC
Guemes 2292
(1722) Merlo, Provincia de Buenos Aires, Argentina
Phone: 549-115-690-8333
Email: wvidetta@ar.inter.net

Hospital Viedma – Cochabamba, Bolivia
Luis Arturo Lavadenz Gomez, MD
Principal Investigator – Viedma
Tiquipaya s/n.
Cochabamba, Bolivia
Phone: 430-1214 7272-9559
Email: arturo_lavadenz@msn.com

Hospital San Juan de Dios – Santa Cruz de la Sierra, Bolivia
Victor Alanis, MD
Principal Investigator – San Juan de Dios
Urb. remamzo 2
el paseo c.a5.
Santa Cruz de la Sierra,Bolivia
Phone: 3341-5032 7049-9888
Email: alanis482@hotmail.com

Hospital Japones – Santa Cruz de la Sierra, Bolivia
Gustavo la Fuente Zerain, MD
Principal Investigador – Japones
Urbbari, Av saturno 115
Santa Cruz de la Sierra, Bolivia
Phone: 3354-7762 7096-1201
Email: gustavolafuente@hotmail.com

Hospital San Juan de Dios -Tarija, Bolivia
Roberto Merida Maldonado, MD
Principal Investigator – Santa Cruz final s/n, Tarija, Bolivia
Phone: 591 70215050
Email: sapinmerida@hotmail.com

Hospital de Especialidades Eugenio Espejo
Edison Manuel Jibaja Vega
Principal Investigator – Colombia y Yaguachi s/n, Quito, Ecuador
Phone:593-2-2379161
Email: mjibaja79@gmail.com

H. Junta de Beneficienica de Guayaquil
Hospital General Luis Vernaza
Attn: Dr. Luis Gonzalez
Loja 700 y Escobedo
Guayaquil, Ecuador
Phone: 539-4-256-0300
Email: lgonzalezz@yahoo.com
## STUDY TEAM ROSTER

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
<th>Address</th>
<th>Phone</th>
<th>Fax</th>
<th>Page</th>
<th>e-mail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randall Chesnut, MD</td>
<td>Principal Investigator</td>
<td>Dept of Neurological Surgery, Box 359924, University of Washington, Seattle, WA 98104</td>
<td>206-390-4548</td>
<td>206-744-9944</td>
<td>206-559-1485</td>
<td><a href="mailto:chesnutr@u.washington.edu">chesnutr@u.washington.edu</a></td>
</tr>
<tr>
<td>Nancy Carney, PhD</td>
<td>Project Director</td>
<td></td>
<td>503-475-6792</td>
<td>503-494-4551</td>
<td>N/A</td>
<td><a href="mailto:carneyn@ohsu.edu">carneyn@ohsu.edu</a></td>
</tr>
<tr>
<td>Nancy Temkin, PhD</td>
<td>Senior Statistician, Director – Data Center</td>
<td>Dept of Neurological Surgery, Box 359924, University of Washington, Seattle, WA 98104</td>
<td>206-744-9315</td>
<td>206-744-9942</td>
<td>N/A</td>
<td><a href="mailto:temkin@u.washington.edu">temkin@u.washington.edu</a></td>
</tr>
<tr>
<td>Sureyya Dikmen, PhD</td>
<td>Director – Outcomes Assmnt.</td>
<td>Dept. of Rehab Medicine Box 356490 University of Washington Seattle, WA 98195</td>
<td>206-685-7529</td>
<td>206-685-3244</td>
<td>N/A</td>
<td><a href="mailto:dikmen@u.washington.edu">dikmen@u.washington.edu</a></td>
</tr>
<tr>
<td>Joanie Machamer, MA</td>
<td>Study Coordinator</td>
<td>Dept. of Rehab Medicine Box 356490 University of Washington Seattle, WA 98195</td>
<td>206-616-0340</td>
<td>206-685-3244</td>
<td>N/A</td>
<td><a href="mailto:machamer@u.washington.edu">machamer@u.washington.edu</a></td>
</tr>
<tr>
<td>Jason Barber</td>
<td>Statistician, Database Manager</td>
<td>Dept of Neurological Surgery, Box 359924, University of Washington, Seattle, WA 98104</td>
<td>206-744-9318</td>
<td>206-744-9942</td>
<td>N/A</td>
<td><a href="mailto:barber@u.washington.edu">barber@u.washington.edu</a></td>
</tr>
<tr>
<td><strong>Fundacion ALAS</strong></td>
<td></td>
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<tr>
<td>Carlos Rondina, MD</td>
<td>Principal</td>
<td>Felipe More</td>
<td>549-</td>
<td>54-</td>
<td>N/A</td>
<td>rondinac@</td>
</tr>
<tr>
<td>Name</td>
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<tr>
<td>Gustavo Petroni, MD</td>
<td>Co-investigator Monitor</td>
<td>España 1734, 10ª 2ª, Rosario (2000), Santa Fe, Argentina</td>
<td>54-341-934-1514</td>
<td>54-341-423-1087</td>
<td><a href="mailto:gustavopetroni@gmail.com">gustavopetroni@gmail.com</a></td>
<td></td>
</tr>
<tr>
<td>Silvia Lujan, MD</td>
<td>Co-investigator Monitor</td>
<td>632 4ª B. Rosario (2000), Santa Fe, Argentina</td>
<td>549-341-560-9239</td>
<td>54-341-423-1087</td>
<td><a href="mailto:silviablujan@gmail.com">silviablujan@gmail.com</a></td>
<td></td>
</tr>
<tr>
<td>Walter Videtta, MD</td>
<td>President, LABIC</td>
<td>Guemes 2292 (1722) Merlo, Provincia de Buenos Aires, Argentina</td>
<td>549-115-690-8333</td>
<td>N/A</td>
<td><a href="mailto:wvidetta@ar.inter.net">wvidetta@ar.inter.net</a></td>
<td></td>
</tr>
<tr>
<td>Freddy Sandi Lora, MD</td>
<td>Bolivia Country Coordinator</td>
<td>Av. Jaime Sudanes 1186 Alto Sopocachi, La Paz, Bolivia</td>
<td>591-7203-3853</td>
<td>591-2-2245 502</td>
<td><a href="mailto:fresandi@hotmail.com">fresandi@hotmail.com</a></td>
<td></td>
</tr>
<tr>
<td>Luis Arturo Lavadenz Gomez, MD</td>
<td>Principal Investigator – Viedma</td>
<td>Tiquipaya s/n. Cochabamba, Bolivia</td>
<td>430-1214 7272-9559</td>
<td>4220 230</td>
<td><a href="mailto:arturo_lavadenz@msn.com">arturo_lavadenz@msn.com</a></td>
<td></td>
</tr>
<tr>
<td>Vianka Valle Eduardo, MD</td>
<td>Co-investigator, Acute care data</td>
<td>Condominio Horizontes. Bloque 4</td>
<td>7222-0370</td>
<td>N/A</td>
<td><a href="mailto:V_anka@hotmail.com">V_anka@hotmail.com</a></td>
<td></td>
</tr>
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<tr>
<td>Jesusa Torrez, Nurse</td>
<td>Co-investigator, Outcomes data</td>
<td>Calle Colombia Nº 815, Cochabamba - Bolivia.</td>
<td>7223 1338 7</td>
<td><a href="mailto:jessmmig@hotmail.com">jessmmig@hotmail.com</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Victor Alanis, MD</td>
<td>Principal Investigator – San Juan de Dios</td>
<td>Urb. remamzo 2 el paseo c.a5. Santa Cruz de la Sierra, Bolivia</td>
<td>3341-5032 7049-9888</td>
<td><a href="mailto:alanis482@hotmail.com">alanis482@hotmail.com</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Katy Panozo Gonzalez, MD</td>
<td>Co-investigator, Acute care data</td>
<td>Alto san pedro: calle Cnl. Franco final 16</td>
<td>7096-1201</td>
<td><a href="mailto:katypanozo@hotmail.com">katypanozo@hotmail.com</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>María Luisa Chávez Bonilla, Nurse</td>
<td>Co-investigator, Outcomes data</td>
<td>Perto Rico, Km 35</td>
<td>70905 316</td>
<td><a href="mailto:marialuisa_cha@hotmail.com">marialuisa_cha@hotmail.com</a></td>
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</tr>
<tr>
<td>Gustavo la Fuente Zerain, MD</td>
<td>Principal Investigator – Japones</td>
<td>Urbari, Av saturno 115 Santa Cruz de la Sierra, Bolivia</td>
<td>3354-7762 7096-1201</td>
<td><a href="mailto:gustavolafuente@hotmail.com">gustavolafuente@hotmail.com</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sergio Peca Charcosi</td>
<td>Co-investigator, Acute care data</td>
<td>Calle1, numero 37. Barrio las charcas</td>
<td>7703-9869</td>
<td><a href="mailto:charocs_utii@hotmail.com">charocs_utii@hotmail.com</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maria del Carmen Valverde</td>
<td>Co-investigator, Outcomes data</td>
<td>Barrio virgin del Lujan Calle 6</td>
<td>70943 803</td>
<td><a href="mailto:mariacarmencita44@hotmail.com">mariacarmencita44@hotmail.com</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roberto Merida Maldonado, MD</td>
<td>Principal Investigator</td>
<td>Santa Cruz final s/n</td>
<td>591 70215 050</td>
<td><a href="mailto:sapinmerida@hotmail.com">sapinmerida@hotmail.com</a></td>
<td></td>
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<td>Name</td>
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<td></td>
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</tr>
<tr>
<td>Ivar Donoso Molina, MD</td>
<td>Co-Investigator</td>
<td>591 70223 687</td>
<td><a href="mailto:ivardonoso@hotmail.com">ivardonoso@hotmail.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maria Isabel Navajas Krutzfeldt, MD</td>
<td>Study Coordinator, Acute care data collection</td>
<td>591 70213 959</td>
<td>Min <a href="mailto:krutzfeld@hotmail.com">krutzfeld@hotmail.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rital Isabel Cervantes Zambrana, MD</td>
<td>Outcomes data collection</td>
<td>591 70212 706</td>
<td><a href="mailto:ritacervantesz@gmail.com">ritacervantesz@gmail.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edison Manuel Jibaja Vega</td>
<td>Principal Investigator</td>
<td>Colombia y Yaguachi s/n Quito, Ecuador</td>
<td>593-2-23791 61</td>
<td><a href="mailto:Mjibaja79@gmail.com">Mjibaja79@gmail.com</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr, Diego Fabian Barahona Pinto</td>
<td>Study Coordinator, Acute care data collection</td>
<td>593-2-25306 05</td>
<td><a href="mailto:dfbarahona@gmail.com">dfbarahona@gmail.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dra. Viviana Nathaly Medranda Pisco</td>
<td>Outcomes data collection</td>
<td>593-2-24470 7</td>
<td><a href="mailto:vivianamedranda@gmail.com">vivianamedranda@gmail.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dra. Katty Alexandra Trelles Vasquez</td>
<td>Outcomes data collection</td>
<td>25077 04</td>
<td><a href="mailto:ktrellesvmd@gmail.com">ktrellesvmd@gmail.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drl Luis Gonzalez</td>
<td>Principal Investigator</td>
<td>Loja 700 y Escobedo Guayaquil, Ecuador</td>
<td>539-4-256-0300</td>
<td><a href="mailto:lgonzalezz@yahoo.com">lgonzalezz@yahoo.com</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr. Saul Zabala</td>
<td>Study Coordinator</td>
<td>593-8-427-8893</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arturo Flor Mosquera</td>
<td>Follow-up</td>
<td>593-9-931-7161</td>
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**DSMB**

<table>
<thead>
<tr>
<th>Name</th>
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<tbody>
<tr>
<td>M. Ross Bullock, MD, PhD</td>
<td>DSMB Chair</td>
</tr>
<tr>
<td>Lidia Artiola, PhD – <em>Through @date</em></td>
<td>Clinical Neuropsychology</td>
</tr>
<tr>
<td>Ramon Diaz-Arrastia, MD, PhD</td>
<td>Neurology</td>
</tr>
<tr>
<td>Mary Foulkes, PhD</td>
<td>Biostatistics</td>
</tr>
<tr>
<td>Jose Suarez, MD</td>
<td>Neurocritical</td>
</tr>
</tbody>
</table>
PRÉCIS

Study Title
Traumatic Brain Injury in Latin America: Lifespan Research
A randomized, outcome masked, clinical trial of management of severe traumatic brain injury with or without monitoring of intracranial pressure in 324 participants with severe traumatic brain injury in Bolivia and Ecuador

Objectives
The primary focus for scientific investigation is to conduct a high quality randomized controlled trial to determine if intracranial pressure (ICP) monitoring to direct treatment of patients with TBI improves medical practice and patient outcomes in a developing country.

Design and Outcomes
Study 1 is a randomized, clinical trial with blinded evaluation of outcome to be conducted at centers in Bolivia and Ecuador. It is a 2-group, parallel design. Outcome is evaluated by mortality, Time to follow commands (measured as time from injury to following simple commands as defined by a score of 6 on the motor scale of the GCS), Length of post-traumatic amnesia (measured by the Galveston Orientation Amnesia Test), Functional status at 3 and 6 months and Neuropsychological assessment at 6 months.

Interventions and Duration
Study 1: Management of patients who are randomized to the ICP Group will be based specifically on the presence of intracranial hypertension and follow the Guidelines for the Management of Severe Brain Injury. Management of patients who are randomized to the Standard Care Group will be consistent with the protocols presently being used in the three study hospitals. Each subject will be managed for intracranial hypertension during their inpatient hospital stay and will be evaluated at 3 months post injury on functional status measures and at 6 months post injury on functional status and neuropsychological measures.

Sample Size and Population
Study 1: 324 patients with severe traumatic brain injury will be randomized on this study and randomization will be stratified on age (<40 vs. ≥40) and GCS (3-5 vs. 6-8).
1. **STUDY OBJECTIVES**

**Primary Objective**

**Specific Aim#1:** In a randomized controlled trial in trauma centers in Bolivia and Ecuador, test the effect on outcomes of management of severe TBI guided by information from ICP monitors vs. a standard empiric protocol.

**Hypothesis #1:** Patients with severe TBI whose acute care treatment is managed using ICP monitors will have significantly lower mortality and better neuropsychological and functional recovery at 6 months post-trauma than those whose treatment is managed with the standard protocol.

**Hypothesis #2:** The incorporation of ICP monitoring into the care of patients with severe TBI will minimize secondary complications and decrease length of stay in ICU.

**Secondary Objectives**

2. **BACKGROUND**

**Rationale**

Describe the patient population to be studied and justify any restrictions on the population. Name and describe the intervention regimens, and justify why these particular interventions have been chosen. Describe and justify the route of administration, dosage regimen, intervention period, etc. Spell out the need, relevance and priority for the study.

This study is being conducted to test the value of information provided by the intracranial pressure (ICP) monitor to direct acute care treatment decisions for patients with severe traumatic brain injury (TBI). Although in the developed world the ICP monitor is considered “standard of care” for these patients, its usefulness to direct treatment decisions has never been tested with a strong research design.

The study centers in Bolivia and Ecuador were selected because they do not currently have ICP monitors, and because they consistently and uniformly use a very specific protocol to treat severe TBI patients. We will randomize patients to either the ICP Monitor Group, or to the Standard Care Group. Treatment decisions for the ICP Monitor Group will be made using information provided by the monitoring, and will be based upon the Guidelines for the Management of Severe Traumatic Brain Injury (Bratton, Bullock, Carney et al., 2007). Treatment decisions for the Standard Care Group will be made using the protocol currently being used in these centers.

**Supporting Data**

Provide the scientific and medical data (e.g., results of Phase I and II studies) that justifies the study, its design, and the intervention groups. The proposed Principal Investigator, Randall Chesnut M.D., has directed numerous projects related to neurotrauma both in the United States and other countries. He has been a major contributor to Guidelines for treatment of severe traumatic brain injury. The abstract for The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Indications for intracranial pressure monitoring (J. Neurotrauma Jun-July, 2000), below, provide the rationale for the study design and intervention.
ICP monitoring per se has never been subjected to a prospective randomized clinical trial (PRCT) to establish its efficacy (or lack thereof) in improving outcome from severe head injury. Hence, there are insufficient data to support its use as a standard. However, there is a large body of published clinical experience that indicates that ICP monitoring (1) helps in the earlier detection of intracranial mass lesions, (2) can limit the indiscriminate use of therapies to control ICP which themselves can be potentially harmful, (3) can reduce ICP by CSF drainage and thus improve cerebral perfusion, (4) helps in determining prognosis, and (5) may improve outcome. ICP monitoring is therefore used by most head injury experts in the United States and is accepted as a relatively low-risk high-yield, modest cost intervention. Comatose head injury patients (GCS 3-8) with abnormal CT scans should undergo ICP monitoring. Comatose patients with normal CT scans have a much lower incidence of intracranial hypertension unless they have two or more of the following features at admission: age over 40, unilateral or bilateral motor posturing, or a systolic blood pressure of less than 90 mm Hg. ICP monitoring in patients with a normal CT scan with two or more of these risk factors is suggested as a guideline. Routine ICP monitoring is not indicated in patients with mild or moderate head injury. However, it may be undertaken in certain conscious patients with traumatic mass lesions at the discretion of the treating physician.

Monitoring-related problems (e.g. catheter-related infections, catheter related hemorrhages) have been rare, occurring in under 1% of cases monitored.

3. STUDY DESIGN

Study 1 – Randomized Trial

Study 1 is a randomized, clinical trial with blinded evaluation of outcome to be conducted at centers in Bolivia and Ecuador. It is a 2-group, parallel design. Within 24 hours of injury (or 24 hours of deterioration, but no later than 72 hours after injury) patients with severe TBI will be randomized to brain injury management based on intracranial pressure (ICP) monitoring (called the “ICP group”) or brain injury management conducted according to a protocol that does not include monitoring of ICP (called the “Standard Care group”). Patients will be followed and evaluated at 6 months after injury.

4. SELECTION AND ENROLLMENT OF SUBJECTS

Inclusion Criteria

- Traumatic brain injury
- GCS ≤ 8 on admission or within first 48 hours after injury
- admission to study hospital within 24 hours of injury
- No foreign object in the brain parenchyma.
- Age > 12
- Randomized:
  - within 24 hours of injury [for patients with GCS ≤ 8 on admission] or
  - within 24 hours of deterioration [patients deteriorating to GCS ≤ 8 within 48 hours of injury]

Exclusion Criteria

- GCS of 3 with bilateral fixed and dilated pupils
Study Enrollment Procedures

Identifying and recruiting candidates for the trial.

When a TBI patient is received in the participating hospital, he/she will be evaluated by an emergency department physician and identified as suitable for the study if the person sustained a traumatic brain injury and has a Glasgow Coma Scale score \(< 8\) (or if intubated, Motor \(< 5\)). Immediate contact will be made with the 24-hour-on-call study coordinator, who will confirm eligibility and request consent from the patient’s legally authorized representative.

Documentation of reasons for ineligibility and for nonparticipation of eligible subjects.

Eligibility will be confirmed using the Screening Form. All potential participants will be documented on the screening form as will reasons for ineligibility and for non-participation of eligible subjects.

Consent (and assent) procedures.

When a patient is identified as eligible for the study, immediate contact will be made with the 24-hour on-call study coordinator, who will confirm eligibility. Severe TBI patients are often unconscious and unable to provide consent until they improve. The study coordinator will come to the bedside of the candidate patient with the attending physician. The physician will introduce the family to the study coordinator. They physician will make sure the family knows the credentials of the study coordinator, and say that this person is going to discuss a research program that is being conducted, and that this person is qualified to do so. The study coordinator will take the family to a place where they can talk confidentially, and will initiate the conversation by finding out what, if anything, the family knows about research. Every relevant aspect of the project will be described. The study coordinator will stop frequently, ask if there are any questions, and request that the family repeat back in their own words what is being discussed, to make sure they understand.

The study coordinator will explain that there is a possibility that the patient’s brain is swelling inside the skull, and if so, the patient could become worse. They will say that there is a technique for knowing if the brain is swelling, and procedures and medicines that could help. They will then explain in detail the placement of the ICP monitor. They will explain that in a small percentage of patients, the placement of the monitor could cause additional damage or infection. The potential advantages of using or not using the monitor will be described, and the care of the patient, with and without the monitor, will be described. The study coordinator will be especially careful to assure the family that they are free to decline consent without consequences, and that they
can withdraw consent at any time. The family will be told even if they say yes, when the patient regains consciousness they will have a chance to agree or refuse to be in the study.

Family members will be provided with contact information for the study coordinator, local co-investigator, Latin American Principal Investigator, and the local Ethical Committee. Written consent will be obtained in the presence of a witness. For patients aged 13 to 20 years, the parent or legal guardian will be approached for consent, and Child Assent will be obtained when the child regains consciousness.

Procedure for obtaining intervention group assignment.

The master randomization list will be generated by the statistician/database manager at the Data Center (DC) at UW (Jason Barber). Randomization will be stratified by site, age (<=40 vs. >40), and GCS (3-5 or if intubated GCSm 1-2 vs GCS 6-8 or if intubated GCSm 3-5). Each site will be provided with an Access database which will be installed on a computer on site that is accessible to all study staff who are authorized to randomize a case. The database will have preloaded 4 password-protected tables with randomization codes for the 4 strata for that site. The tables will contain assignments blocked to ensure near balance on treatment assignment. The site personnel will enter the subject’s ID, age, and total GCS or motor GCS as well as the initials of the person randomizing the case. They will also verify that the site has a functioning monitor and an ICU bed available for the subject. This information and the date and time will be captured on the database. The program will retrieve the assignment for the next case in the appropriate stratum and display the assignment on the screen. Subjects will be randomized after consent without checking for contraindications to monitor placement. Any contraindications that occur must be corrected as rapidly as possible and catheter implantation performed for those randomized to the ICP monitor group (as noted in section A1a of the treatment protocol).

5. STUDY INTERVENTIONS

Interventions, Administration, and Duration

Treatment arms. There are two arms in this study, the ICP Monitor Group and the Standard Care Group. Management of patients who are randomized to the ICP Group will be based specifically on the presence of intracranial hypertension and follow the Guidelines for the Management of Severe Brain Injury. Management of patients who are randomized to the Standard Care Group will be consistent with the protocols presently being used in the three study hospitals.

Treatment protocol: We strongly suggest using these interventions whenever available and/or possible.

1. Patient monitoring measures
   a. Place patient on mechanical ventilation (VM)
   b. Place continuous SaPO2 and EtCO2 monitors
   c. Insert indwelling urinary catheter to monitor urine output
   d. Insert arterial catheter for arterial mean pressure monitoring
e. Insert central venous catheter for infusion of solutions and central venous pressure monitoring.

f. Monitor neurological clinical status each hour
   i. Pupils
   ii. GCS
   iii. etc

2. General measures
   a. Head positioning 30º
   b. Head and neck in neutral position and aligned
   c. Avoid hyperthermia
      i. Defined as central temperature ≥ 38 º C
      1. Non-drug measures (cooling)
      2. Dipirona (Metamizole sodium)
   d. Early enteral nutritional support
      i. Before 48 hours
      ii. 25 Kcal/kg weight
   e. Pharmacologic prophylactic of post traumatic seizures
      i. Phenytoin (IV or PO)
      1. Load and maintenance dose as is being giving in each hospital
   f. Gastric bleeding prophylaxis
      i. Ranitidine or Omeprazol
   g. Avoid decubitus lesions
   h. Deep venous thrombosis prophylaxis
i. Frequent tracheal suctioning with sterile technique to prevent pulmonary infections

3. Routine CT scans
   a. First CT: on Hospital admission
   b. Second CT: 48 hours after the first CT
   c. Third CT: 5-7 days after the first CT

Guidelines for the Management of Severe Traumatic Brain Injury Patients:

Standard Care Group

The guidelines are presented below and are also summarized in Figures 1 and 2.
Figure 1.

Protocol can be modified according to:
- Clinical judgement (e.g. early escalation)
- Mass lesion (post-op protocol care based on CT)
- Neuroworsening (treated per protocol)

This protocol could be modified:
- By clinical judgment (i.e. DC or barbiturates could be used earlier on)
- Mass lesion on CT scans (procedure to evacuate if it is indicated and then continuing with the protocol based on CT findings)
- Neuroworsening (NW) whenever occurs should be treated as follows (see next)
1. Patient monitoring measures: We strongly suggest using these interventions whenever available and/or possible.
a. Place continuous SaO2 and EtCO2 monitors

b. Insert indwelling urinary catheter to monitor urine output

c. Insert arterial catheter for arterial pressure monitoring

d. Insert central venous catheter for infusion of solution and central venous pressure monitoring

e. Monitor clinical neurological status each hour
   i. Pupil size and reactivity
   ii. GCS

f. Obtain brain CT
   i. To evaluate evolution 48 hours after the admission CT
   ii. To evaluate evolution 5-7 days after the admission CT
   iii. As needed based on patient clinical condition

2. General management measures

a. Place patient on mechanical ventilation, goal SaO2 > 90% and PaO2 > 60 mmHg

b. Use adequate sedation and analgesia
   i. Acceptable medications include benzodiazepines, opioids, propofol and low dose barbiturates
      1. Low dose barbiturate dosing:
         a. Thiopental (Pentothal) 1-2 mg/kg/hr IV continuous infusion (approx 1.5-3 gm/day)

c. Maintain head of bed at 30°

d. Maintain head and neck aligned and in neutral position

e. Actively monitor body temperature and treat hyperthermia

f. Hyperthermia defined as central temperature ≥ 38°C
   i. Non-pharmaceutical cooling measures
      1. Cooling blanket, ice packs
   ii. Pharmaceutical cooling measures
      1. Dipirona (Metamizole sodium)
g. Early enteral nutritional support
   i. Initiate within 48 hours of injury
   ii. Give 25 Kcal/kg patient weight per day
h. Pharmacologic prophylaxis for early post traumatic seizures
   i. Phenytoin (IV or PO)
      1. Loading and maintenance doses as per individual hospital guidelines
      2. Continue for 7-28 days
   i. Gastric bleeding prophylaxis
      i. Ranitidine or Omeprazole (IV or PO)
         1. Administer as per individual hospital guidelines
j. Prevent decubitus lesions and treat as indicated
k. Deep venous thrombosis prophylaxis
l. Frequent tracheal suctioning with sterile technique to prevent pulmonary infections
m. Maintain Hb ≥ 7 mg/dL, use blood transfusions as needed

3. CT scans
   a. First CT: upon hospital admission
   b. Second CT: 48 hours after the first CT
   c. Third CT: 5-7 days after the first CT
   d. Additional CT scans as needed based on patient clinical condition

4. Treatment Goals for adequate cerebral perfusion and oxygenation
   a. Avoid hypotension - systolic blood pressure (SBP) > 90 mmHg, mean arterial pressure (MAP) > 70 mmHg
   b. Arterial blood oxygen saturation (SaO2) > 90% or PaO2 > 60 mm Hg

5. Initial therapeutic interventions
   a. Normal saline solution (0.9% NaCl) to obtain a CVP of 10-12 cmH2O
   b. Vasopressors when necessary to obtain a SBP > 90 mmHg or mean arterial pressure (MAP) > 70 mmHg
   c. Maintain PaCO2 35-40 mmHg if CT is normal
i. In Cochabamba, correct for altitude and maintain PaCO2 32-36 mmHg
d. If a space-occupying lesion exists, surgical evacuation is indicated if possible

6. Specific therapeutic interventions—Standard (Non-Monitored) Therapy

a. After optimized sedation and analgesia, hyperventilation and hyperosmotic therapy should be started simultaneously if there is evidence of edema on CT, as indicated as following:

1. Compressed peri-mesencephalic cisterns

2. Midline shift

3. Cortical sulcal compression / effacement

b. Mild hyperventilation
   i. Maintain PaCO2 30-35 mmHg (PaCO2 28-32 mmHg in Cochabamba)

c. Hyperosmolar/Hypertonic Therapy
   i. Mannitol should be used first except in the following situations (HHH):
      a. Arterial Hypotension
      b. Hypovolemia
      c. Hyponatremia

2. Hyperosmolar (Mannitol) therapy guidelines and dosing
   a. Plasma osmolarity or tonicity should be monitored at least every 12-24 hours
      i. Plasma osmolarity or tonicity should be calculated using the following formulae:
         1. Osmolarity = 2 * (Na) + (BUN/ 2.8) + (Glucose/18)
         2. Tonicity = 2 * (Na + K) + (Glucose/18)
      ii. Hyperosmolar (Mannitol) therapy should be suspended for plasma osmolarity > 320 or tonicity > 340
   b. Mannitol dosing regimen using 20% Mannitol bolus:
      i. 100ml (20gm) IV every 3-4 hours for the first 3 days, then
      ii. 80ml (16gm) IV every 3-4 hours on day 4, then
iii. 60ml (12gm) IV every 3-4 hours on day 5, then

iv. 40ml (8gm) IV every 3-4 hours on day 6 and suspend

3. Hypertonic saline therapy guidelines and dosing
   a. Hypertonic saline should only be used in cases of HHH as described above
   b. Plasma osmolarity or tonicity and serum sodium should be monitored at least every 12-24 hours
      i. Plasma osmolarity or tonicity should be calculated using the following formulae:
         1. \[ \text{Osmolarity} = 2 \times (\text{Na}) + (\text{BUN}/2.8) + (\text{Glucose}/18) \]
         2. \[ \text{Tonicity} = 2 \times (\text{Na} + K) + (\text{Glucose}/18) \]
      ii. Hypertonic saline therapy should be suspended for plasma osmolarity > 360 or tonicity > 380 or serum sodium > 160
   c. Hypertonic saline dosing regimen using 5%NaCl solution bolus:
      i. 80ml normal saline (0.9%NaCl) + 20ml 20%NaCl = 100ml 5%NaCl solution
      ii. 100ml IV every 4-12 hours for 6 days then suspend
   d. High dose IV barbiturates
      i. Use after hyperventilation and hyperosmolar/hypertonic therapies
      ii. Should be used if second CT shows evidence of compressed PMC
      iii. Dosing: \text{Thiopental (Pentothal) 2.5-4 mg/kg/hr IV continuous infusion for 3 days (approx 4-6 gm/day)}
   iv. Hypotension must be avoided

7. Neuroworsening requires increased therapeutic intensity level, including decompressive craniectomy when necessary and available. Any one or all of the following therapeutic interventions should be utilized based on patient conditions.
   a. Neuroworsening defined as:
      1. Decrease in the motor GCS ≥ 2
      2. New loss of pupil reactivity
3. Interval development of pupil asymmetry of ≥ 2mm
4. New focal motor deficit
5. Herniation syndrome

ii. **Hypertonic therapy:**

1. **Additional** mannitol dosing regimen using 20% Mannitol bolus:
   
   i. 200ml (40gm) IV every 3-4 hours for 1 day, then
   
   ii. 100ml (20gm) IV every 3-4 hours for 2 days, then
   
   iii. 80ml (16gm) IV every 3-4 hours on day 4, then
   
   iv. 60ml (12gm) IV every 3-4 hours on day 5, then
   
   v. 40ml (8gm) IV every 3-4 hours on day 6 and suspend

b. High dose mannitol at 0.5 – 1 gm/kg per dose should be used in the case of acute neurological deterioration and as a temporizing measure prior to decompressive craniectomy if there is no response to medical management. The above duration of treatment (6 days) should be followed only when neurosurgical intervention is not available.

c. Contraindicated in patients with HHH
   
   i. **Use hypertonic saline**

d. **Hypertonic saline – doses as above**

iii. Increase hyperventilation (HV)

   1. Maintain PaCO2 of 25-30 mmHg (PaCO2 22-28 mmHg in Cochabamba)

   2. Use for shortest time period possible to reverse neurological deterioration

   3. If no response, stop HV and use barbiturates

iv. High dose IV barbiturates

   1. **Thiopental (Pentothal) 2.5-4 mg/kg/hr IV continuous infusion for 3 days**

   2. **Hypotension must be avoided**

v. Furosemide 20mg IV every 8 hours
vi. Head CT is strongly suggested if possible

8. Second tier therapy to be considered in salvageable patients under conditions such as:
   a. To be considered in case of:
      i. Persistent neuroworsening not responding to an increased therapeutic intensity level (as indicated above). CT is recommended, if possible.
      ii. Follow-up CT (eg day 5 CT) showing Inadequate response to treatment such as persistent edema
   b. Primary options
      i. Decompressive craniectomy
      ii. High dose IV barbiturates:
         1. Thiopental (Pentothal) 2.5-4 mg/kg/hr IV continuous infusion (approx. 4-6 gm/day)
         2. Hypotension must be avoided
   c. Other options
      i. Hyperventilation to maintain PaCO2 25-30 mmHg (PaCO2 22-28 mmHg in Cochabamba), use for shortest time period possible to reverse neurological deterioration
      ii. Hypothermia
      iii. Lund therapy

9. Management following decompressive craniectomy
   a. Use adequate sedation and analgesia
   b. Mild hyperventilation to maintain PaCO2 30-35 mmHg (PaCO2 28-32 mmHg in Cochabamba)
   c. Hyperosmolar/hypertonic therapy
      i. Use after sedation/analgesia is optimized
      ii. Mannitol should be used first, except in the following situations (HHH):
         a. Arterial Hypotension
         b. Hypovolemia
         c. Hyponatremia
2. Mannitol therapy guidelines and dosing
   a. Plasma osmolarity or tonicity should be monitored at least every 12-24 hours
   b. Plasma osmolarity or tonicity should be calculated using the following formulae:
      1. Osmolarity = 2 * (Na) + (BUN/ 2.8) + (Glucose/18)
      2. Tonicity = 2 * (Na + K) + (Glucose/18)
   c. Hyperosmolar (Mannitol) therapy should be suspended for plasma osmolarity > 320 or tonicity > 340
   d. Continue the pre-operative mannitol dosing regimen using 20% Mannitol bolus:
      i. 100ml (20gm) IV every 3-4 hours for the first 3 days, then
      ii. 80ml (16gm) IV every 3-4 hours on day 4, then
      iii. 60ml (12gm) IV every 3-4 hours on day 5, then
      iv. 40ml (8gm) IV every 3-4 hours on day 6 and suspend

3. Hypertonic saline therapy guidelines and dosing
   a. Hypertonic saline should only be used in cases of HHH as described above
   b. Plasma osmolarity or tonicity and serum sodium should be monitored at least every 12-24 hours
      i. Plasma osmolarity or tonicity should be calculated using the following formulae:
         a. Osmolarity = 2 * (Na) + (BUN/ 2.8) + (Glucose/18)
         b. Tonicity = 2 * (Na + K) + (Glucose/18)
      2. Hypertonic saline therapy should be suspended for plasma osmolarity > 360 or tonicity > 380 or serum sodium > 160
   c. Continue the pre-operative hypertonic saline dosing regimen using 5%NaCl solution bolus:
i. 80ml normal saline (0.9%NaCl) + 20ml 20%NaCl = 100ml 5%NaCl solution

ii. 100ml IV every 4-12 hours for 6 days then suspend

d. High dose IV barbiturates
   
   i. Use after hyperventilation and hyperosmolar/hypertonic therapies
      
      1. **Dosing: Thiopeptal (Pentothal) 2.5-4 mg/kg/hr IV continuous infusion for 3 days**

      2. **Hypotension must be avoided**

e. Obtain head CT within 24 hours following decompressive craniectomy
   
   i. If edema improved, stop sedation, hyperventilation, hyperosmolar/hypertonic therapy, and high dose barbiturate therapy and evaluate neurologic exam and GCS

   ii. If edema not improved or worse, continue sedation, hyperventilation, hyperosmolar/hypertonic therapy, and high dose barbiturate therapy as above

10. **Contraindicated treatments**

   a. **Corticosteroids for brain injury treatment**

   b. **Use of anticonvulsants for prophylaxis of late epilepsy (beyond 28 days)**

**Guidelines for the Management of Severe Traumatic Brain Injury Patients:**

**ICP Monitor Group**

1. Required patient monitoring measures

   a. Place ICP monitor

      i. **If the initial placement of the ICP monitor is delayed due to contraindications (eg coagulopathy), then the contraindication must be corrected as rapidly as possible and catheter implantation be performed as soon as the contraindication is removed.**

      ii. **In the case of an ICP monitor failure due to catheter breakage, unintentional removal of catheter, or any other damage or compromise of catheter every attempt should be made to replace the catheter with a new properly functioning one.**

      iii. **Every attempt should be made to insert a new ICP monitor following a cranial operative procedure.**
2. Additional patient monitoring measures: We strongly suggest using these interventions whenever available and/or possible.

   a. Place continuous SaO2 and EtCO2 monitors
   b. Insert indwelling urinary catheter to monitor urine output
   c. Insert arterial catheter for arterial pressure monitoring
   d. Insert central venous catheter for infusion of solution and central venous pressure monitoring
   e. Monitor clinical neurological status each hour
      i. Pupil size and reactivity
      ii. GCS
   f. Obtain brain CT
      i. To evaluate evolution 48 hours after the admission CT
      ii. To evaluate evolution 5-7 days after the admission CT
      iii. As needed based on patient clinical condition

3. General management measures

   a. Place patient on mechanical ventilation, goal SaO2 > 90% and PaO2 > 60 mmHg
   b. Use adequate sedation and analgesia
      i. Acceptable medications include benzodiazepines, opioids, propofol and low dose barbiturates
         1. Low dose barbiturate dosing:
            a. Thiopental (Pentothal) 1-2 mg/kg/hr IV continuous infusion (approx. 1.5-3 gm/day)
   c. Maintain head of bed at 30º
   d. Maintain head and neck aligned and in neutral position
   e. Actively monitor body temperature and treat hyperthermia
      i. Hyperthermia defined as central temperature ≥ 38ºC
      ii. Non-pharmaceutical cooling measures
         1. Cooling blanket, ice packs
      iii. Pharmaceutical cooling measures
1. Dipirona (Metamizole sodium)

f. Early enteral nutritional support
   i. Initiate within 48 hours of injury
   ii. Give 25 Kcal/kg patient weight per day

g. Pharmacologic prophylaxis for early post traumatic seizures
   i. Phenytoin (IV or PO)
      1. Loading and maintenance doses as per individual hospital guidelines
      2. Continue for 7-28 days

h. Gastric bleeding prophylaxis
   i. Ranitidine or Omeprazole (IV or PO)
      1. Administer as per individual hospital guidelines
   i. Prevent decubitus lesions and treat as indicated

j. Deep venous thrombosis prophylaxis

k. Frequent tracheal suctioning with sterile technique to prevent pulmonary infections

l. Maintain Hb ≥ 7 mg/dL, use blood transfusions as needed

4. CT scans
   a. First CT: upon hospital admission
   b. Second CT: 48 hours after the first CT
   c. Third CT: 5-7 days after the first CT
   d. Additional CT scans as needed based on patient clinical condition

5. Treatment Goals for adequate cerebral perfusion and oxygenation
   a. ICP ≤ 20 mmHg
   b. Cerebral Perfusion Pressure (CPP) 50-70 mmHg
   c. Arterial blood oxygen saturation (SaO2) > 90% or PaO2 > 60 mm Hg

6. Initial Therapeutic Interventions
   a. Normal saline solution (0.9% NaCl) to obtain a CVP of 10-12 cmH2O
b. Vasopressors when necessary to obtain a systolic blood pressure (SBP) > 90 mmHg or mean arterial pressure (MAP) > 70 mmHg prior to ICP monitoring (use CPP after monitoring begins).

c. Maintain PaCO2 35-40 mmHg if CT is normal
   
   i. In Cochabamba, correct for altitude and maintain PaCO2 32-36 mmHg.

d. If a space-occupying lesion exists, surgical evacuation is indicated if possible

7. Specific therapeutic interventions - **ICP Monitor with Elevated ICP Treatment algorithm.** Use the following treatment interventions sequentially when ICP is elevated or not responding to basic treatment. **Note that clinically significant ICP elevation (not resolving within 5 minutes) requires treatment, which should be reflected by an increase in the Therapeutic Intensity Level (TIL) for that hour. Failure of ICP response after 20 minutes should prompt further treatment.**

a. Maintain CPP between 50-70 mmHg
   
   i. Every effort should be made to insert an arterial line for continuous MAP monitoring

   ii. If arterial line cannot be placed then calculate MAP from non-invasive blood pressure monitoring every hour to calculate CPP

b. Ventricular drainage should be considered if available. If an intraparenchymal catheter is already inserted, consider **placing the ventricular drain separately.** Drainage of intraventricular fluid should be intermittent, with removal of the smallest volume of fluid necessary to control intracranial pressure and used for the shortest period of time possible. **It is suggested that drainage be for two minutes and the ventricular catheter then be clamped and the PIC rechecked. When both an intraparenchymal monitor and a ventricular catheter are present, the intraparenchymal device should be used to measure the pressure. Note that the ventricular catheter should be clamped when measuring the pressure using either monitor to ensure accuracy.**

c. Neuromuscular blockade should be used, suspend if ICP not responding

d. Mild hyperventilation to maintain PaCO2 30-35 mmHg (PaCO2 28-32 mmHg in Cochabamba)

e. Hyperosmolar/hypertonic therapy
   
   i. Mannitol should be used first except in the following situations (HHH):

   a. Arterial Hypotension

   b. Hypovolemia

   c. Hyponatremia
2. Hyperosmolar (Mannitol) therapy guidelines and dosing
   a. Plasma osmolarity or tonicity should be monitored at least every 12-24 hours
      i. Plasma osmolarity or tonicity should be calculated using the following formulae:
         1. Osmolarity = 2 \times (Na) + (BUN/ 2.8) + (Glucose/18)
         a. Tonicity = 2 \times (Na + K) + (Glucose/18)
      ii. Hyperosmolar therapy should be suspended for plasma osmolarity > 320 or tonicity > 340
   b. Mannitol dosing regimen using 20% Mannitol bolus:
      i. For ICP elevation > 20 mmHg give 0.25-1 gm/kg 20% Mannitol bolus
      ii. Extra doses can be administered for sustained elevation of ICP if plasma osmolarity < 320
3. Hypertonic saline therapy guidelines and dosing
   a. Hypertonic saline should only be used in cases of HHH as described above
   b. Plasma osmolarity or tonicity and serum sodium should be monitored every 12-24 hours
      i. Plasma osmolarity or tonicity should be calculated using the following formulae:
         1. Osmolarity = 2 \times (Na) + (BUN/ 2.8) + (Glucose/18)
         2. Tonicity = 2 \times (Na + K) + (Glucose/18)
      ii. Hypertonic saline therapy should be suspended for plasma osmolarity > 360 or tonicity > 380 or serum sodium > 160
   c. Hypertonic saline dosing regimen using 5%NaCl solution bolus:
      i. 80ml normal saline (0.9%NaCl) + 20ml 20%NaCl = 100ml 5%NaCl solution
ii. 100ml IV given over 1 hour, may repeat as needed for sustained elevations in ICP if plasma osmolarity $< 360$ and serum sodium $< 160$

f. When increasing the therapeutic intensity level obtain a CT scan if possible

8. Neuroworsening requires increased therapeutic intensity level, including decompressive craniectomy when necessary and available. Any one or all of the following therapeutic interventions should be utilized based on patient conditions.

a. Neuroworsening defined as:
   1. Decrease in the motor GCS $\geq 2$
   2. New loss of pupil reactivity
   3. Interval development of pupil asymmetry $> 2$mm
   4. New focal motor deficit
   5. Herniation syndrome

ii. Mannitol dosing regimen using 20% Mannitol bolus:
   1. For ICP elevation $> 20$ mmHg give 0.25-1 gm/kg 20% Mannitol bolus
   2. Extra doses can be administered for sustained elevation of ICP if plasma osmolarity $< 320$

iii. Increase hyperventilation (HV)
   1. Maintain PaCO2 of 25-30 mmHg (PaCO2 22-28 mmHg in Cochabamba)
   2. Use for shortest time period possible to reverse neurological deterioration

b. If no response, stop HV and use barbiturates
   i. High dose IV barbiturates
      1. Thiopental (Pentothal) 2.5-4 mg/kg/hr IV continuous infusion for 3 days
      2. Hypotension must be avoided
   c. Head CT is strongly suggested if possible

9. Second tier therapy to be considered in salvageable patients under conditions such as:
   a. To be considered in case of:
i. ICP not responding to first tier therapy

ii. Persistent neuroworsening not responding to an increased therapeutic intensity level (as indicated above). CT is recommended, if possible.

iii. Follow-up CT (eg day 5 CT) showing Inadequate response to treatment such as persistent edema

b. Primary options

i. Decompressive craniectomy

ii. High dose IV barbiturates:
   1. Thiopental (Pentothal) 2.5-4 mg/kg/hr IV continuous infusion (approx. 4-6 gm/day)
   2. Hypotension must be avoided

c. Other options

i. Hyperventilation to maintain PaCO2 25-30 mmHg (PaCO2 22-28 mmHg in Cochabamba), use for shortest time period possible to reverse neurological deterioration

ii. Hypothermia

iii. Lund therapy

10. Management following decompressive craniectomy

a. Every attempt should be made to insert a new ICP monitor post-operatively, using techniques such as:
   1. Ventriculostomy
   2. Placing another bolt through an Harborview peninsula left along the margins of the craniectomy

ii. If placement of the new ICP monitor is problematic, contact Gustavo Petroni, MD (mobile telephone +549-341-514-7543, home telephone +54-341-482-7588, fax +54-341-423-1087, e-mail gustavopetroni@gmail.com) or Silvia Lujan, MD, (mobile telephone +549-341-560-9239, home telephone +54-341-440-2056, fax +54-341-423-1087, e-mail silviablujan@gmail.com) immediately.

b. Use adequate sedation and analgesia

c. Mild hyperventilation to maintain PaCO2 30-35 mmHg (PaCO2 28-32 mmHg in Cochabamba)

d. If ICP monitor is placed, treat ICP elevations > 20 as indicated above.
11. Intracranial pressure definitions
   a. Treatable intracranial hypertension:
      i. ICP > 20 mmHg for > 5 minutes
   b. Treatment failure:
      i. ICP not reduced to ≤ 20 mmHg within 20 minutes after a treatment intervention is initiated, and
      ii. Persistent elevation in ICP > 20 mmHg requires increase in therapeutic intensity level

12. Investigation of the patient with intracranial hypertension: After assessment of the following factors and initiation of appropriate interventions as indicated below, if the interventions are ineffective in reducing ICP, increase the therapeutic intensity level.
   a. Check for factors that could increase ICP
   b. Pain or agitation: consider increasing sedation/analgesia
   c. Respiratory agitation, consider the following:
      i. Stopping the procedure
      ii. Lidocaine IV or ET (endotracheal tube)
      iii. Technique modification
   d. Patient manipulation and rotation, consider the following:
      i. Stopping the procedure
      ii. Increasing sedation/analgesia
      iii. Technique modification
   e. Endotracheal tube (ET) problems, consider the following:
      i. Change the ET holder
      ii. Change the ET tube care techniques
   f. Elevated intrathoracic pressure or elevated PEEP, consider the following:
      i. Drain any hemopneumothorax
      ii. Change ventilator technique
   g. Raised intra-abdominal pressure: consider decompressive laparotomy
   h. Evidence of seizures: consider evaluation and treatment
i. Check laboratory and vital signs values
   i. Hyperthermia: consider reducing the temperature to < 38°C
   ii. Increased PaCO₂: consider increasing ventilatory rate
   iii. Hypoxia: consider increasing fraction of inspired oxygen
   iv. Abnormal CPP:
      1. Consider increasing MAP with fluids or vasopressors
      2. Consider reducing ICP with sedation and analgesia, hyperventilation, hyperosmolar/hypertonic therapy, and/or high dose barbiturates
   v. Hyponatremia: consider correcting plasma electrolytes
j. If you feel that the intracranial situation may have changed, obtain head CT when possible

13. ICP monitor removal:
   a. Consider removal of catheter if ICP ≤ 20 mmHg for ≥ 24 hours WITHOUT treatment
   b. Confounding factors that may require longer monitoring:
      i. Hemodynamic instability
      ii. Need for intraoperative monitoring during extracranial surgery
      iii. “Clinical judgment”

14. Contraindicated treatments
   a. Corticosteroids for brain injury treatment
   b. Prophylactic hyperventilation
   c. Use of anticonvulsants for prophylaxis of late epilepsy (beyond 28 days)

Adherence Assessment

Time of monitor insertion and removal is collected as are ICP values, TIL, and neuroworsening. This will be used descriptively and is not incorporated in the primary analysis.

6. CLINICAL AND LABORATORY EVALUATIONS

Schedule of Evaluations

<table>
<thead>
<tr>
<th></th>
<th>Screening</th>
<th>Baseline</th>
<th>During Hospitalization</th>
<th>3 Month</th>
<th>6 Month</th>
</tr>
</thead>
</table>

MOP– Version 7 July 10th, 2012
The definitions for the Schedule of Evaluations included in section 6.2 define the evaluations, provide timelines, and include special considerations or instructions for evaluations.

**Screening Form**
**Purpose**
The screening form includes study inclusion and exclusion criteria, consent status and information about the person’s injury before and after admission to the study hospital. This form is filled out on all persons who are screened for the study.

*Who is responsible*
Study coordinator at each hospital

**ICU/ED Form**
**Purpose**
This form documents date of ICU admission and discharge, whether ICP was monitored or not and if so by what method and details about timing of ICP monitoring and reason for ICP monitor removal if applicable. One form is filled out for each ICU admission of each participant.

*Who is responsible*
Study coordinator at each hospital

**ICU/ED Nurse’s Form**
**Purpose**
This form collects information on the subject’s vital signs and Therapeutic Intensity Level (TIL) collected on an hourly basis. One form is filled out for each day the participant is in the ICU, for the full ICU stay. If the participant does not go to the ICU then one form is filled out for each day the patient is in the ED.

*Who is responsible*
Study coordinator at each hospital

**Neuroworsening Form**
**Purpose**
Neuroworsening is the deterioration of the clinical status of a patient with a head injury and is defined by the occurrence of one or more of the following objective criteria.

- A spontaneous decrease in Glasgow Coma Scale Motor score of 2 or more points (compared with the previous examination)
- A new loss of pupillary reactivity
• Interval development of pupillary asymmetry of $\geq 2$ mm
• Deterioration in neurological status sufficient to warrant immediate medical or surgical intervention.

A neuroworsening form is filled out for each episode of neuroworsening experienced by the research subject.

**Who is responsible**
Study coordinator at each hospital

*Neurosurgery and Other Surgery Form*

**Purpose**
All surgeries, including neurosurgery and other surgery for each research subject are recorded on this form. The date of surgery, anesthesia start and stop times, service code, procedure code and side of procedure are recorded.

**Who is responsible**
Study coordinator at each hospital

*AIS Form*

**Purpose**
The AIS form is based on the first 24 hours post injury. The highest severity score per body region is recorded.

**Who is responsible**
Study coordinator at each hospital

*CT Form*

**Purpose**
A CT Scan form is filled out for each CT done on subjects enrolled in the study. A CT scan form is also filled out for Subjects who are screened only and not enrolled on the study, if the scan was done prior to ICU admission.

**Who is responsible**
Study coordinator at each hospital

*Adverse Event Form*

**Purpose**
To report adverse events

**Who is responsible**
Study coordinator at each hospital

*Serious Adverse Event and/or Possibly Related to Study Intervention – Initial Report and Follow-up Forms*

**Purpose**
To report serious adverse events and their resolution.
Who is responsible
Study coordinator at each hospital

Pre-injury Family Form/Pre-injury Patient Form

Purpose
This questionnaire collects information on the patient’s demographic characteristics, pre-injury educational level, living situation, main activity status, income, alcohol and drug use, and medical history. The Pre-injury Family Form is administered as soon as possible after the research subject is enrolled in the study. This measure must be completed prior to hospital discharge of the subject. The Pre-injury Patient Form involves the same questions asked of the research subject when she/he is able.

Who is responsible
Study coordinator or outcome examiner at each hospital

Hospital Discharge Form

Purpose
This form captures information about hospital discharge including date of discharge, neurological status at discharge and discharge referral.

Who is responsible
Study coordinator at each hospital

Study Information Form

Purpose
This form collects the dates of events that may occur at anytime during the course of an individual’s participation on the study, including date of consent by participant, date of withdrawal of consent, date of last study contact for those who were not followed at 6 months post injury, date and cause of death and protocol violations.

Who is responsible
Study coordinator at each hospital

Personal and Contact Information Form

Purpose
Contact information for the participant is collected on this form in order to facilitate scheduling the outcome evaluations. In addition, contact information of friends and relatives of the participant who will remain in contact with him or her if they move is also collected for this purpose. This information is collected before hospital discharge and updated at the 3-month evaluation.

Who is responsible
Study coordinator or outcome examiner at each hospital
3 Month Outcome Evaluation Form

Purpose
The results of the Galveston Orientation and Amnesia Test, Glasgow Outcome Scale-Extended and Disability Rating Scale administered at 3-months post injury are coded on this CRF.

Who is responsible
Outcome examiner at each hospital

6 Month Outcome Evaluation Form

Purpose
The results of the Galveston Orientation and Amnesia Test, Glasgow Outcome Scale-Extended and Disability Rating Scale administered at 6-months post injury are coded on this CRF.

Who is responsible
Outcome examiner at each hospital

6 Month Neuropsychological Coding Form

Purpose
The results of the 6-month neuropsychological evaluation are coded on this CRF.

Who is responsible
Outcome examiner at each hospital

7. MANAGEMENT OF ADVERSE EXPERIENCES
ICP-monitoring related adverse experiences include:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>ICP catheter related infection</td>
</tr>
<tr>
<td>02</td>
<td>ICP catheter breakage</td>
</tr>
<tr>
<td>03</td>
<td>Unplanned ICP catheter removal</td>
</tr>
<tr>
<td>04</td>
<td>ICP catheter related hemorrhage</td>
</tr>
</tbody>
</table>

Management of related adverse experiences
Include:
- A list of expected adverse experiences for each study intervention
- Criteria for subject management and modification of the study intervention regimen
- Procedures for modification (forms, additional labs, and change in regimen)
- List alphabetically by adverse experience

8. CRITERIA FOR INTERVENTION DISCONTINUATION

ICP monitoring can be stopped and the catheter removed when ICP < 20 mmHg for ≥ 24 hours WITHOUT treatment. Factors that may suggest monitoring beyond this point include: Hemodynamic instability, intraoperative monitoring for extracranial surgery, or ‘clinical sense’.
9. **STATISTICAL CONSIDERATIONS**

**General Design Issues**

This study is a randomized, clinical trial with blinded evaluation of outcome to be conducted at centers in Bolivia and Ecuador. It is a 2-group, parallel design. Within 24 hours of injury (or 24 hours of deterioration, but no later than 72 hours after injury) patients with severe TBI will be randomized to brain injury management based on intracranial pressure (ICP) monitoring (called the “ICP group”) or brain injury management conducted according to a protocol that does not include monitoring of ICP (called the “Standard Care group”). Randomization will be stratified on site, age (≤40 vs. >40), and GCS (3-5 or, if intubated, GCS motor 1-2 vs, GCS 6-8 or, if intubated, GCS motor 3-5). Patients will be followed and evaluated by a blinded assessor at 3 and 6 months after injury.

**Hypothesis #1:** Patients with severe TBI whose acute care treatment is managed using ICP monitors will have significantly lower mortality and better neuropsychological and functional recovery at 6 months post-trauma than those whose treatment is managed with the standard protocol.

**Hypothesis #2:** The incorporation of ICP monitoring into the care of patients with severe TBI will minimize complications and decrease length of stay in ICU.

**Outcomes**

**Primary outcome (including definition)**

The primary outcome is a composite measure based on mortality, time to follow commands, Sum of Errors on the Galveston Orientation and Amnesia Test (GOAT), and the measures of functional level and neuropsychological performance. For each measure, the participants are ranked from 1 (worst) to n (best). To increase interpretability, the ranks are converted to percentiles, giving the percent at or worse than the participant’s score. For each person, the percentiles on the different measures are averaged. (O’Brien, 1984)

The outcome variables are:

- Mortality
- Time to follow commands (measured as time from injury to following simple commands as defined by a score of 6 on the motor scale of the GCS)
- Sum of Errors on the GOAT (Levin et al., 1979)
- Functional status at 3 and 6 months
- Neuropsychological assessment (Table 1).

**Functional Status:** The Disability Rating Scale (DRS), and the Glasgow Outcome Scale Extended (GOS-E) will be used to measure functioning level in everyday life. The DRS (Rappaport et al 1982) is a brief measure of impairment, disability and participation. Only the assessment of eye opening, communication ability and motor response will be used in the analysis. The GOS-E (Wilson et al1998) is the most commonly used measure of functional outcome in traumatic brain injury. This measure is the extension of the original Glasgow Outcome Scale, developed to address limitations with the original measure including unreliability and insensitivity to change. They have
all been translated and used extensively in previous research in Latin America by this research group. Total scores from the GOSE and the DRS will be used in the composite measure.

**Neuropsychological Test Battery:** A battery of measures that examines important neuropsychological constructs which are sensitive to the integrity of brain functions, including traumatic brain injury, will be used. The selection of the neuropsychological outcome measures is based on the work of the University of Washington investigators’ prior work with TBI, the recommendations from the NINDS conference addressing outcome measurement in clinical trials involving moderate or severe traumatic brain injury [Clifton, 1992], and the measures selected for the Traumatic Brain Injury Clinical Trials Network of the National Center for Medical Rehabilitation Research. These are widely used published instruments with considerable psychometric work. In addition, through the international work of Drs. Robert Heaton and Mariana Cherner, these measures have been translated, adapted and normed for monolingual Spanish speakers, and have been used in Latin countries. This is an important benefit for this application. In choosing the measures, considerations were also given so that: 1) they cover different aspects of functioning that are clinically relevant and likely to be affected by head injury; 2) the measures possess good psychometric properties with respect to sensitivity, validity, and reliability, and 3) the measures are appropriate for use with a broad spectrum of head injury severity and likely to be responsive to treatment effects directed at improving outcome. Tests of a variety of cognitive functions are included because head injury can impact any or all of the functions depending upon severity. The areas assessed are clinically relevant because they are prevalent and a major cause of disabilities in this population after the acute stage of injury.

The neuropsychological domains and the measures used to examine them follows:

- **Mental Status** (Mini-Mental State Examination – Folstein et al., 1975; Strauss et al., 2006)
- **Working Memory** (Paced Auditory Serial Addition Test – Heaton et al., 2004)
- **Speed of Information Processing** (WAIS III Digit Symbol, and Symbol Search subtests – Wechsler 1997, Heaton et al 2002; Color Trails part 1—Maj, 1993; Strauss et al., 2006; Trail Making Test Part A – Strauss et al., 2006)
- **Learning and Recall** (Spanish Verbal Learning Test – Artiola i Fortuny et al., 2000; Brief Visuospatial Memory Test Revised – Benedict 1997, Cherner et al. 2007; Strauss et al., 2006)
- **Motor Speed & Dexterity** (Grooved Pegboard Test- Klove 1963)

Scores used in the Composite measure include the MMSE total score, the Spanish Verbal Learning Test total learning score and Long Delay Free Recall, the Brief Visuospatial Memory Test Revised total learning number correct, and delay correct, WAIS III Digit Symbol and Symbol Search scores, Color Trails 2 time to completion, number correct on PASAT and three subcomposite scores where tests are grouped together to each form 1 variable to be entered into the composite. The first is Grooved Pegboard dominant and non-dominant times, The second subcomposite is composed of Color Trails 1 and Trail Making Test Part A times to completion, , The third subcomposite is composed of total correct on COWAT, Category Fluency Test for Animals, and Actions... Before ranking and entering the composite (or subcomposite) each
neuropsychological test score will be regressed on age, sex and years of education to decrease variability. The residuals are ranked and entered onto the composite or subcomposite. Use of T-scores based on the norms for monolingual Spanish-speakers was considered, but uninjured Bolivians did not have scores with the expected mean of 50 and there was a substantial relationship between years of education and the T-scores for some measures.

Table 1. Measures of patient outcome

<table>
<thead>
<tr>
<th>Hospital Discharge</th>
<th>3 months post injury</th>
<th>6 months post injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>GOAT</td>
<td>GOAT</td>
</tr>
<tr>
<td>Time to follow commands</td>
<td>GOS-E²</td>
<td>GOS-E</td>
</tr>
<tr>
<td>GOAT¹</td>
<td>DRS³</td>
<td>DRS</td>
</tr>
<tr>
<td>Length of ICU stay⁵</td>
<td></td>
<td>Neuropsychological Battery</td>
</tr>
<tr>
<td>Complications⁵</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ Galveston Orientation Amnesia Test
² Glasgow Outcome Scale - Extended
³ Disability Rating Scale
⁵ Outcomes used to test hypothesis 2.

Secondary outcomes

Sample Size and Accrual

Sample and randomization. We anticipate enrolling 9 cases per month. Thus, over 12 months we expect to accumulate data on 108 patients, totaling 324 patients for the 3-year enrollment period of the study. There are no goals for sample size in each stratum. The null hypothesis is no treatment difference. A sample size of 324 patients (162/group) gives the study 80% power to detect an average improvement of 10 percentage points on the percent with good or moderate recovery on the GOS accompanied by similar improvement on the other outcome measures. Similar improvement is defined as an equal change in the log odds for mortality and for individual categories of the GOS-E and as a similar percent reduction in the deficit for neurobehavioral measures. Deficits are estimated as the difference between performance of trauma controls with no head injury and patients with Glasgow Coma Scale scores 3-8 in University of Washington studies. [For example, the severely injured group had an average PIQ of 86, while the controls averaged 110. Thus the deficit is considered to be 24 points.] The power is based on a computer simulation of the composite test proposed for the primary hypothesis.

With a sample size of 324 (162/treatment), the study has 80% power to detect a difference of 20 percentage points in any of the complications, e.g. 30% with ICP monitoring vs. 50% without. There will also be 80% power to detect a difference of .4 standard deviations in ICU length of stay.

Data Monitoring

The Data and Safety Monitoring Board (DSMB) for the study has been appointed by NINDS. The DSMB monitors study quality, safety of participants, and efficacy. Monitoring performance of the study usually includes reviewing patient recruitment, flow of forms, quality control of the data, adequacy of medical monitoring, adverse effect reporting, adherence to protocol, and appropriateness of protocol changes with regard to scientific integrity.
Monitoring safety usually includes reviewing risk of harm inherent in participating in the study, adverse events (type, incidence, and severity), and effect of protocol changes on risk. Monitoring efficacy usually includes reviewing data (blinded or unblinded), planned and/or unplanned interim analyses, stopping rules, their implementation, and resulting decisions, results and conclusions.

**Interim analyses.** One interim analysis is planned after half the patients reach the 6-month assessment, to determine efficacy. The interim analysis will use O'Brien-Fleming (O'Brien et al. 1979) boundaries to decide whether to terminate because of a positive effect of ICP-guided management. The test on the composite outcome at the interim analysis will be run with a nominal significance level of approximately 0.005. This allows a final test at almost the nominal significance level (approximately 0.048) while still allowing early termination of the project if a definitively positive result is obtained early. In addition, to terminate early because of efficacy, analysis of at least one of the individual outcomes—mortality or Glasgow Outcome Scale Extended—must indicate significant improvement with ICP-guided management at the one-sided nominal .05 level.

This is a trial for which, in the US at least, there is strong feeling that the experimental treatment (ICP monitoring) is superior. Stopping early for futility, i.e. because the study is unlikely to be able to demonstrate that ICP monitoring is superior, will leave a wide confidence interval on the effect that is not likely to be convincing. Therefore, we propose no futility analysis be done for this trial to allow the study to yield the tightest estimate of effect (or lack thereof).

**Safety.** Interim analyses will be performed every 6 months, i.e. for each Data and Safety Monitoring Board meeting, during patient accession. In addition to descriptive summarizations of accrual and adverse events, survival comparisons will be made. We will consider that a safety problem exists if any of these analyses show significantly higher mortality in the ICP-guided group at the one-sided nominal .05 level. We will consider that a serious accrual problem exists if the accrual rate is less than 2/3 that expected

**Data Analyses**

**Hypothesis #1.** Patients with severe TBI whose acute care treatment is managed using ICP monitors will have significantly lower mortality, shorter time to follow commands, shorter length of post-traumatic amnesia, better functional recovery at 3 and 6 months, and better neuropsychological recovery at 6 months post-trauma than those whose treatment is managed with the standard protocol.

**Primary data analysis.** The null hypothesis is that there will be no difference in outcomes between management groups. This hypothesis will be tested by comparing the two groups on a composite measure based on mortality, time to follow commands, length of post-traumatic amnesia, and the measures of functional level and neuropsychological performance. For each measure, the participants are ranked from 1 (worst) to n (best). To increase interpretability, the ranks are converted to percentiles, giving the percent at or worse than the participant’s score. For each person, the percentiles on the different measures are averaged. (O’Brien, 1984) The hypothesis is tested by a blocked Wilcoxon test (Lehmann, 1975) comparing the average percentiles for people in the two treatment groups after controlling for center, TBI severity group and age group. Death is considered to be the worst outcome, and “too neurologically impaired to be tested” is considered to be next on the neuropsychological measures. A 2-sided .05 significance level will be used. Analysis will be according to the intention-to-treat principle, i.e., all randomized cases will be followed and included with their assigned treatment group regardless of the management protocol.
actually used. To supplement the composite test of the overall hypothesis, individual measures will be summarized for each group. Before ranking and entering the composite (or subcomposite) each neuropsychological test score will be regressed on age, sex and years of education to decrease variability. The residuals are ranked and entered onto the composite or subcomposite. Use of T-scores based on the norms for monolingual Spanish-speakers was considered, but uninjured Bolivians did not have scores with the expected mean of 50 and there was a substantial relationship between years of education and the T-scores for some measures.

**Rationale for the primary analysis method.** The composite outcome is sensitive to treatments for which the direction of the effect is the same on each component measure. That is what we would expect if one management protocol were more effective than the other. The method of analysis requires few assumptions about the distribution of the individual measures making up the composite or the intercorrelation among them.

**Hypothesis #2.** The incorporation of ICP monitoring into the care of patients with severe TBI will minimize complications and decrease length of stay in ICU.

**Primary data analysis.** Length of stay in the ICU will be analyzed using a blocked Wilcoxon test with blocking on center, GCS group and age group. The most frequent complications (major respiratory problems, sepsis, decubitus ulcers) as well as any non-neurologic complication will be summarized as present/absent and analyzed separately using a Mantel-Haenszel test with stratification as indicated for length of stay in the ICU. A 2-sided significance level of .01 will be used for each test to account for the multiple comparisons.

**Rationale for primary analysis method.** Since the management strategies could well have different effects on the different components of the hypothesis, creation of a composite would not be appropriate. Use of the lower significance level (Bonferroni correction) ensures we will not declare an effect on any of the outcomes if there is none (Type I error) more than 5% of the time overall. We will stratify on the same factors as they are likely to affect complications in addition to functional or neuropsychological outcome.

**Sub-group analyses of sex/gender and race/ethnicity.** We will conduct sub-group analyses to determine if there are any clinically important differences in the intervention effect among these groups.

10. **DATA COLLECTION, SITE MONITORING, AND ADVERSE EXPERIENCE REPORTING**

10.1 Data Flow

**Records to Be Kept**

During the study, the case report forms will be kept at the site and in Rosario. Any identified records will be kept in locked file cabinets or locked offices. After the study is complete and the database has been locked, the forms will be sent to UW for long-term storage in compliance with the legal requirements.

**Role of Data Management**
Each center will have two primary data collectors – one for the acute care setting and one for outcomes assessments. The acute care data collector is the study coordinator. They will collect baseline and hospital information from the patients’ charts onto the study Case Report Forms (CRF). The outcomes data collector is the outcomes examiner. They will transcribe patient information from the outcome assessment forms onto the study CRF. The outcomes data collector will be masked to the treatment group. The CRFs are paper forms with two copies. One copy will remain with the patients’ records at the study center. The other copy will be hand-carried by the Monitor to the study lab in Rosario, Argentina.

In Rosario, patient data will be entered twice by two individuals independently onto a password-protected Access database using screens designed to look like the paper forms. The program will automatically identify inconsistencies between the two data entries, as well as out-of-range errors. After errors are corrected the files will be transmitted to the project’s Data Center at the University of Washington (UW). The UW data manager will further monitor data for inconsistencies and unusual values. Baseline CRFs should be completed within one week of injury. Hospital CRFs should be completed within 2 weeks of hospital discharge. Outcome CRFs should be completed within 2 weeks of outcome assessment. Data should be entered within 4 weeks of receipt in Rosario. Queries should be sent within 2 weeks of entry and should be answered within 1 month.

Changes will be made both on the forms at the site (by the study coordinator) and at Rosario by the person doing data entry. Original value should be crossed through with a single line, the new value written in, and the change initialed and dated. Changes will be entered at Rosario. All changes to the entered forms will be automatically logged with the prior value, the date and time of the change, and the identification of the person making the change.

Quality Assurance

The data quality control program will be overseen by the study biostatistician, Dr. Temkin. Medical data, including injury severity information, will be collected by the study clinicians under the supervision of the study Monitors, Drs. Petroni and Lujan. The neurobehavioral examiners will be trained and certified by Dr. Mariana Cherner at the University of California in San Diego (UCSD) who is a bilingual neuropsychologist with experience in cross cultural neuropsychological studies. After the examiners are certified, the results of their first 10 tested cases will be reviewed at UCSD to ensure valid testing. Subsequently 10% of their cases will be reviewed to prevent drifting. Dr. Dikmen will oversee the training, data collection and quality control of the neuropsychological and functional status measures.

All personnel collecting data will be extensively trained in their tasks. All scoring and coding of neurobehavioral measures will be double-checked by Dr. Lujan. Any unusual cases will be discussed with the Medical Committee or Outcome Committee to resolve the coding difficulties. All coded data will be double entered by experienced data-entry operators into an Access database. On-line range and consistency checks and cross-form consistency checks will further enhance data quality. All discrepancies or unusual values will be checked and resolved by the data supervisor, Ms Machamer. All data will be maintained on password-protected files on a secure server that is backed up nightly. Ten percent samples will be chosen by the data center and sent to the Monitors to be checked against source documents.

Adverse Experience Reporting
The study intervention is conducted while the person is in the ICU, but adverse events that occur while the person is in the hospital should be included on the form. Adverse events do not need to be related to the study intervention to be reported. For each adverse event, fill in a line on the Complication form with the date the adverse event was first noted, the adverse event code (from the list below), a short description and the initials of the person filling out the line. A line on the complication form should be filled in as soon as an adverse event is noted. The form should not be given to the monitor to be taken for data entry until the person has been discharged. If a person has no adverse events, fill in 1 line of the adverse event form with the code 31 which represents ‘None’. If an adverse event is thought to be possibly related to the study intervention, follow the procedure below for intervention related adverse events. Adverse event codes 1-4 (ICP-monitoring-related complications) are always considered to be possibly intervention related.

### ADVERSE EVENT/COMPLICATION CODES

<table>
<thead>
<tr>
<th>Code</th>
<th>Adverse event/complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>ICP catheter related infection</td>
</tr>
<tr>
<td>02</td>
<td>ICP monitoring system malfunction</td>
</tr>
<tr>
<td>03</td>
<td>Unplanned ICP catheter removal</td>
</tr>
<tr>
<td>04</td>
<td>ICP catheter related hemorrhage</td>
</tr>
<tr>
<td>05</td>
<td>CSF leak</td>
</tr>
<tr>
<td>06</td>
<td>Cerebral abscess</td>
</tr>
<tr>
<td>07</td>
<td>New or expanding lesion</td>
</tr>
<tr>
<td>08</td>
<td>Ventriculitis</td>
</tr>
<tr>
<td>09</td>
<td>Seizure</td>
</tr>
<tr>
<td>10</td>
<td>Hydrocephalus</td>
</tr>
<tr>
<td>11</td>
<td>Death</td>
</tr>
<tr>
<td>12</td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>13</td>
<td>Acute lung injury</td>
</tr>
<tr>
<td>14</td>
<td>ARDS</td>
</tr>
<tr>
<td>15</td>
<td>Sepsis</td>
</tr>
<tr>
<td>16</td>
<td>Septic shock</td>
</tr>
<tr>
<td>17</td>
<td>Coagulopathy</td>
</tr>
<tr>
<td>18</td>
<td>Nosocomial pneumonia</td>
</tr>
<tr>
<td>19</td>
<td>Community-acquired pneumonia</td>
</tr>
<tr>
<td>20</td>
<td>Wound infection</td>
</tr>
<tr>
<td>21</td>
<td>Decubitus ulcers</td>
</tr>
<tr>
<td>22</td>
<td>Pulmonary thromboembolism</td>
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<tr>
<td>23</td>
<td>Deep vein thrombosis</td>
</tr>
<tr>
<td>24</td>
<td>Acute renal Failure</td>
</tr>
<tr>
<td>25</td>
<td>Urinary infection</td>
</tr>
<tr>
<td>26</td>
<td>Gastrointestinal hemorrhage</td>
</tr>
<tr>
<td>27</td>
<td>Hyponatremia (&lt; 135)</td>
</tr>
<tr>
<td>28</td>
<td>Hypernatremia (&gt; 145 meq)</td>
</tr>
<tr>
<td>29</td>
<td>Other water and ionic disorders</td>
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<td>30</td>
<td>Other</td>
</tr>
<tr>
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<td>None</td>
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**Serious adverse event (SAE):** Any adverse experience that results in any of the following outcomes is considered a serious adverse event:

- Death
• Life-threatening adverse experience
• Unplanned inpatient hospitalization or prolongation of existing hospitalization
• Persistent or significant disability/incapacity
• Congenital abnormality/birth defect.
• Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
• Examples of such medical events include:
  o Allergic bronchospasm requiring intensive treatment in an ED or at home
  o Blood dyscrasias or convulsions that do not result in inpatient hospitalization

Serious adverse events will be reported to the Medical Safety Monitor (Freddy Arturo Sandi Lora, MD, mobile telephone +591-7203-3853, home telephone +591-2241-3657, fax +591-2-2245502, email fresandi@hotmail.com) and the Monitors (Gustavo Petroni, MD, mobile telephone +549-341-514-7543, home telephone +54-341-482-7588, fax +54-341-423-1087, e-mail gustavopetroni@gmail.com or Silvia Luja, MD, mobile telephone +54-341-560-9239, home telephone +54-341-440-2056, fax +54-341-423-1087, e-mail silviablujan@gmail.com) by the acute care data collector or site PI using the Serious Adverse Event and/or Possibly Related to Study Intervention Form – Initial Report within 2 business days of finding out about the event. The site PI is responsible for reporting the event to the site IRB if that is required. The report can be sent to the Medical Safety Monitor and Monitors electronically (with a signed copy being retained at the site) or, if that is not possible, the information can be telephoned or faxed. Site personnel must do their best to communicate with the Medical Safety Monitor and Monitors quickly, whether that be by phone, e-mail or fax. If the communication is by e-mail or fax, the Medical Safety Monitor and Monitors should confirm that the report was received. The Medical Safety Monitor or Monitors will communicate with the site personnel as needed and make any additions to the form. The Medical Safety Monitor will sign the revised form and send the form to the Monitors within 5 business days. The Monitor will forward the form to the ALAS PI (Dr. Rondina), translate the form into English and forward the English version electronically to the overall PI (Dr., Chesnut) and UW Study Coordinator (Kelley Chaddock, chaddk@u.washington.edu), within 5 business days. If required, the Monitor will also fill out a UW Human Subjects Adverse Event Report (http://www.washington.edu/research/hsd/forms_paper.php?topic=1) and forward it to the UW Study Coordinator along with a copy of the subject’s signed consent form. The UW Study Coordinator will be responsible for getting the appropriate forms to PI for signature and sending the information to the PI, and the UW IRB (Application title: Neurotrauma Research in Latin America: Lifespan Analysis, Application number: 33888, Committee B). She will also be responsible for updating of the spreadsheet of SAE and PRAEs to be sent by Nancy Temkin to the DSMB at the intervals requested by Ms. Odenkirchen (send to: Joanne Odenkirchen, jo21x@nih.gov). The Serious Adverse Event and/or Possibly Related to Study Intervention Form – Initial Report is filled out with the information that can be determined soon after the event is identified by study personnel. For any event with final outcome undetermined at the time of initial report, a Serious/Possibly Intervention Related Adverse Event – Follow-up form should be filled out when the outcome is known or a month has passed since the last report. A Serious/Possibly Intervention Related Adverse Event – Follow-up form should be filled out and sent to the Monitor monthly until either the SAE is resolved or the 6 month study period is over. The follow-ups are forwarded to
everyone receiving the initial report except the UW IRB. Serious Adverse Events should be reported during the entire 6 month study period. Outcome examiners will report to the site PI if they learn of a participant’s death or if the participant says they had an unplanned hospitalization. The site PI will then follow up on late SAE/PRAEs and report them just as is done for SAEs/PRAEs during initial hospitalization.

**Intervention Related Adverse Event/ Unexpected Adverse Event:** Adverse events that are thought to be possibly related to the intervention will be reported using the same procedures as for Serious Adverse Events (except a UW Human Subjects Adverse Event Report is not required unless the event qualifies as a serious adverse event or is unexpected). ICP catheter related infection, ICP monitoring system malfunction (including catheter breakage, catheter obstruction, catheter malposition, or machine malfunction), unplanned ICP catheter removal and ICP catheter related hemorrhage are known responses to the study intervention and should always be considered as possibly related to the intervention. Any other adverse event that occurs after ICP monitor insertion and could not readily have been produced by the subject’s clinical state or due to environmental causes or other interventions is considered unexpected.

**Relatedness of an adverse event to the intervention**

1. **Not related:** An event is considered to be not related to the study intervention if the subject has not yet had an ICP monitor implanted (or attempted to be implanted).

2. **Improbable:** A relationship between the event and the study intervention is considered to be improbable if an ICP monitor has been implanted (or implantation has been attempted) but the event could readily have been produced by the subject’s clinical state or due to environmental causes or other interventions and the event is not known to be related to ICP monitoring. (Events with known relationship are: ICP catheter related infection, ICP monitoring system malfunction (including catheter breakage, catheter obstruction, catheter malposition, or machine malfunction), unplanned ICP catheter removal and ICP catheter related hemorrhage.)

3. **Possible:** A relationship between the event and the study intervention is considered to be possible if an ICP monitor has been implanted (or implantation has been attempted) and the event could not readily have been produced by the subject’s clinical state or due to environmental causes or other interventions and the event is not known to be related to ICP monitoring.

4. **Probable:** A relationship between the event and the study intervention is considered to be probable if an ICP monitor has been implanted (or implantation has been attempted) and the event is known to be related to ICP monitoring. (Events with known relationship are: ICP catheter related infection, ICP monitoring system malfunction (including catheter breakage, catheter obstruction, catheter malposition, or machine malfunction), unplanned ICP catheter removal and ICP catheter related hemorrhage.)

11. **HUMAN SUBJECTS**

Institutional Review Board (IRB) Review and Informed Consent

The informed consent document and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed consent form will be obtained from the subject or their representative. For subjects
who cannot consent for themselves, such as those below the legal age, a parent, legal
guardian, or person with power of attorney, must sign the consent form; additionally, the
subject's assent must also be obtained if he or she is able to understand the nature,
significance, and risks associated with the study. The consent form will describe the
purpose of the study, the procedures to be followed, and the risks and benefits of
participation. A copy of the consent form will be given to the subject, parent, or legal
guardian, and this fact will be documented in the subject’s record.

Subject Confidentiality

All laboratory specimens, evaluation forms, reports, video recordings, and other
records that leave the site will be identified only by the Study Identification Number (SID)
to maintain subject confidentiality. All records will be kept in a locked file cabinet. All
computer entry and networking programs will be done using SIDs only. Clinical
information will not be released without written permission of the subject, except as
necessary for monitoring by IRB, the FDA, the NINDS, the OHRP, the sponsor, or the
sponsor’s designee.

Study Modification/Discontinuation

The study may be modified or discontinued at any time by the IRB, the NINDS, the
sponsor, the OHRP, the FDA, or other government agencies as part of their duties to ensure
that research subjects are protected.

12. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures
developed by the Executive Committee. Any presentation, abstract, or manuscript will be
made available for review by the NINDS prior to submission.

13. REFERENCES

Adelson, Bratton, Carney et al., (2003). Guidelines for the acute medical management of
severe traumatic brain injury in infants, children and adolescents. *Pediatric Critical Care
Medicine*, 4(3), S1-S74.


Benedict RH. (1997) Brief Visuospatial Memory Test-Revised. Psychological Assessment
Resources, Inc., Odessa, FL.

*Neuropsychologia*, 5, 135-140.

Bratton, Bullock, Carney et al. (2007). Guidelines for the Management of Severe Traumatic


List of Changes in the Protocol  
December 2009 - July 2012

December 28, 2008:  
Updated Adverse Event Reporting Section  
Updated contact information for Drs Petroni, Lujan and Lora

December 29, 2008  
Revised Procedure for obtaining intervention group assignment

December 30, 2008  
Remove randomization form (now included in screening form)  
Change name of Serious Adverse Event Form to Serious Adverse Event and/or Possibly Related to Study Intervention – Initial Report and Follow-up Forms  
Remove FIM  
Change Hopkins Verbal Learning Test-Revised to Spanish Verbal Learning Test  
Add fax number for Dr. Freddy Sandi Lora

January 8, 2009  
Alterations to treatment protocols  
Since the first DSMB meeting, a number of areas of uncertainly among the study teams have come to light. This was particularly during the start-up phase, where the protocols came into direct clinical applications. Although the Standard Protocol represented the three centres’ approach to managing TBI prior to this study, it actually is a concatenation of management strategies from each centre and its execution requires modification at each location. As well, on-site observations of clinical care revealed aspects of the protocols that didn’t fit as well as possible with the realities of management in Bolivia. For instance, the quality of the midazolam available for sedation appeared variable, a situation that apparently is within the limits of their medical experience (and not within ours in the US). This prompted altering the sedation protocols to allow the use of low dose barbiturates which are commonly used in Latin America and appear to have more consistent quality.

We have separated out the two protocols to facilitate their clarity and availability at the bedside. Their availability as stand alone protocols sections makes them more user-friendly. In doing this, we have inserted the basic management sections (prior to divergence of the two study protocols) into each section.

A lot of attention has been paid to clarifying the steps and their application within both treatment approaches. Both protocols have been extensively reformatted, with increased explanatory text. Where this is definitely new, it has been bolded in the accompanying documents.

We have added the use of tonicity to both protocols in following hyperosmotic treatment since serum BUN values are much less clinically available. We also allowed the checking of these values to be acceptable at 24 hour intervals (versus the 12 hour intervals initially specified) as the shorter interval is not reasonable within their clinical world.

We corrected a typographic error in describing the target values. Previously, the SaO2 and PaO2 values had been mixed (eg SaO2 > 60 mm Hg).

We added a section regarding the management of patients following decompressive craniectomy, as this was unclear at all three centres. It specifies continuing the pre-operative management plans and getting a follow-up CT scan. Altering the treatment will depend on the
appearance of the CT and the clinical examination in the Standard Approach, supplemented by post-operative ICP data in the Monitored Approach. In some patients, they are concerned that post-operative ICP monitoring may not be possible. We have described approaches to avoid this but have also outlined a management plan to use if such obtains (similar to the Standard Approach).

Since neuroworsening represents a new “stand alone” concept, we have greatly expanded this section and included it within each protocol. For the Monitoring Group, we have re-stated the necessity of responding to intracranial hypertension within 5 minutes and that such responses should be reflected in the TIL (which we will use as an internal QA check for our monthly reports). We have clarified the protocol for using ventricular drainage when a ventriculostomy is in place. Since these patients will have initially been monitored using an intraparenchymal device, we have requested that this be kept (whenever possible) and used to transduce the ICP.

We have added a section on contraindicated treatments (from the TBI Guidelines).

**February 5-27, 2009**
Added in AE section (inadvertently removed in last revision)
Changed data entry from 2 to 4 weeks of receipt
Updated ‘Relatedness of adverse event to the intervention’
Changed names of 2 outcome forms
Updated randomization procedure
Added Mini-Mental State Examination to list of neuropsychological measures
Revised the references
Cleaned up the formatting for Study Intervention
Revised the treatment protocol for ICP monitoring group

**June 8th - June 16th, 2009**
Further specify inclusion/exclusion criteria
Change phenytoin from 7-30 days to 7 – 28 days
Revised the treatment protocol for the ICP monitoring group
Changed who would receive Serious Adverse Event reports at the UW
Updated the email address for Dr. Silvia Lujan

**October 26-27, 2009**
Inclusion of Tarija center
Modification of mild hyperventilation section of the Standard (Non-Monitored) Therapy group

**November, 2009 – February, 2010**
Inclusion of Espejo center
Inclusion of 3 figures to explain treatment protocol in non ICP group
Modification of figures depicting study sites
More detail on test scores in the composite measure
Update the references

**August 2010 – July 2012**
Added Hospital Vernaza to list of sites
Corrected various typos
Dropped Wechsler Memory Scale III Spatial Span August 2010
Dropped Disability Rating Scale Feeding, Toileting, Grooming, Level of Functioning and Employability subtests January 2011
Revised composite score to reflect these changes and to clarify age, sex and education adjustment for neuropsychological measures; to clarify subcomposites July 2012
SAE procedures were corrected July 2012

All changes during this time period were made prior to database lock and breaking of the blind
2.B. STAFF ROSTER

The grantee center is the University of Washington. The study sites are Hospital Japones in Santa Cruz de la Sierra, Bolivia, Hospital San Juan de Dios in Santa Cruz de la Sierra, Hospital Viedma in Cochabamba, Bolivia, Hospital San Juan de Dios in Tarija, Bolivia and Hospital Espejo in Quito, Ecuador. These centers are institutions in which members of the Latin American Brain Injury Consortium (LABIC) work. The administrative entity with financial oversight is Fundacion ALAS in Rosario, Argentina. Table 1 is the Study Staff Roster.

2.C. STUDY ORGANIZATION AND RESPONSIBILITIES

Figure 3. Study Organization
Table 1. Staff Roster

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
<th>Address</th>
<th>Phone</th>
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</thead>
<tbody>
<tr>
<td>Randall Chesnut, MD</td>
<td>Principal Investigator</td>
<td>Dept of Neurological Surgery, Box 359924, University of Washington, Seattle, WA 98104</td>
<td>206-390-4548</td>
<td>206-744-9944</td>
<td>206-559-1485</td>
<td><a href="mailto:chesnutr@u.washington.edu">chesnutr@u.washington.edu</a></td>
</tr>
<tr>
<td>Nancy Carney, PhD</td>
<td>Project Director</td>
<td></td>
<td>503-475-6792</td>
<td>503-494-4551</td>
<td>N/A</td>
<td><a href="mailto:carneyn@ohsu.edu">carneyn@ohsu.edu</a></td>
</tr>
<tr>
<td>Nancy Temkin, PhD</td>
<td>Senior Statistician, Director – Data Center</td>
<td>Dept of Neurological Surgery, Box 359924, University of Washington, Seattle, WA 98104</td>
<td>206-744-9315</td>
<td>206-744-9942</td>
<td>N/A</td>
<td><a href="mailto:temkin@u.washington.edu">temkin@u.washington.edu</a></td>
</tr>
<tr>
<td>Sureyya Dikmen, PhD</td>
<td>Director – Outcomes Assmnt.</td>
<td>Dept. of Rehab Medicine Box 356490 University of Washington Seattle, WA 98195</td>
<td>206-685-7529</td>
<td>206-685-3244</td>
<td>N/A</td>
<td><a href="mailto:dikmen@u.washington.edu">dikmen@u.washington.edu</a></td>
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<tr>
<td>Joanie Machamer, MA</td>
<td>Study Coordinator</td>
<td>Dept. of Rehab Medicine Box 356490 University of Washington Seattle, WA 98195</td>
<td>206-616-0340</td>
<td>206-685-3244</td>
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<td><a href="mailto:machamer@u.washington.edu">machamer@u.washington.edu</a></td>
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<tr>
<td>Jason Barber</td>
<td>Statistician, Database Manager</td>
<td>Dept of Neurological Surgery, Box 359924, University of Washington, Seattle, WA 98104</td>
<td>206-744-9318</td>
<td>206-744-9942</td>
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<td><a href="mailto:barber@u.washington.edu">barber@u.washington.edu</a></td>
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Fundacion ALAS
<table>
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<tr>
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<tr>
<td>Carlos Rondina, MD</td>
<td>Principal Investigator – L.A.</td>
<td><a href="mailto:rondinac@arnet.com.ar">rondinac@arnet.com.ar</a></td>
</tr>
<tr>
<td></td>
<td>Felipe More</td>
<td>549-341-389-7908</td>
</tr>
<tr>
<td>Gustavo Petroni, MD</td>
<td>Co-investigator Monitor</td>
<td>54-341-485-5074</td>
</tr>
<tr>
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<tr>
<td>Silvia Lujan, MD</td>
<td>Co-investigator Monitor</td>
<td><a href="mailto:gustavopetroni@gmail.com">gustavopetroni@gmail.com</a></td>
</tr>
<tr>
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<td>Data collection supervisor</td>
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<tr>
<td>Walter Videtta, MD</td>
<td>President, LABIC</td>
<td><a href="mailto:wvidetta@ar.inter.net">wvidetta@ar.inter.net</a></td>
</tr>
<tr>
<td>Freddy Sandi Lora, MD</td>
<td>Bolivia Country Coordinator</td>
<td><a href="mailto:fresandi@hotmail.com">fresandi@hotmail.com</a></td>
</tr>
<tr>
<td>Luis Arturo Lavadenz Gomez, MD</td>
<td>Principal Investigator – Viedma</td>
<td><a href="mailto:arturo_lavadenz@msn.com">arturo_lavadenz@msn.com</a></td>
</tr>
<tr>
<td>Vianka Valle Eduardo, MD</td>
<td>Co-investigator,</td>
<td><a href="mailto:V_anka@hotmail.com">V_anka@hotmail.com</a></td>
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<tr>
<td><strong>Hospital San Juan de Dios – Santa Cruz de la Sierra, Bolivia</strong></td>
<td></td>
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<tr>
<td>Jesusa Torrez, Nurse</td>
<td>Co-investigator, Outcomes data collection</td>
<td>Calle Colombia N° 815 Cochabamba - Bolivia.</td>
</tr>
<tr>
<td>Victor Alanis, MD</td>
<td>Principal Investigator – San Juan de Dios</td>
<td>Urb. remamzo 2 el paseo c.a.5. Santa Cruz de la Sierra, Bolivia</td>
</tr>
<tr>
<td>Katy Panozo Gonzalez, MD</td>
<td>Co-investigator, Acute care data collection</td>
<td>Alto san pedro: calle Cnl. Franco final 16</td>
</tr>
<tr>
<td>María Luisa Chávez Bonilla, Nurse</td>
<td>Co-investigator, Outcomes data collection</td>
<td>Perto Rico, Km 35</td>
</tr>
<tr>
<td><strong>Hospital Japones – Santa Cruz de la Sierra, Bolivia</strong></td>
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<tr>
<td>Gustavo la Fuente Zerain, MD</td>
<td>Principal Investigador – Japones</td>
<td>Urbari, Av saturno 115 Santa Cruz de la Sierra, Bolivia</td>
</tr>
<tr>
<td>Sergio Peca Charcosi</td>
<td>Co-investigator, Acute care data collection</td>
<td>Calle 1, numero 37. Barrio las charcas</td>
</tr>
<tr>
<td>Maria del Carmen Valverde</td>
<td>Co-investigator, Outcomes data collection</td>
<td>Barrio virgin del Lujan Calle 6</td>
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<tr>
<td><strong>Hospital San Juan de Dios – Tarija, Bolivia</strong></td>
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<tr>
<td>Roberto Merida Maldonado, MD</td>
<td>Principal Investigator</td>
<td>Santa Cruz final s/n</td>
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<tr>
<td>Name and Position</td>
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<tr>
<td>Ivar Donoso Molina, MD</td>
<td>Co-Investigator</td>
<td>591 70223 687</td>
</tr>
<tr>
<td>Maria Isabel Navajas Krutzfeldt, MD</td>
<td>Study Coordinator, Acute care data collection</td>
<td>591 70213 959</td>
</tr>
<tr>
<td>Rital Isabel Cervantes Zambrana, MD</td>
<td>Outcomes data collection</td>
<td>591 70212 706</td>
</tr>
<tr>
<td>Edison Manuel Jibaja Vega</td>
<td>Principal Investigator</td>
<td>Colombia y Yaguachi s/n Quito, Ecuador</td>
</tr>
<tr>
<td>Dr, Diego Fabian Barahona Pinto</td>
<td>Study Coordinator, Acute care data collection</td>
<td>593-2-25306 05</td>
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<tr>
<td>Dra. Viviana Nathaly Medranda Pisco</td>
<td>Outcomes data collection</td>
<td>593-2-24470 7</td>
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<td>Dra. Katty Alexandra Trelles Vasquez</td>
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<td>25077 04</td>
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<tr>
<td>Drl Luis Gonzalez</td>
<td>Principal Investigator</td>
<td>Loja 700 y Escobedo Guayaquil, Ecuador</td>
</tr>
<tr>
<td>Dr. Saul Zabala</td>
<td>Study Coordinator</td>
<td>593-8-427-8893</td>
</tr>
<tr>
<td>Arturo Flor Mosquera</td>
<td>Follow-up</td>
<td>593-9-931-7161</td>
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**DSMB**

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<th>Name and Position</th>
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<tr>
<td>M. Ross Bullock, MD, PhD</td>
<td>DSMB Chair</td>
</tr>
<tr>
<td>Lidia Artiola, PhD</td>
<td>Clinical Neuropsychology</td>
</tr>
<tr>
<td>Ramon Diaz-Arrastia, MD, PhD</td>
<td>Neurology</td>
</tr>
<tr>
<td>Mary Foulkes, PhD</td>
<td>Biostatistics</td>
</tr>
<tr>
<td>Jose Suarez, MD</td>
<td>Neurocritical</td>
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</tbody>
</table>
University of Washington [UW] is the application institution. The Principal Investigator, Randall Chesnut, MD, the Project Director, Nancy Carney, PhD, the Primary Statistician, Nancy Temkin, PhD, and the Primary Neuropsychologist, Sureyya Dikmen, PhD, are faculty in the Department of Neurological Surgery at U.W.

University of Washington [UW] Biostatistics Center [BC] will serve as the U.S. Data Center, using their system for data management. The BC has forms, protocols, equipment, and staff in place that will be able to serve the needs of the multi-center trial.

University of California San Diego [UCSD] will subcontract to UW and serve as the trainers and auditors of the neuropsychological evaluations which are a part of our outcome assessment. UCSD personnel have translated and normed a neuropsychological test battery for monolingual Spanish speakers and have used it in Latin countries. They have trained and managed people in other countries in the administration and scoring of these tests. They will go to Bolivia and Ecuador and train the team that will deliver this battery of tests. They will do ongoing quality checks throughout data collection.

Fundacion ALAS will subcontract to UW and serve two purposes. First, ALAS will receive and manage all funds that will be used in Latin America to carry out the R01. ALAS Director and personnel have established direct reporting systems to UW sponsored projects personnel.

Second, ALAS will be the Latin American Data Center. All data will be collected in paper form at each study site. The paper forms will be delivered to ALAS in Rosario, Argentina. Two ALAS personnel will double-enter the data into Access which will be transmitted directly to the BC at University of Washington.

Latin American Brain Injury Consortium [LABIC] will provide the network of hospitals and professionals that will be the study sites, key investigators, data collectors, and study coordinators for this project. They will subcontract directly to Fundacion ALAS for reimbursement for their services.

The study hospitals will be sites for treating the severe TBI patients, and for enrolling them into the study and collecting data at the acute care and outcomes levels. All study hospitals and study personnel are members of LABIC.

2.D. TRAINING PLAN

A comprehensive training plan is being carried out in 4 phases:

Phase I. – Initial Meetings

Two initial meetings were conducted in Bolivia with the research teams in the 3 study hospitals, one in May and one in November of 2007. In May, the study protocol was reviewed, study staff were interviewed, needs were assessed in each hospital, and a basic structure for training and communication was established. This meeting was directed by Drs. Chesnut, Carney, Rondina, Videtta, Lujan, and Petroni. In November an extended team visited Bolivia, including Drs. Temkin and Dikmen, and James Pridgeon and Kelley Chadduk from the U.W. administrative team. By this time, all study personnel had been identified for each hospital, so the 2-day meeting was attended by a total of 45 people. Each phase of the study, the flow of the patients, the procedures for
randomization, blinding, data collection and transfer, lines of communication, etc. were described and discussed in detail.

**Phase II – Study-specific, On-site Trainings**

Drs. Chesnut, Rondina, Petroni and Videtta have conducted two on-site trainings in the protocol for using the ICP monitor, and for treatments based upon information from the monitor. They will return to Bolivia two more times before the beginning of the study to provide two more such trainings. A similar procedure will be followed for the two new sites in Tarija, Bolivia and Quito, Ecuador.

Drs. Petroni and Lujan are currently training the staff at each site in study procedures. This includes comprehensive sessions that cover all the study areas: research participant identification, inclusion and exclusion criteria, consenting, randomization processes, scoring the Glasgow Coma Scale, CT categorization, and completing all baseline and hospitalization forms and data flow systems. At the completion of each 2 to 3 day training session, practice forms are completed using real patient data.

Outcomes assessment training was initiated at the all-team meeting in November. The neurobehavioral examiners will be trained and certified by Dr. Mariana Cherner at the University of California in San Diego (UCSD) who is a bilingual neuropsychologist with experience in cross cultural neuropsychological studies. After the examiners are certified, the results of their first 10 tested cases will be reviewed at UCSD to ensure valid testing. Subsequently 10% of their cases will be reviewed to prevent drifting. Dr. Dikmen will oversee the training, data collection and quality control of the neuropsychological and functional status measures.

**Phase III – General Training – Fundamentals of Research**

Dr. Carney is the P.I. of a trauma research training program in Argentina funded by FIC, and Drs. Petroni and Lujan are instructors in that program. The curriculum of this training program is being used to teach all of the investigators in this study the fundamentals of clinical research. The training is being provided both in person – during the on-site study-specific training sessions (Phase II), and also virtually. All lectures are translated and will be available on the private pages of the study website. Study staffs’ ongoing review of the posted material will be monitored.

**Phase IV – Follow-up Training**

Follow-up training sessions will be conducted using the Eluminate software provided by the FIC and now installed on all of the computers at the study sites. These trainings will be managed by Drs. Petroni and Lujan. All study staff will be required to participate in the follow-up sessions. In addition, inter-rater reliability will be tested every month initially, and every 3 months after we are confident that the reliability is adequate.

**2.E. COMMUNICATIONS PLAN**
Figure 3. illustrates the Communication Plan. Central to communication are Drs. Petroni and Lujan. They have been the key trainers in this project, and were the data collectors for previous research projects conducted by this team. Together they will be on site in Bolivia 20 out of every 30 days for the first full year of the study. All study staff will have active and direct communication with Drs. Petroni and Lujan. Depending upon the nature of the questions or needs, Drs. Petroni and Lujan will direct all questions and requests to the appropriate entity – either the country coordinator, Fundacion ALAS, LABIC, or the University of Washington. The solid lines in Figure 3 illustrate this formal communication structure.

The dotted lines illustrate the underlying, informal communications structure. We have stressed throughout all set-up phases of this project that all study staff must feel free to communicate with each other as needed. While formal lines of communication ensure stability and structure, informal lines of communication ensure a sense of trust, partnership, and openness that is essential to the success of this project.

Our tools for communication include in-person, e-mail, telephone, and a web-based system that will include chat capacity, daily updates of the protocol and data definitions, and postings of the status of all study sites.

Formal reporting will occur daily through web-based postings of patient accession status at each site, as well as through pre-specified monthly, quarterly, and annual reports.

**Figure 4. Communications Plan**
2.F. RECRUITMENT PLAN

When a TBI patient is received in the participating hospital, he/she will be evaluated by an emergency department physician and by the in-house on-call neurosurgeon and identified as suitable for the study if the person sustained a traumatic brain injury and has a Glasgow Coma Scale score ≤ 8 (or if intubated, Motor ≤ 5). Immediate contact will be made with the 24-hour-on-call study coordinator, who will confirm eligibility and request consent from the patient’s legally authorized representative. Eligibility will be confirmed using the Screening Form. All potential participants will be documented on the screening form.

2.G. STUDY FLOW

An overview of the study that describes the study’s major steps is provided in Figure 5.

2.H. SCREENING AND ELIGIBILITY CRITERIA
The screening form includes a screening identification number, patient initials, date of screening, information about the person’s injury and its severity, study inclusion and exclusion criteria and consent status. Potential participants will be identified by a unique screening number that will be assigned with a numeric code identifying the hospital and the participant. The participant number is assigned chronologically. Potential participants who meet all inclusion criteria and have no exclusion criteria will be approached for informed consent onto the study.

**Eligibility Criteria**

**Inclusion Criteria**
- Admission to study hospital within 24 hours of injury
- Closed head trauma
- GCS ≤ 8 on admission or if intubated, GCS Motor ≤ 5, within first 48 hours after injury
- No foreign object in brain parenchyma
- Randomized:
  - within 24 hours of injury [for patients with GCS ≤ 8 on admission]
  - within 24 hours of deterioration [patients deteriorating to GCS ≤ 8 within 48 hours of injury]
- Age > 12

**Exclusion Criteria**
- GCS of 3 with bilateral fixed and dilated pupils and/or decision to not actively treat prior to enrolment into study
- No beds available in ICU
- No ICP monitor available
- Pregnancy
- Prisoner
- No consent
- Non-survivable injury
- Other (e.g., Pre-injury life expectancy under 1 year)
- Pre-existing neurological disability that would not allow follow-up
Figure 5 Study Flow

TBI admission

- GCS ≤ 8?
  - Eligible by I/E Criteria?
    - Exclude
  - Consents to RCT?
    - ICU bed available ≤ 24 hrs
    - ICU bed available?
      - Randomisation in ICU ≤ 24 hrs post injury
        - Enter into RCT
    - Consents to Obs?
      - Close screening form
      - Exclude
    - Open screening form

- Worsens to ≤ 8 within 24 hrs?
2.1. INFORMED CONSENT AND HIPAA

When a patient is identified as eligible for the study, immediate contact will be made with the 24-hour on-call study coordinator, who will confirm eligibility. Severe TBI patients are often unconscious and unable to provide consent until they improve. The study coordinator will come to the bedside of the candidate patient with the attending physician. The physician will introduce the family to the study coordinator. They will make sure the family knows the credentials of the study coordinator, and say that this person is going to discuss a research program that is being conducted, and that this person is qualified to do so. The study coordinator will take the family to a place where they can talk confidentially, and will initiate the conversation by finding out what, if anything, the family knows about research. Every relevant aspect of the project will be described. The study coordinator will stop frequently, ask if there are any questions, and request that the family repeat back in their own words what is being discussed, to make sure they understand.

The study coordinator will explain that there is a possibility that the patient’s brain is swelling inside the skull, and if so, the patient could become worse. They will say that there is a technique for knowing if the brain is swelling, and procedures and medicines that could help. They will then explain in detail the placement of the ICP monitor. They will explain that in a small percentage of patients, the placement of the monitor could cause additional damage or infection. The potential advantages of using or not using the monitor will be described, and the care of the patient, with and without the monitor, will be described. The study coordinator will be especially careful to assure the family that they are free to decline consent without consequences, and that they can withdraw consent at any time. The family will be told even if they say yes, when the patient regains consciousness they will have a chance to agree or refuse to be in the study.

Family members will be provided with contact information for the study coordinator, local co-investigator, Latin American Principal Investigator, and the local Ethical Committee. Written consent will be obtained in the presence of a witness. For patients aged 13 to 20 years, the parent or legal guardian will be approached for consent, and Child Assent will be obtained when the child regains consciousness.
A sample Consent Form is located in Appendix A and a sample Child Assent Form is in Appendix B.

Although HIPAA procedures do not apply in Latin America, participant confidentiality is taken very seriously and all study staff have been extensively trained in the importance and procedures of patient confidentiality. A list linking patient identity with the patient number will be maintained electronically, in a file separate from the case report forms, in a password protected file. All hard copy case report forms will be kept in a locked cabinet in the study hospitals. One copy will be sent to the data center in Rosario, where data entry will occur. These copies will also be maintained in locked cabinets.

2.J. RANDOMIZATION

The master randomization list will be generated by the statistician/database manager at the Data Center at UW (Jason Barber). Randomization will be stratified by site, age (≤40 vs. >40), and GCS (3-5 or if intubated GCSm 1-2 vs GCS 6-8 or if intubated GCSm 3-5). Each site will be provided with an Access database which will be installed on a computer on site that is accessible to all study staff who are authorized to randomize a case. The database will have preloaded 4 password-protected tables with randomization codes for the 4 strata for that site. The tables will contain assignments blocked to ensure near balance on treatment assignment. The site personnel will enter the subject’s ID, age, and total GCS or motor GCS as well as the initials of the person randomizing the case (see Figure 6 for a copy of the randomization screen). They will also verify that the site has a functioning monitor and an ICU bed available for the subject. This information and the date and time will be captured on the database. The program will retrieve the assignment for the next case in the appropriate stratum and display the assignment on the screen.

Figure 6. Randomization Screen
In case the site computer is unavailable, the site will call the emergency cell phone which will be carried 24/7 by an investigator from the CC. The emergency CC investigator will use the CC version of the site randomization program if it is available or else flip a coin and communicate the assignment to the site and send out e-mail notification to the site, CC, and DC. The statistician/database manager at the Data Center at UW will fill in the assignments made manually in the next slot for the treatment assignment given in the appropriate stratum and send the Access database back to the site. Access will then randomize future cases into the first unfilled assignment in the stratum, even though later lines in the randomization database have been filled in. Subjects will be randomized after consent without checking for contraindications. Any contraindications that occur must be corrected as rapidly as possible and catheter implantation performed for those randomized to the ICP monitor group (as noted in section A1a of the treatment protocol). Any person who has been randomized remains in the study in the group they were randomized to. Even if:

- The patient dies
- They never got the assigned treatment
- They got the wrong treatment
- The family decides to withdraw study treatment or all treatment
- The family decides to move the patient to a non-study hospital
- The family decides to take the patient home

There is no need to have the family sign another consent. Remind them that the study very much needs to know how the patient is doing at 3 and 6 months. This is true regardless of their
decisions and regardless of how the patient is doing. Thank them (in advance) for their willingness to provide this information. (The family or patient can decide to withdraw from the study entirely including all follow-up but if they say they want to withdraw, please clarify whether they mean they are not willing to provide any follow-up information and are not willing to allow use of information that is put into medical records because of clinical care),

2.K. STUDY INTERVENTION

Interventions, Administration, and Duration

Treatment arms. There are two arms in this study, the ICP Monitor Group and the Standard Care Group. Management of patients who are randomized to the ICP Monitor Group will be based specifically on the presence of intracranial hypertension and follow the Guidelines for the Management of Severe Brain Injury. Management of patients who are randomized to the Standard Care Group will be consistent with the agreed upon guidelines presently being used in the three study hospitals.

We strongly suggest using these interventions whenever available and/or possible

a. Patient monitoring measures
   i. Place patient on mechanical ventilation (VM)
   ii. Place continuous SaPO2 monitor and EtCO2 monitors
   iii. Insert indwelling urinary catheter to monitor urine output
   iv. Insert arterial catheter for arterial mean pressure monitoring
   v. Insert central venous catheter for infusion of solutions and central venous pressure monitoring.
   vi. Monitor neurological clinical status each hour
      1. Pupils
         a. GCS
         b. etc.
   vii. Brain CT
      1. To evaluate evolution 48 hours after the admission CT
      2. To evaluate evolution 5-7 days after the admission CT
      3. p.r.n.
b. General measures
   
i. Head positioning 30º
   
ii. Head and neck in neutral position and aligned
   
iii. Avoid hyperthermia
      
1. Defined as central temperature $\geq 38 ^\circ C$
   
a. Non-drug measures (cooling)
   
b. Dipirona (Metamizole sodium)
   
iv. Early enteral nutritional support
   
1. Before 48 hours
   
2. 25 Kcal/kg weight
   
v. Pharmacologic prophylactic of post traumatic seizures
   
1. Phenytoin (IV or PO)
   
A. Load and maintenance dose as is being giving in each hospital
   
vi. Gastric bleeding prophylaxis
   
1. Ranitidine or Omeprazol
   
vii. Avoid decubitus lesions
   
viii. Deep venous thrombosis prophylaxis
   
ix. Frequent tracheal suctioning with sterile technique to prevent pulmonary infections
   
c. Routine CT scans
   
1. First CT: on Hospital admission
   
2. Second CT: 48 hours after the first CT
   
3. Third CT: 5-7 days after the first CT

**GUIDELINES FOR THE MANAGEMENT OF SEVERE TRAUMATIC BRAIN INJURY PATIENTS:**

**Standard Care Group**

The guidelines are presented below and are also summarized in Figures 7 and 8.

Figure 7.
Figure 7

Patient Admission

General Resuscitation

Basic TBI Therapy

Admission CT

¿Swelling?

No

Continue Basic Therapy

48 hr CT

¿Swelling?

No

Consider awakening

Taper ICP Therapy

Yes

Add basic ICP therapy
 Mild hyperventilation (PaCO₂ 30-35) (Option)
 Hyperosmolar therapy - scheduled dosing

48 hr CT

¿Swelling?

No

¿Swelling?

Yes

Continue basic ICP Therapy

5th day CT

¿Swelling?

No

F/U CT

Yes

Escalate ICP therapy
- Neuroworsening protocol
- Consider 2nd Tier Treatment

Consider 2nd Tier Treatment

Protocol can be modified according to:
- Clinical judgement (e.g. early escalation)
- Mass lesion (post-op protocol care based on CT)
- Neuroworsening (treated per protocol)
This protocol could be modified:

- By clinical judgment (i.e., DC or barbiturates could be used earlier on)
- Mass lesion on CT scans (procedure to evacuate if it is indicated and then continuing with the protocol based on CT findings)
- Neuroworsening (NW) whenever occurs should be treated as follows (see next)

Figure 8.
Figure 8

Neuroworsening defined as:
- Decrease in the motor GCS > 2
- New loss of pupil reactivity
- Development of pupil asymmetry of > 2 mm
- New focal motor deficit
- Herniation syndrome

Emergent therapy
- Adjust analgesia/sedation
- Hyperosmolar treatment
- Hyperventilation

¿Emergent CT available?  Yes → ¿Surgical lesion?  Yes → Surgery

¿Emergent CT available?  No

Readdress CT Availability

¿Emergent CT available?  No

Initiate Neuroworsening Therapy:
- Strongly consider ventricular drainage if possible
- Increase hyperosmolar agent dosing
- Add/increase hyperventilation
- Minimize duration
- Add scheduled furosemide
- Consider high dose barbiturates
- Consider decompressive craniectomy

¿Response to treatment?  Yes → Continue new regimen

¿Response to treatment?  No

Evaluate futility versus decompressive craniectomy

Resume prior ICP therapy
1. Patient monitoring measures: We strongly suggest using these interventions whenever available and/or possible.
   a. Place continuous SaO2 and EtCO2 monitors
   b. Insert indwelling urinary catheter to monitor urine output
   c. Insert arterial catheter for arterial pressure monitoring
   d. Insert central venous catheter for infusion of solution and central venous pressure monitoring
   e. Monitor clinical neurological status each hour
      i. Pupil size and reactivity
      ii. GCS
   f. Obtain **brain** CT
      i. To evaluate evolution 48 hours after the admission CT
      ii. To evaluate evolution 5-7 days after the admission CT
      iii. As needed based on patient clinical condition

2. General management measures
   a. Place patient on mechanical ventilation, goal SaO2 > 90% and PaO2 > 60 mmHg
   b. Use adequate sedation and analgesia
      i. Acceptable medications include benzodiazepines, opioids, propofol and low dose barbiturates
         1. Low dose barbiturate dosing:
            a. **Thiopental (Pentothal)** 1-2 mg/kg/hr IV continuous infusion (approx 1.5-3 gm/day)
   c. Maintain head of bed at 30°
   d. Maintain head and neck aligned and in neutral position
   e. Actively monitor body temperature and treat hyperthermia
   f. Hyperthermia defined as central temperature $\geq 38^\circ$C
      i. Non-pharmaceutical cooling measures
         1. Cooling blanket, ice packs
      ii. Pharmaceutical cooling measures
1. Dipirona (Metamizole sodium)

   g. Early enteral nutritional support
      i. Initiate within 48 hours of injury
      ii. Give 25 Kcal/kg patient weight per day

   h. Pharmacologic prophylaxis for early post traumatic seizures
      i. Phenytoin (IV or PO)
         1. Loading and maintenance doses as per individual hospital guidelines
         2. Continue for 7-28 days
      i. Gastric bleeding prophylaxis
         i. Ranitidine or Omeprazole (IV or PO)
            1. Administer as per individual hospital guidelines

   j. Prevent decubitus lesions and treat as indicated

   k. Deep venous thrombosis prophylaxis

l. Frequent tracheal suctioning with sterile technique to prevent pulmonary infections

   m. Maintain Hb ≥ 7 mg/dL, use blood transfusions as needed

3. CT scans
   a. First CT: upon hospital admission
   b. Second CT: 48 hours after the first CT
   c. Third CT: 5-7 days after the first CT
   d. Additional CT scans as needed based on patient clinical condition

4. Treatment Goals for adequate cerebral perfusion and oxygenation
   a. Avoid hypotension - systolic blood pressure (SBP) > 90 mmHg, mean arterial pressure (MAP) > 70 mmHg

   b. Arterial blood oxygen saturation (SaO2) > 90% or PaO2 > 60 mm Hg

5. Initial therapeutic interventions
   a. Normal saline solution (0.9% NaCl) to obtain a CVP of 10-12 cmH2O
b. Vasopressors when necessary to obtain a SBP > 90 mmHg or mean arterial pressure (MAP) > 70 mmHg

c. Maintain PaCO2 35-40 mmHg if CT is normal
   i. In Cochabamba, correct for altitude and maintain PaCO2 32-36 mmHg

d. If a space-occupying lesion exists, surgical evacuation is indicated if possible

6. Specific therapeutic interventions—Standard (Non-Monitored) Therapy

a. After optimized sedation and analgesia, hyperventilation and hyperosmotic therapy should be started simultaneously if there is evidence of edema on CT, as indicated as following:

   1. Compressed peri-mesencephalic cisterns
   2. Midline shift
   3. Cortical sulcal compression / effacement

b. Mild hyperventilation
   i. Maintain PaCO2 30-35 mmHg (PaCO2 28-32 mmHg in Cochabamba)

c. Hyperosmolar/Hypertonic Therapy
   i. Mannitol should be used first except in the following situations (HHH):
      a. Arterial Hypotension
      b. Hypovolemia
      c. Hyponatremia

   2. Hyperosmolar (Mannitol) therapy guidelines and dosing
      a. Plasma osmolarity or tonicity should be monitored at least every 12-24 hours
         i. Plasma osmolarity or tonicity should be calculated using the following formulae:
            1. Osmolarity = 2 * (Na) + (BUN/2.8) + (Glucose/18)
            2. Tonicity = 2 * (Na + K) + (Glucose/18)
         ii. Hyperosmolar (Mannitol) therapy should be suspended for plasma osmolarity > 320 or tonicity > 340
      b. Mannitol dosing regimen using 20% Mannitol bolus:
1. 100ml (20gm) IV every 3-4 hours for the first 3 days, then

2. 80ml (16gm) IV every 3-4 hours on day 4, then

3. 60ml (12gm) IV every 3-4 hours on day 5, then

4. 40ml (8gm) IV every 3-4 hours on day 6 and suspend

3. Hypertonic saline therapy guidelines and dosing
   a. Hypertonic saline should only be used in cases of HHH as described above
   b. Plasma osmolarity or tonicity and serum sodium should be monitored at least every 12-24 hours
      i. Plasma osmolarity or tonicity should be calculated using the following formulae:
         1. Osmolarity = 2 * (Na) + (BUN/ 2.8) + (Glucose/18)
         2. Tonicity = 2 * (Na + K) + (Glucose/18)
      ii. Hypertonic saline therapy should be suspended for plasma osmolarity > 360 or tonicity > 380 or serum sodium > 160
   c. Hypertonic saline dosing regimen using 5%NaCl solution bolus:
      i. 80ml normal saline (0.9%NaCl) + 20ml 20%NaCl = 100ml 5%NaCl solution
      ii. 100ml IV every 4-12 hours for 6 days then suspend
   d. High dose IV barbiturates
      i. Use after hyperventilation and hyperosmolar/hypertonic therapies
      ii. Should be used if second CT shows evidence of compressed PMC
      iii. Dosing: Thiopental (Pentothal) 2.5-4 mg/kg/hr IV continuous infusion for 3 days (approx 4-6 gm/day)
   iv. Hypotension must be avoided

7. Neuroworsening requires increased therapeutic intensity level, including decompressive craniectomy when necessary and available. Any one or all of the following therapeutic interventions should be utilized based on patient conditions.
a. Neuroworsening defined as:

1. Decrease in the motor GCS ≥ 2
2. New loss of pupil reactivity
3. Interval development of pupil asymmetry of ≥ 2mm
4. New focal motor deficit
5. Herniation syndrome

ii. Hypertonic therapy:

1. **Additional** mannitol dosing regimen using 20% Mannitol bolus:
   
i. 200ml (40gm) IV every 3-4 hours for 1 day, then
   ii. 100ml (20gm) IV every 3-4 hours for 2 days, then
   iii. 80ml (16gm) IV every 3-4 hours on day 4, then
   iv. 60ml (12gm) IV every 3-4 hours on day 5, then
   v. 40ml (8gm) IV every 3-4 hours on day 6 and suspend

b. High dose mannitol at 0.5 – 1 gm/kg per dose should be used in the case of acute neurological deterioration and as a temporizing measure prior to decompressive craniectomy if there is no response to medical management. The above duration of treatment (6 days) should be followed only when neurosurgical intervention is not available.

c. Contraindicated in patients with HHH

   i. **Use hypertonic saline**

d. Hypertonic saline – **doses as above**

iii. Increase hyperventilation (HV)

1. Maintain PaCO2 of 25-30 mmHg (PaCO2 22-28 mmHg in Cochabamba)
2. Use for shortest time period possible to reverse neurological deterioration
3. If no response, stop HV and use barbiturates

iv. High dose IV barbiturates
1. Thiopental (Pentothal) 2.5-4 mg/kg/hr IV continuous infusion for 3 days

2. Hypotension must be avoided
   v. Furosemide 20mg IV every 8 hours
   vi. Head CT is strongly suggested if possible

8. Second tier therapy to be considered in salvageable patients under conditions such as:
   a. To be considered in case of:
      i. Persistent neuroworsening not responding to an increased therapeutic intensity level (as indicated above). CT is recommended, if possible.
      ii. Follow-up CT (eg day 5 CT) showing Inadequate response to treatment such as persistent edema

b. Primary options
   i. Decompressive craniectomy
   ii. High dose IV barbiturates:
      1. Thiopental (Pentothal) 2.5-4 mg/kg/hr IV continuous infusion (approx. 4-6 gm/day)
      2. Hypotension must be avoided

c. Other options
   i. Hyperventilation to maintain PaCO2 25-30 mmHg (PaCO2 22-28 mmHg in Cochabamba), use for shortest time period possible to reverse neurological deterioration
   ii. Hypothermia
   iii. Lund therapy

9. Management following decompressive craniectomy
   a. Use adequate sedation and analgesia
   b. Mild hyperventilation to maintain PaCO2 30-35 mmHg (PaCO2 28-32 mmHg in Cochabamba)
   c. Hyperosmolar/hypertonic therapy
      i. Use after sedation/analgesia is optimized
      ii. Mannitol should be used first, except in the following situations (HHH):
a. Arterial Hypotension

b. Hypovolemia

c. Hyponatremia

2. Mannitol therapy guidelines and dosing

a. Plasma osmolarity or tonicity should be monitored at least every 12-24 hours

b. Plasma osmolarity or tonicity should be calculated using the following formulae:

1. Osmolarity = 2 * (Na) + (BUN/2.8) + (Glucose/18)

2. Tonicity = 2 * (Na + K) + (Glucose/18)

ii. Hyperosmolar (Mannitol) therapy should be suspended for plasma osmolarity > 320 or tonicity > 340

c. Continue the pre-operative mannitol dosing regimen using 20% Mannitol bolus:

i. 100ml (20gm) IV every 3-4 hours for the first 3 days, then

ii. 80ml (16gm) IV every 3-4 hours on day 4, then

iii. 60ml (12gm) IV every 3-4 hours on day 5, then

iv. 40ml (8gm) IV every 3-4 hours on day 6 and suspend

3. Hypertonic saline therapy guidelines and dosing

a. Hypertonic saline should only be used in cases of HHH as described above

b. Plasma osmolarity or tonicity and serum sodium should be monitored at least every 12-24 hours

i. Plasma osmolarity or tonicity should be calculated using the following formulae:

a. Osmolarity = 2 * (Na) + (BUN/2.8) + (Glucose/18)

b. Tonicity = 2 * (Na + K) + (Glucose/18)
2. Hypertonic saline therapy should be suspended for plasma osmolarity > 360 or tonicity > 380 or serum sodium > 160

c. Continue the pre-operative hypertonic saline dosing regimen using 5%NaCl solution bolus:
   i. 80ml normal saline (0.9%NaCl) + 20ml 20%NaCl = 100ml 5%NaCl solution
   ii. 100ml IV every 4-12 hours for 6 days then suspend

d. High dose IV barbiturates
   i. Use after hyperventilation and hyperosmolar/hypertonic therapies
      1. Dosing: Thiopental (Pentothal) 2.5-4 mg/kg/hr IV continuous infusion for 3 days
      2. Hypotension must be avoided

e. Obtain head CT within 24 hours following decompressive craniectomy
   i. If edema improved, stop sedation, hyperventilation, hyperosmolar/hypertonic therapy, and high dose barbiturate therapy and evaluate neurologic exam and GCS
   ii. If edema not improved or worse, continue sedation, hyperventilation, hyperosmolar/hypertonic therapy, and high dose barbiturate therapy as above

10. Contraindicated treatments
   a. Corticosteroids for brain injury treatment
   b. Use of anticonvulsants for prophylaxis of late epilepsy (beyond 28 days)

Guidelines for the Management of Severe Traumatic Brain Injury Patients:

ICP Monitor Group

1. Required patient monitoring measures
   a. Place ICP monitor
      i. If the initial placement of the ICP monitor is delayed due to contraindications (eg coagulopathy), then the contraindication must be corrected as rapidly as possible and catheter implantation be performed as soon as the contraindication is removed.
ii. In the case of an ICP monitor failure due to catheter breakage, unintentional removal of catheter, or any other damage or compromise of catheter every attempt should be made to replace the catheter with a new properly functioning one.

iii. Every attempt should be made to insert a new ICP monitor following a cranial operative procedure.

2. Additional patient monitoring measures: We strongly suggest using these interventions whenever available and/or possible.
   a. Place continuous SaO2 and EtCO2 monitors
   b. Insert indwelling urinary catheter to monitor urine output
   c. Insert arterial catheter for arterial pressure monitoring
   d. Insert central venous catheter for infusion of solution and central venous pressure monitoring
   e. Monitor clinical neurological status each hour
      i. Pupil size and reactivity
      ii. GCS
   f. Obtain brain CT
      i. To evaluate evolution 48 hours after the admission CT
      ii. To evaluate evolution 5-7 days after the admission CT
      iii. As needed based on patient clinical condition

3. General management measures
   a. Place patient on mechanical ventilation, goal SaO2 > 90% and PaO2 > 60 mmHg
   b. Use adequate sedation and analgesia
      i. Acceptable medications include benzodiazepines, opioids, propofol and low dose barbiturates
         1. Low dose barbiturate dosing:
            a. Thiopental (Pentothal) 1-2 mg/kg/hr IV continuous infusion (approx. 1.5-3 gm/day)
   c. Maintain head of bed at 30°
   d. Maintain head and neck aligned and in neutral position
e. Actively monitor body temperature and treat hyperthermia
   i. Hyperthermia defined as central temperature $\geq 38^\circ$C
   ii. Non-pharmaceutical cooling measures
      1. Cooling blanket, ice packs
   iii. Pharmaceutical cooling measures
      1. Dipirona (Metamizole sodium)

f. Early enteral nutritional support
   i. Initiate within 48 hours of injury
   ii. Give 25 Kcal/kg patient weight per day

g. Pharmacologic prophylaxis for early post traumatic seizures
   i. Phenytoin (IV or PO)
      1. Loading and maintenance doses as per individual hospital guidelines
      2. Continue for 7-28 days

h. Gastric bleeding prophylaxis
   i. Ranitidine or Omeprazole (IV or PO)
      1. Administer as per individual hospital guidelines
   i. Prevent decubitus lesions and treat as indicated

j. Deep venous thrombosis prophylaxis

k. Frequent tracheal suctioning with sterile technique to prevent pulmonary infections

l. Maintain Hb $\geq 7$ mg/dL, use blood transfusions as needed

4. CT scans
   a. First CT: upon hospital admission
   b. Second CT: 48 hours after the first CT
   c. Third CT: 5-7 days after the first CT
   d. Additional CT scans as needed based on patient clinical condition

5. Treatment Goals for adequate cerebral perfusion and oxygenation
   a. ICP $\leq 20$ mmHg
b. Cerebral Perfusion Pressure (CPP) 50-70 mmHg

c. **Arterial blood oxygen saturation (SaO2) > 90% or PaO2 > 60 mm Hg**

6. **Initial Therapeutic Interventions**
   a. Normal saline solution (0.9% NaCl) to obtain a CVP of 10-12 cmH2O
   b. Vasopressors when necessary to obtain a systolic blood pressure (SBP) > 90 mmHg or mean arterial pressure (MAP) > 70 mmHg **prior to ICP monitoring** (use CPP after monitoring begins).
   c. Maintain PaCO2 35-40 mmHg if CT is normal
      i. In Cochabamba, correct for altitude and maintain PaCO2 32-36 mmHg.
   d. If a space-occupying lesion exists, surgical evacuation is indicated if possible

7. **Specific therapeutic interventions**—ICP Monitor with Elevated ICP Treatment algorithm. Use the following treatment interventions sequentially when ICP is elevated or not responding to basic treatment. Note that clinically significant ICP elevation (not resolving within 5 minutes) requires treatment, which should be reflected by an increase in the Therapeutic Intensity Level (TIL) for that hour. Failure of ICP response after 20 minutes should prompt further treatment.
   a. Maintain CPP between 50-70 mmHg
      i. Every effort should be made to insert an arterial line for continuous MAP monitoring
      ii. If arterial line cannot be placed then calculate MAP from non-invasive blood pressure monitoring every hour to calculate CPP
   b. Ventricular drainage should be considered if available. If an intraparenchymal catheter is already inserted, consider placing the ventricular drain separately. Drainage of intraventricular fluid should be intermittent, with removal of the smallest volume of fluid necessary to control intracranial pressure and used for the shortest period of time possible. It is suggested that drainage be for two minutes and the ventricular catheter then be clamped and the PIC rechecked. When both an intraparenchymal monitor and a ventricular catheter are present, the intraparenchymal device should be used to measure the pressure. Note that the ventricular catheter should be clamped when measuring the pressure using either monitor to ensure accuracy.
   c. Neuromuscular blockade should be used, suspend if ICP not responding
   d. Mild hyperventilation to maintain PaCO2 30-35 mmHg (PaCO2 28-32 mmHg in Cochabamba)
   e. Hyperosmolar/hypertonic therapy
i. Mannitol should be used first except in the following situations (HHH):

   a. Arterial Hypotension
   b. Hypovolemia
   c. Hyponatremia

2. Hyperosmolar (Mannitol) therapy guidelines and dosing

   a. Plasma osmolarity or tonicity should be monitored at least every 12-24 hours

      i. Plasma osmolarity or tonicity should be calculated using the following formulae:

         1. Osmolarity = \( 2 \times (\text{Na}) + (\text{BUN}/2.8) + (\text{Glucose}/18) \)

         a. Tonicity = \( 2 \times (\text{Na} + \text{K}) + (\text{Glucose}/18) \)

      ii. Hyperosmolar therapy should be suspended for plasma osmolarity > 320 or tonicity > 340

   b. Mannitol dosing regimen using 20% Mannitol bolus:

      i. For ICP elevation > 20 mmHg give 0.25-1 gm/kg 20% Mannitol bolus

      ii. Extra doses can be administered for sustained elevation of ICP if plasma osmolarity < 320

3. Hypertonic saline therapy guidelines and dosing

   a. Hypertonic saline should only be used in cases of HHH as described above

   b. Plasma osmolarity or tonicity and serum sodium should be monitored every 12-24 hours

      i. Plasma osmolarity or tonicity should be calculated using the following formulae:

         1. Osmolarity = \( 2 \times (\text{Na}) + (\text{BUN}/2.8) + (\text{Glucose}/18) \)

         2. Tonicity = \( 2 \times (\text{Na} + \text{K}) + (\text{Glucose}/18) \)
ii. Hypertonic saline therapy should be suspended for plasma osmolarity > 360 or tonicity > 380 or serum sodium > 160

c. Hypertonic saline dosing regimen using 5%NaCl solution bolus:

i. 80ml normal saline (0.9%NaCl) + 20ml 20%NaCl = 100ml 5%NaCl solution

ii. 100ml IV given over 1 hour, may repeat as needed for sustained elevations in ICP if plasma osmolarity < 360 and serum sodium < 160

f. When increasing the therapeutic intensity level obtain a CT scan if possible

8. Neuroworsening requires increased therapeutic intensity level, including decompressive craniectomy when necessary and available. Any one or all of the following therapeutic interventions should be utilized based on patient conditions.

a. Neuroworsening defined as:

1. Decrease in the motor GCS ≥ 2
2. New loss of pupil reactivity
3. Interval development of pupil asymmetry of ≥ 2mm
4. New focal motor deficit
5. Herniation syndrome

ii. Mannitol dosing regimen using 20% Mannitol bolus:

1. For ICP elevation > 20 mmHg give 0.25-1 gm/kg 20% Mannitol bolus
2. Extra doses can be administered for sustained elevation of ICP if plasma osmolarity < 320

iii. Increase hyperventilation (HV)

1. Maintain PaCO2 of 25-30 mmHg (PaCO2 22-28 mmHg in Cochabamba)
2. Use for shortest time period possible to reverse neurological deterioration

b. If no response, stop HV and use barbiturates

i. High dose IV barbiturates
1. Thiopental (Pentothal) 2.5-4 mg/kg/hr IV continuous infusion for 3 days

2. Hypotension must be avoided

   c. Head CT is strongly suggested if possible

9. Second tier therapy to be considered in salvageable patients under conditions such as:

   a. To be considered in case of:

      i. ICP not responding to first tier therapy

      ii. Persistent neuroworsening not responding to an increased therapeutic intensity level (as indicated above). CT is recommended, if possible.

      iii. Follow-up CT (eg day 5 CT) showing Inadequate response to treatment such as persistent edema

b. Primary options

   i. Decompressive craniectomy

   ii. High dose IV barbiturates:

      1. Thiopental (Pentothal) 2.5-4 mg/kg/hr IV continuous infusion (approx. 4-6 gm/day)

      2. Hypotension must be avoided

c. Other options

   i. Hyperventilation to maintain PaCO2 25-30 mmHg (PaCO2 22-28 mmHg in Cochabamba), use for shortest time period possible to reverse neurological deterioration

   ii. Hypothermia

   iii. Lund therapy

10. Management following decompressive craniectomy

   a. Every attempt should be made to insert a new ICP monitor post-operatively, using techniques such as:

      1. Ventriculostomy

      2. Placing another bolt through an Harborview peninsula left along the margins of the craniectomy

   ii. If placement of the new ICP monitor is problematic, contact Gustavo Petroni, MD (mobile telephone +549-341-514-7543, home telephone +54-341-
b. Use adequate sedation and analgesia

c. Mild hyperventilation to maintain PaCO2 30-35 mmHg (PaCO2 28-32 mmHg in Cochabamba)

d. If ICP monitor is placed, treat ICP elevations > 20 as indicated above.

11. Intracranial pressure definitions

a. Treatable intracranial hypertension:
   i. ICP > 20 mmHg for > 5 minutes

b. Treatment failure:
   i. ICP not reduced to ≤ 20 mmHg within 20 minutes after a treatment intervention is initiated, and
   ii. Persistent elevation in ICP > 20 mmHg requires increase in therapeutic intensity level

12. Investigation of the patient with intracranial hypertension: After assessment of the following factors and initiation of appropriate interventions as indicated below, if the interventions are ineffective in reducing ICP, increase the therapeutic intensity level.

a. Check for factors that could increase ICP

b. Pain or agitation: consider increasing sedation/analgesia

c. Respiratory agitation, consider the following:
   i. Stopping the procedure
   ii. Lidocaine IV or ET (endotracheal tube)
   iii. Technique modification

d. Patient manipulation and rotation, consider the following:
   i. Stopping the procedure
   ii. Increasing sedation/analgesia
   iii. Technique modification

e. Endotracheal tube (ET) problems, consider the following:
   i. Change the ET holder
ii. Change the ET tube care techniques

f. Elevated intrathoracic pressure or elevated PEEP, consider the following:
   i. Drain any hemopneumothorax
   ii. Change ventilator technique

g. Raised intra-abdominal pressure: consider decompressive laparotomy

h. Evidence of seizures: consider evaluation and treatment

i. Check laboratory and vital signs values
   i. Hyperthermia: consider reducing the temperature to < 38°C
   ii. Increased PaCO2: consider increasing ventilatory rate
   iii. Hypoxia: consider increasing fraction of inspired oxygen
   iv. Abnormal CPP:
      1. Consider increasing MAP with fluids or vasopressors
      2. Consider reducing ICP with sedation and analgesia, hyperventilation, hyperosmolar/hypertonic therapy, and/or high dose barbiturates
   v. Hyponatremia: consider correcting plasma electrolytes

j. If you feel that the intracranial situation may have changed, obtain head CT when possible

13. ICP monitor removal:

   a. Consider removal of catheter if ICP \leq 20 \text{ mmHg} \text{ for } \geq 24 \text{ hours WITHOUT treatment}

   b. Confounding factors that may require longer monitoring:
      i. Hemodynamic instability
      ii. Need for intraoperative monitoring during extracranial surgery
      iii. “Clinical judgment”

14. Contraindicated treatments

   a. Corticosteroids for brain injury treatment
   b. Prophylactic hyperventilation
   c. Use of anticonvulsants for prophylaxis of late epilepsy (beyond 28 days)
2.L. BLINDING AND UNBLINDING

The acute care personnel are not blinded to study treatment. The outcome examiner will be given the contact information for each surviving case, but will not be told the treatment group. The outcome examiner will avoid the ICU, so they will not inadvertently see the treatment group. There is no reason the outcome examiner will be told the treatment group for any subject.

2.M. PARTICIPANT EVALUATION AND FOLLOW-UP

*The treatment variable* is assignment to management using the ICP monitor or not, and subsequent treatments based on information from the ICP monitor vs. information from clinical evaluation.

**Baseline variables** measured on admission and prior to randomization, that may be used to increase precision of the treatment comparison are:

- Demographics
- Abbreviated Injury Scores
- Head CT findings
- GCS
- Pupillary response
- Hypoxia
- Hypotension

**Explanatory variables** measured during ICU/hospital stay that may be used to better understand a treatment difference (or lack thereof) are:

- Clinical signs of increased Intracranial Pressure [Actual ICP values will also be collected in the ICP monitor group.]
- Therapeutic Intensity Level [TIL] and specific interventions employed
- Complications such as respiratory problems, sepsis and decubitus ulcers

**Outcomes**

**Primary outcome**

The primary outcome is a composite measure based on mortality, time to follow commands, Sum of Errors on the Galveston Orientation and Amnesia Test (GOAT), and the measures of functional level and neuropsychological performance. For each measure, the participants are ranked from 1 (worst) to n (best). To increase interpretability, the ranks are converted to percentiles, giving the percent at or worse than the participant’s score. For each person, the percentiles on the different measures are averaged. (O’Brien, 1984)

**The outcome variables** are:

- Mortality
• Time to follow commands (measured as time from injury to following simple commands as defined by a score of 6 on the motor scale of the GCS)
• Sum of Errors on the Galveston Orientation Amnesia Test (Levin et al., 1979),
• Functional status at 3 and 6 months
• Neuropsychological assessment at 6 months post injury (Table 2).

Functional Status: The Disability Rating Scale (DRS), and the Glasgow Outcome Scale Extended (GOS-E) will be used to measure functioning level in everyday life. The DRS (Rappaport et al 1982) is a brief measure of impairment, disability and participation. Only the assessment of eye opening, communication ability and motor response will be used in the analysis. The GOS-E (Wilson et al 1998) is the most commonly used measure of functional outcome in traumatic brain injury. This measure is the extension of the original Glasgow Outcome Scale, developed to address limitations with the original measure including unreliability and insensitivity to change. They have all been translated and used extensively in previous research in Latin America by this research group. Total scores on the GOSE and the DRS will be used in the composite measure.

Neuropsychological Test Battery: A battery of measures that examines important neuropsychological constructs which are sensitive to the integrity of brain functions, including traumatic brain injury, will be used (see Appendix C for a description of the measures and Appendix F for a copy of the tests). The selection of the neuropsychological outcome measures is based on the work of the University of Washington investigators’ prior work with TBI, the recommendations from the NINDS conference addressing outcome measurement in clinical trials involving moderate or severe traumatic brain injury [Clifton, 1992], and the measures selected for the Traumatic Brain Injury Clinical Trials Network of the National Center for Medical Rehabilitation Research. These are widely used published instruments with considerable psychometric work. In addition, through the international work of Drs. Robert Heaton and Mariana Cherner, these measures have been translated, adapted and normed for monolingual Spanish speakers, and have been used in Latin countries. This is an important benefit for this application. In choosing the measures, considerations were also given so that: 1) they cover different aspects of functioning that are clinically relevant and likely to be affected by head injury; 2) the measures possess good psychometric properties with respect to sensitivity, validity, and reliability, and 3) the measures are appropriate for use with a broad spectrum of head injury severity and likely to be responsive to treatment effects directed at improving outcome. Tests of a variety of cognitive functions are included because head injury can impact any or all of the functions depending upon severity. The areas assessed are clinically relevant because they are prevalent and a major cause of disabilities in this population after the acute stage of injury.

The neuropsychological domains and the measures used to examine them follows:

4. Mental State (Mini-Mental State Examination – Folstein et al., 1975; Strauss et al., 2006)
5. Working Memory (Paced Auditory Serial Addition Test – Heaton et al, 2004;)
7. Learning and Recall (Spanish Verbal Learning Test – Artiola i Fortuny et al., 2000 Brief Visuospatial Memory Test Revised -Benedict 1997, Cherner et al.2007; Strauss et al., 2006)

9. Motor Speed & Dexterity (Grooved Pegboard Test- Klove 1963)

Scores used in the Composite measure include the MMSE total score, the Spanish Verbal Learning Test total learning score and Long Delay Free Recall, the Brief Visuospatial Memory Test Revised total learning number correct and delay correct, WAIS III Digit Symbol and Symbol Search scores, Color Trails 2 time to completion, number correct on PASAT and three subcomposite scores where tests are grouped together to each form 1 variable to be entered into the composite. The first is composed of Grooved Pegboard dominant and non-dominant times. The second subcomposite is composed of Color Trails 1 and Trail Making Test Part A times to completion. The third subcomposite is composed of total correct on COWAT, Category Fluency Test for Animals, and Actions. Before ranking and entering the composite (or subcomposite) each neuropsychological test score will be regressed on age, sex and years of education to decrease variability. The residuals are ranked and entered onto the composite or subcomposite. Use of T-scores based on the norms for monolingual Spanish-speakers was considered, but uninjured Bolivians did not have scores with the expected mean of 50 and there was a substantial relationship between years of education and the T-scores for some measures.

Table 2. Measures of patient outcome

<table>
<thead>
<tr>
<th>Hospital Discharge</th>
<th>3 months post injury</th>
<th>6 months post injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>GOAT</td>
<td>GOAT</td>
</tr>
<tr>
<td>Time to follow commands</td>
<td>GOS-E²</td>
<td>GOS-E</td>
</tr>
<tr>
<td>GOAT¹</td>
<td>DRS³</td>
<td>DRS</td>
</tr>
<tr>
<td>Length of ICU stay⁶</td>
<td></td>
<td>Neuropsychological Battery⁵</td>
</tr>
<tr>
<td>Complications⁵</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ Galveston Orientation Amnesia Test  
² Glasgow Outcome Scale - Extended  
³ Disability Rating Scale  
⁴ See Appendix C for description of the measures.  
⁵ Outcomes used to test hypothesis 2.

2.N. PARTICIPANT RETENTION

In our study, a participant will be counted as retained when he or she completes the scheduled follow-up visit at 6-months post injury. All members of the study staff (e.g., Principal Investigator, Acute care Investigator and Follow up investigator) must make every effort to complete each patient’s study visit within the allowable visit window for the duration of the study. High rates of patient retention must be maintained throughout the study. Ideally, each Hospital should strive for 100% retention, but recognizing that this ideal may not always be attainable, each Hospital must make every effort to meet the target retention of at least 90% of enrolled study patients.
Retention Plan and Strategies
The Investigators of each Hospital will be responsible for establishing a patient retention plan. This plan should incorporate the following points:

- Be sure that family and the patient (when he/she is consented) fully understand what is involved in the follow-ups before enrolment. Information to be discussed includes, when the follow-up will occur, where it will occur, what will be covered and how long it will take.
- Emphasize the value of the patient’s involvement in the study during the informed consent process and subsequently at follow-up visits.
- Collect detailed contact information on the Personal and Contact Information Form with the family when the consent is signed or before hospital discharge. Update this information with the patient when he or she is enrolled in the study. The Personal and Contact Information Form collects detailed information for the patient including home address, home phone, work phone, cell phone and email address. It also collects the names and contact information for people who would know how to contact the participant in the future if he or she should move. Thorough completion of this measure will make future contacts more successful and maximize participant retention.
- At Hospital discharge the follow up investigator will receive this information in order to contact the patient at 3 and 6 months post injury. The Outcome Examiner will actively review each item on the Personal and Contact Information Form with the participant at the 3-month follow-up to determine whether the information is still current and will update anything that has changed.
- Use mapping techniques to establish the location of participant residences, if necessary.
- Use appropriate and timely visit reminder strategies, such as phone calls the week before a scheduled visit.
- Give the patient an appointment card with the scheduled contact or visit date and time noted.
- Set up appointments in the required visit window and try, whenever possible, to schedule it at the most convenient time for the participant. For example, if the participant is still attending outpatient appointments at the hospital then try to schedule the study appointment at a time that coincides with his other hospital appointment so only one trip is needed.
- Assist participants in making transportation arrangements if necessary.
- Offer in-person contact with participants in their homes or other community locations if the participant does not want to come in for the appointment.
- Make the visits as short and pleasant as possible for the patient. Do not keep participants waiting.
- It is recommended that each Hospital use a participant visit tracking sheet which will easily identify when participants’ scheduled visits are due.
- Prepare a calendar of scheduled visits for each enrolled patient, based on the injury date. Note the dates of all scheduled visits in the patient’s file for easy reference.

If an appointment is missed:

11. Attempt to re-contact and reschedule as soon as possible. Continue these efforts per the local retention plan until contact is made.

12. Try to contact the participant at different times of the day and the week, including evenings and weekends.
13. Use all available methods to contact the participant (e.g. phone, mail, home visits, and e-mail, calling other people listed on the Personal and Contact Information Form about how to reach the participant). Also make use of other available public information sources, such as phone and post office directories and other public registries.

The window for testing at each outcome assessment is ± 1 week. Every effort should be made to complete the assessment during the window. If the assessment cannot be done within the window, the outcome data collector should talk with the Monitor and the two, in consultation with Dr. Dikmen, will decide whether and how to pursue the subject further.

2.O. CONCOMITANT MEDICATIONS

No concomitant medications are restricted in the protocol.

2.P. SAFETY REPORTING

Adverse event reporting

The study intervention is conducted while the person is in the ICU, but adverse events that occur while the person is in the hospital should be included on the form. Adverse events do not need to be related to the study intervention to be reported. For each adverse event, fill in a line on the Complication form with the date the adverse event was first noted, the adverse event code (from the list below), a short description and the initials of the person filling out the line. **A line on the complication form should be filled in as soon as an adverse event is noted.** The form should not be given to the monitor to be taken for data entry until the person has been discharged. If a person has no adverse events, fill in 1 line of the adverse event form with the code 31 which represents ‘None’. **If an adverse event is thought to be possibly related to the study intervention, follow the procedure below for intervention related adverse events.** Adverse event codes 1-4 (ICP-monitoring-related complications) are always considered to be possibly intervention related.

**ADVERSE EVENT/COMPLICATION CODES**

<table>
<thead>
<tr>
<th>Code</th>
<th>Adverse event/complication</th>
</tr>
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<tbody>
<tr>
<td>01</td>
<td>ICP catheter related infection</td>
</tr>
<tr>
<td>02</td>
<td>ICP monitoring system malfunction</td>
</tr>
<tr>
<td>03</td>
<td>Unplanned ICP catheter removal</td>
</tr>
<tr>
<td>04</td>
<td>ICP catheter related hemorrhage</td>
</tr>
<tr>
<td>05</td>
<td>CSF leak</td>
</tr>
<tr>
<td>06</td>
<td>Cerebral abscess</td>
</tr>
<tr>
<td>07</td>
<td>New or expanding lesion</td>
</tr>
<tr>
<td>08</td>
<td>Ventriculitis</td>
</tr>
<tr>
<td>09</td>
<td>Seizure</td>
</tr>
<tr>
<td>10</td>
<td>Hydrocephalus</td>
</tr>
<tr>
<td>11</td>
<td>Death</td>
</tr>
<tr>
<td>12</td>
<td>Cardiac arrest</td>
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<tr>
<td>13</td>
<td>Acute lung injury</td>
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<tr>
<td>14</td>
<td>ARDS</td>
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<td>15</td>
<td>Sepsis</td>
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<tr>
<td>16</td>
<td>Septic shock</td>
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<tr>
<td>17</td>
<td>Coagulopathy</td>
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<tr>
<td>18</td>
<td>Nosocomial pneumonia</td>
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<td>19</td>
<td>Community-acquired pneumonia</td>
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<tr>
<td>20</td>
<td>Wound infection</td>
</tr>
<tr>
<td>21</td>
<td>Decubitus ulcers</td>
</tr>
<tr>
<td>22</td>
<td>Pulmonary thromboembolism</td>
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<tr>
<td>23</td>
<td>Deep vein thrombosis</td>
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<tr>
<td>24</td>
<td>Acute renal Failure</td>
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<tr>
<td>25</td>
<td>Urinary infection</td>
</tr>
<tr>
<td>26</td>
<td>Gastrointestinal hemorrhage</td>
</tr>
<tr>
<td>27</td>
<td>Hyponatremia (&lt; 135)</td>
</tr>
<tr>
<td>28</td>
<td>Hypernatremia (&gt; 145meq)</td>
</tr>
<tr>
<td>29</td>
<td>Other water and ionic disorders</td>
</tr>
<tr>
<td>30</td>
<td>Other</td>
</tr>
<tr>
<td>31</td>
<td>None</td>
</tr>
</tbody>
</table>

**Serious adverse event (SAE):** Any adverse experience that results in any of the following outcomes is considered a serious adverse event:

A. Death
B. Life-threatening adverse experience
C. Unplanned inpatient hospitalization or prolongation of existing hospitalization
D. Persistent or significant disability/incapacity
E. Congenital abnormality/birth defect.
F. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
J. Examples of such medical events include:
   o Allergic bronchospasm requiring intensive treatment in an ED or at home
   o Blood dyscrasias or convulsions that do not result in inpatient hospitalization

Serious adverse events will be reported to the Medical Safety Monitor (Freddy Arturo Sandi Lora, MD, mobile telephone +591-7203-3853, home telephone +591-2241-3657, fax +591-2-2245502, email fresandi@hotmail.com) and the Monitors (Gustavo Petroni, MD, mobile telephone +549-341-514-7543, home telephone +54-341-482-7588, fax +54-341-423-1087, e-mail gustavopetroni@gmail.com or Silvia Lujan, MD, mobile telephone +549-341-560-9239, home telephone +54-341-440-2056, fax +54-341-423-1087, e-mail silviablujan@gmail.com) by the acute care data collector or site PI using the Serious Adverse Event and/or Possibly Related to Study Intervention Form – Initial Report within 2 business days of finding out about the event. The site PI is responsible for reporting the event to the site IRB if that is required. The report can be sent to the Medical Safety Monitor and Monitors electronically (with a signed copy being retained at the site) or, if that is not possible, the information can be telephoned or faxed. Site personnel must do their best to communicate with the Medical Safety Monitor and Monitors quickly, whether that be by phone, e-mail or fax. If the communication is by e-mail or fax, the Medical Safety Monitor and Monitors should confirm that the report was received. The Medical Safety Monitor or Monitors will communicate with the site personnel as needed and make any additions to the form. The Medical Safety Monitor will sign the revised form and send the form to the Monitors within 5
business days. The Monitor will forward the form to the ALAS PI (Dr. Rondina), translate the form into English and forward the English version electronically to the overall PI (Dr. Chesnut) and UW Study Coordinator (Kelley Chaddock, chaddk@u.washington.edu), within 5 business days. If required, the Monitor will also fill out a UW Human Subjects Adverse Event Report (http://www.washington.edu/research/hsd/forms_paper.php?topic=1) and forward it to the UW Study Coordinator along with a copy of the subject’s signed consent form. The UW Study Coordinator will be responsible for getting the appropriate forms to PI for signature and sending the information to the PI, and the UW IRB (Application title: Neurotrauma Research in Latin America: Lifespan Analysis, Application number: 33888, Committee B). She will also be responsible for the updating of the spreadsheet of SAE and PRAEs to be sent by Nancy Temkin to the DSMB at the intervals requested by Ms. Odenkirchen (send to: Joanne Odenkirchen, jo21x@nih.gov). The Serious Adverse Event and/or Possibly Related to Study Intervention Form – Initial Report is filled out with the information that can be determined soon after the event is identified by study personnel. For any event with final outcome undetermined at the time of initial report, a Serious/ Possibly Intervention Related Adverse Event – Follow-up form should be filled out when the outcome is known or a month has passed since the last report. A Serious/Possibly Intervention Related Adverse Event – Follow-up form should be filled out and sent to the Monitor monthly until either the SAE is resolved or the 6 month study period is over. The follow-ups are forwarded to everyone receiving the initial report except the UW IRB. Serious Adverse Events should be reported during the entire 6 month study period. Outcome examiners will report to the site PI if they learn of a participant’s death or if the participant says they had an unplanned hospitalization. The site PI will then follow up on late SAE/PRAEs and report them just as is done for SAEs/PRAEs during initial hospitalization.

**Intervention Related Adverse Event/ Unexpected Adverse Event:**

Adverse events that are thought to be possibly related to the intervention will be reported using the same procedures as for Serious Adverse Events (except a UW Human Subjects Adverse Event Report is not required unless the event qualifies as a serious adverse event or is unexpected). ICP catheter related infection, ICP monitoring system malfunction (including catheter breakage, catheter obstruction, catheter malposition, or machine malfunction), unplanned ICP catheter removal and ICP catheter related hemorrhage are known responses to the study intervention and should always be considered as possibly related to the intervention. Any other adverse event that occurs after ICP monitor insertion and could not readily have been produced by the subject’s clinical state or due to environmental causes or other interventions is considered unexpected.

**Relatedness of an adverse event to the intervention**

14. **Not related:** An event is considered to be not related to the study intervention if the subject has not yet had an ICP monitor implanted or attempted to be implanted.

15. **Improbable:** A relationship between the event and the study intervention is considered to be improbable if an ICP monitor has been implanted(or implantation has been attempted) **but** the event could readily have been produced by the subject’s clinical state or due to environmental causes or other interventions and the event is not known to be related to ICP monitoring. (Events with known relationship are : ICP catheter related infection, ICP monitoring system malfunction (including catheter breakage, catheter obstruction, catheter malposition, or machine malfunction)), unplanned ICP catheter removal and ICP catheter related hemorrhage.)
16. **Possible:** A relationship between the event and the study intervention is considered to be possible if an ICP monitor has been implanted (or implantation has been attempted) and the event could not readily have been produced by the subject’s clinical state or due to environmental causes or other interventions and the event is not known to be related to ICP monitoring.

17. **Probable:** A relationship between the event and the study intervention is considered to be probable if an ICP monitor has been implanted (or implantation has been attempted) and the event is known to be related to ICP monitoring. (Events with known relationship are: ICP catheter related infection, ICP monitoring system malfunction (including catheter breakage, catheter obstruction, catheter malposition, or machine malfunction), unplanned ICP catheter removal and ICP catheter related hemorrhage.)

## 2.Q DATA AND SAFETY MONITORING RESPONSIBILITIES

The Data and Safety Monitoring Board (DSMB) for the study has been appointed by NINDS. The DSMB monitors study quality, safety of participants, and efficacy. Monitoring performance of the study usually includes reviewing patient recruitment, flow of forms, quality control of the data, adequacy of medical monitoring, adverse effect reporting, adherence to protocol, and appropriateness of protocol changes with regard to scientific integrity.

Monitoring safety usually includes reviewing risk of harm inherent in participating in the study, adverse events (type, incidence, and severity), and effect of protocol changes on risk.

Monitoring efficacy usually includes reviewing data (blinded or unblinded), planned and/or unplanned interim analyses, stopping rules, their implementation, and resulting decisions, results and conclusions.

### DSMB Membership

Members of the DSMB are appointed by NINDS. The DSMB members are:

- M. Ross Bullock, MD, neurosurgeon, University of Miami, Chair
- Lidia Artiola, neuropsychologist (through xxx)
- Ramon Diaz-Arastia, neurologist, University of Texas Southwestern Medical School
- Mary Foulkes, biostatistician, George Washington University
- Jose Suarez, neurocritical care, Baylor College of Medicine

## 2.R STUDY COMPLIANCE

A protocol deviation is defined as any change, omission, or deviation from the study design or protocol research procedures, which is under the control of the investigator and has not been approved by the Ethics Committee. A deviation is a minor protocol violation. Changes or alterations in the conduct of the study that do not have a major impact on the safety or welfare of the subject, or the integrity, accuracy and/or reliability of the study data are considered minor deviations from protocol.
A protocol violation is defined as any change, omission or deviation from the study design, or procedures of a research protocol, that affects the safety or welfare of the subject and/or the integrity, accuracy and/or reliability of study data. A violation is a major deviation from protocol. Violations include any of the following characteristics:

1. The deviation has harmed or presents a significant or substantial risk of harm to the subject of investigation.
2. The deviation compromises the scientific integrity of the data collected for the study.
3. The deviation represents a voluntary breach of regulations of the protection of human subjects or the study policies or procedures by the investigator(s).

Protocol deviations and violations include (but are not limited to) the following list.

PROTOCOL VIOLATIONS (*1) AND DEVIATIONS (*2)
(this list of examples is not exhaustive)

A. **Informed consent process:**
   a. Obtaining informed consent after starting the procedures of the study (*1)
      Missing signature of the representative of the patient (*1)
   b. Using an invalid consent form (consent form without approval from the ethics committee (*1)
   c. Missing informed consent form (*1)
   d. Lack of the signature of the researcher (*2)
   e. Using an old version of the consent form (but one that had been approved) (*2)
   f. Competent patient not asked to sign consent themself (*2)

B. **Randomization** (includes eligibility, resource availability):
   a. Randomizing cases who are ineligible (either because of their characteristics or because an ICU bed or ICP monitor is not available; *1).
   b. No randomization of cases who are eligible (i.e. “selection bias;” *1).

C. **Intervention** (group assignment, cross over, etc.):
   a. Placing an ICP monitor in cases assigned to the standard treatment (*1).
   b. Not placing an ICP monitor in cases assigned to the ICP treatment group (*1) unless a medical contraindication has developed.
   c. Prematurely stopping monitoring in cases assigned to the ICP monitoring group (*1)
   d. Failing to replace the catheter after a shift or malfunction.
   e. Failure to continue with ICP monitoring after decompressive craniectomy.
      i. Monitoring can continue either in different location w/ a second catheter or in the same place with the original one).
      ii. If they cannot replace the catheter to other location because technical problems (i.e. bilateral craniectomy) this is NOT a protocol violation (and they must follow with the ICP protocol).
   f. Continuing monitoring longer than specified in the protocol (*2).
D. **Treatment** (following the guidelines and treatment group protocols):
   a. First CT not obtained at admission (*1)
   b. Second and third CTs not obtained at specified times (*2)
   c. Therapeutic intensity level not increased when indicated—less than 1 hour delay (*2).
   d. Therapeutic intensity level not increased when indicated—over 1 hour delay (*1)
   e. Either treatment protocol not followed appropriately (*2)

E. **Follow up:**
   a. Failure to obtain follow-up information on a case (*1)
   b. Failure to test according to the protocol without noting the deviation on the coding sheet (*1)
   c. Failure to test according to the protocol but noting the deviation on the coding sheet (*2)
   d. Testing outside the specified time window (*2)

F. **Data management** (deviations that compromise the scientific integrity of the trial)
   a. Unintentional loss of data
   b. Failure to report Serious Adverse Events (*1)
   c. Falsification of medical records or research data (*1)
   d. Infringement of confidentiality (*1)
   e. Repeated or continuous negligence in the performance of study procedures (*1)
   f. Correcting errors by erasing or blotting out original value (some way other than a single line through the incorrect data) (*2)
   g. Failure to initial and date changes (*2)
   h. Delayed reporting of Serious Adverse Events or Probably Related Adverse Events (*2)

Protocol violations will be reported on a monthly basis electronically. The monthly report of protocol violations will be sent to the overall PI (Dr. Chesnut), the Medical Safety Monitor (Dr. Sandi Lora) and the UW Data Center (Ms. Chaddock). The UW Data Center will forward the report to others as appropriate. The overall PI (Dr. Chesnut) and the DSMB will determine consequences to the site as the result of protocol violations. The Monitors and the site PIs will have no influence in this matter. Protocol deviations will also be reported on a regular basis. Protocol violations will be summarized for each DSMB meeting.

2.S. **DATA COLLECTION AND STUDY FORMS**

**Source Documentation**

Patient medical data is collected on source documents from the medical record. Study information is recorded on paper case report forms (CRF).

**Study Forms**

The study forms and collection schedule are listed in Table 3. A general description of each CRF and who is responsible for completing it is summarized below. Study CRFs are located in
Appendix D. Each CRF contains information about how to collect the information on the form. In addition, detailed information about each question on each form is contained in the Data Dictionary in Appendix C. The forms will be produced at Rosario. Initially they will be photocopied to ensure that they are working well. After revision, if necessary, the forms will be printed on NCR paper. The study coordinator is responsible for making folders of forms for each subject. Instructions about assembling the folders will be posted on the website. Once the forms are printed on NCR paper, any additional changes will be made as addendums as reprinting the forms is very costly.

Table 3. Study Forms and collection schedule

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>During Hospitalization</th>
<th>3 Month</th>
<th>6 Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening form</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU/ED Form</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU/ED Nurse’s form</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroworsening Form</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurosurgery and other surgery Form</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIS</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT Form</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Event</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious Adverse Event</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pre-injury family form</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-injury patient form</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Hospital discharge form</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study information form</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personal &amp; contact information form</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Month Outcome Evaluation Form</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Month Outcome Evaluation Form</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>6 Month neuropsychological coding sheet</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

*Italics indicate form is filled out as needed*

**Screening Form**

**Purpose**
The screening form includes study inclusion and exclusion criteria, consent status and information about the person’s injury before and after admission to the study hospital. This form is filled out on all persons who are screened for the study.
Who is responsible
Study coordinator at each hospital

ICU Form
Purpose
This form documents date of ICU admission and discharge, whether ICP was monitored or not and if so by what method and details about timing of ICP monitoring and reason for ICP monitor removal if applicable. One form is filled out for each ICU admission of each participant.

Who is responsible
Study coordinator at each hospital

ICU Nurse’s Form
Purpose
This form collects information on the subject’s vital signs and Therapeutic Intensity Level (TIL) collected on an hourly basis. One form is filled out for each day the participant is in the ICU, for the full ICU stay.

Who is responsible
Study coordinator at each hospital

Neuroworsening Form
Purpose
Neuroworsening is the deterioration of the clinical status of a patient with a head injury and is defined by the occurrence of one or more of the following objective criteria.

- A spontaneous decrease in Glasgow Coma Scale Motor score of 2 or more points (compared with the previous examination)
- A new loss of pupillary reactivity
- Interval development of pupillary asymmetry of ≥ 2 mm
- Deterioration in neurological status sufficient to warrant immediate medical or surgical intervention.

A neuroworsening form is filled out for each episode of neuroworsening experienced by the research subject.

Who is responsible
Study coordinator at each hospital

Neurosurgery and Other Surgery Form
Purpose
All surgeries, including neurosurgery and other surgery for each research subject are recorded on this form. The date of surgery, anesthesia start and stop times, service code, procedure code and side of procedure are recorded.

Who is responsible
Study coordinator at each hospital
AIS Form

Purpose
The AIS form is based on the first 24 hours post injury. The highest severity score per body region is recorded.

Who is responsible
Study coordinator at each hospital

CT Form

Purpose
A CT Scan form is filled out for each CT done on subjects enrolled in the study. A CT scan form is also filled out for Subjects who are screened only and not enrolled on the study, if the scan was done prior to ICU admission.

Who is responsible
Study coordinator at each hospital

Adverse Event Form

Purpose
To report adverse events

Who is responsible
Study coordinator at each hospital

Serious Adverse Event and/or Possibly Related to Study Intervention – Initial Report and Follow-up Forms

Purpose
To report serious adverse events and their resolution.

Who is responsible
Study coordinator at each hospital

Pre-injury Family Form/Pre-injury Patient Form

Purpose
This questionnaire collects information on the patient’s demographic characteristics, pre-injury educational level, living situation, main activity status, income, alcohol and drug use, and medical history. The Pre-injury Family Form is administered as soon as possible after the research subject is enrolled in the study. This measure must be completed prior to hospital discharge of the subject. The Pre-injury Patient Form involves the same questions asked of the research subject when she/he is able.
Who is responsible
Study coordinator or outcome examiner at each hospital

Hospital Discharge Form
Purpose
This form captures information about hospital discharge including date of discharge, neurological status at discharge and discharge referral.

Who is responsible
Study coordinator at each hospital

Study Information Form
Purpose
This form collects the dates of events that may occur at anytime during the course of an individual’s participation on the study, including date of consent by participant, date of withdrawal of consent, date of last study contact for those who were not followed at 6 months post injury, date and cause of death and protocol violations.

Who is responsible
Study coordinator at each hospital

Personal and Contact Information Form
Purpose
Contact information for the participant is collected on this form in order to facilitate scheduling the outcome evaluations. In addition, contact information of friends and relatives of the participant who will remain in contact with him or her if they move is also collected for this purpose. This information is collected before hospital discharge and updated at the 3-month evaluation.

Who is responsible
Study coordinator or outcome examiner at each hospital

3 Month Outcome Evaluation Form
Purpose
The results of the Galveston Orientation and Amnesia Test, Glasgow Outcome Scale-Extended and Disability Rating Scale administered at 3-months post injury are coded on this CRF.

Who is responsible
Outcome examiner at each hospital

6 Month Outcome Evaluation Form
Purpose
The results of the Galveston Orientation and Amnesia Test, Glasgow Outcome Scale-Extended, and Disability Rating Scale administered at 6-months post injury are coded on this CRF.
**Who is responsible**
Outcome examiner at each hospital

**6 Month Neuropsychological Coding Form**

**Purpose**
The results of the 6-month neuropsychological evaluation are coded on this CRF.

**Who is responsible**
Outcome examiner at each hospital

The CRFs will be produced and distributed by the study staff located in Rosario, Argentina. If additional forms are needed, contact one of the Monitors. Each participant’s CRFs will be placed in individual folders at the study site and stored in locked file cabinets.

**Data Flow**

Each center will have two primary data collectors – one for the acute care setting and one for outcomes assessments. The acute care data collector is the study coordinator. They will collect baseline and hospital information from the patients’ charts onto the study Case Report Forms (CRF). The outcomes data collector is the outcomes examiner. They will transcribe patient information from the outcome assessment forms onto the study CRF. The outcomes data collector will be masked to the treatment group. The CRFs are paper forms with two copies. One copy will remain with the patients’ records at the study center. The other copy will be hand-carried by the Monitor to the study lab in Rosario, Argentina.

In Rosario, patient data will be entered twice by two individuals independently onto a password-protected Access database using screens designed to look like the paper forms. The program will automatically identify inconsistencies between the two data entries, as well as out-of-range errors. After errors are corrected the files will be transmitted to the project’s Data Center at the University of Washington (UW). The UW data manager will further monitor data for inconsistencies and unusual values.

Baseline CRFs should be completed within one week of injury. Hospital CRFs should be completed within 2 weeks of hospital discharge. Outcome CRFs should be completed within 2 weeks of outcome assessment. Data should be entered within 4 weeks of receipt in Rosario. Queries should be sent within 2 weeks of entry and should be answered within 1 month.

Changes will be made both on the forms at the site (by the study coordinator) and at Rosario by the person doing data entry. Original value should be crossed through with a single line, the new value written in, and the change initialed and dated. Changes will be entered at Rosario. All changes to the entered forms will be automatically logged with the prior value, the date and time of the change, and the identification of the person making the change.

**Retention of Study Documentation**
During the study, the forms will be kept at the site and in Rosario. After the study is complete and the database has been locked, the forms will be sent to UW for long-term storage in compliance with the legal requirements.

**Administrative Forms**

Administrative forms include:

- Study staff at each site and their authorization (e.g. randomize cases, complete forms, conduct outcome assessments).

- Protocol Deviation and Violation

**2.T. DATA MANAGEMENT**

Information about data entry and data correction procedures, and the audit trail of all data changes are covered under the ‘Data Flow’ section. Procedures involving data monitoring, report generation and data transmission to the Data Center are found in the ‘Quality Control Procedures’ section.

**2.U. QUALITY CONTROL PROCEDURES**

Quality control will be overseen by the study biostatistician, Dr. Temkin. Medical data, including injury severity information, will be collected by the study clinicians under the supervision of Drs. Petroni, Rondina and Lujan. They are training the staff at each site in study procedures and how to correctly complete the CRFs. The neurobehavioral examiners will be trained and certified by Dr. Mariana Cherner at the University of California in San Diego (UCSD) who is a bilingual neuropsychologist with experience in cross cultural neuropsychological studies. After the examiners are certified, the results of their first 10 tested cases will be reviewed at UCSD to ensure valid testing. Subsequently 10% of their cases will be reviewed to prevent drifting. Dr. Dikmen will oversee the training, data collection and quality control of the neuropsychological and functional status measures.

The study coordinators are trained and certified by Drs. Gustavo Petroni and Silvia Lujan, the study Monitors. Training sessions cover all the study areas, including research participant identification, inclusion and exclusion criteria, consent, and randomization processes, scoring the Glasgow Coma Scale, CT categorization and completing all baseline and hospitalization forms and data flow systems. At the completion of each 2 to 3 day training session, practice forms are completed using real patient data.

All personnel collecting data will be extensively trained in their tasks. All scoring and coding of neurobehavioral measures will be double-checked by Dr. Lujan. Any unusual cases will be discussed with the Medical Committee or Outcome Committee to resolve the coding difficulties. All coded data will be entered independently by two experienced data-entry operators into an Access database. Inconsistencies between the data-entry operators will be immediately identified by the database and will be rectified by the second data-entry operator. On-line range and within
form consistency checks will be run in Rosario after the form has been entered. Queries will be sent to the site and corrections made as described under data flow. The database will be sent quarterly to Seattle where cross-form consistency checks will be run. Additional queries will be sent to the sites (through Rosario) and changes made as described under data flow. All discrepancies or unusual values will be checked and resolved by the data supervisor in Rosario. Ms. Machamer at the University of Washington will work with her counterpart in Rosario to ensure high-quality data.

All data sent to Seattle will be maintained on password-protected files on a secure server that is backed up nightly. As additional quality assurance, each 6 months, the biostatistician/database manager will select about 10% of the cases, and send the data as represented in the Seattle database to Rosario. The Monitor will take the data sent for these cases on a site visit where the database values will be compared to source documents and site copies of the CRFs. Any discrepancies will be noted and discussed with the study coordinator to further train the study staff. If the discrepancy rate due to site error is over 5%, further training will be conducted. Continued high error rates will be cause to put the site on probation or potentially discontinue the site.

For analysis, data will be transferred to SPSS or SAS using DBMSCopy. Reports monitoring the progress of the study will be generated monthly to help the investigators identify areas such as enrollment or follow-up rates that might need specific attention. Study table and figure templates for report generation are in Appendix E. Analyses for the DSMB meetings, as well as for publications and presentations will be performed using SAS or SPSS.

2.V. STUDY COMPLETION AND CLOSEOUT PROCEDURES

When we accomplish the target sample size, or when the DSMB specifies that the study should end, the following is the intention for closeout:

#1. All records will remain in place until follow-up has been accomplished on all patients, consistent with DSMB specifications.

#2. All hard copy records will be transferred to the data center in Rosario, Argentina, to complete data entry.

#3. All test materials will be transferred to University of Washington for long-term storage (30 years, according to Washington State law).

#4. Patient identification will be retained for 10 years, to allow for extended research.

2.W. POLICIES

2.W.1. Confidentiality

All study staff have been extensively trained in the importance and procedures of patient confidentiality, and in how to manage data entry. A list linking patient identity with the patient number will be maintained electronically, in a file separate from the case report forms, in a password protected file. All hard copy case report forms will be kept in a locked cabinet in the study hospitals. One copy will be sent to the data center in Rosario, where data entry will occur. These copies will also be maintained in locked cabinets.

Data will be sent electronically from Rosario to the data center at University of Washington. Jason Barber, the Data Manager, will receive the data, and will prepare reports for distribution to
the DSMB and the Executive Committee. Executive Committee reports will only consist of descriptive information necessary to determine if target numbers are being met, data quality is acceptable, etc. Reports for the DSMB will consist of the pre-specified information the DSMB will need in order to make decisions about continuing the study. Otherwise the data will not be distributed. Mr. Barber will store and back up the dataset, and perform systems tests, according to the procedures of the data center at University of Washington.

2.W.2. Publication

Access to the data for analysis and publication will occur as follows:

A Publication Committee will be assembled consisting of representatives of the core research group, Fundacion ALAS, LABIC, and each study hospital. This committee will be responsible for approving the protocols for analysis, and the subsequent publications. Investigators will submit proposals for analysis to the Publication Committee for review.

The primary publication of the results of the randomized trial will be directed by the Principal Investigator, Randall Chesnut, M.D. All hospitals will have access to their own data, as well as to the aggregated data of the entire study. A study hospital may conduct analysis of its own data independent of approval by other study hospitals, or by the Publication Committee. However, submission for publication must be approved by the Publication Committee. An investigator may conduct analysis of the aggregated data of the entire study after receiving approval by the Publication Committee. The Publication Committee will secure approval of each study hospital for the proposed analysis, and will also approve submission for publication.

2.X. MOP MAINTENANCE

The MOP is maintained and updated throughout the study by Ms. Machamer. Each page of the MOP is numbered and contains a version number and date. In the event that the MOP is updated, the version number and date will be revised accordingly. The Rosario, Argentina study staff are responsible for translating and distributing the updated MOP with instructions about replacement.
REFERENCES


List of Changes in the MOP
December 28 – January 8, 2009

December 28, 2008:
Updated Adverse Event Reporting Section
Updated contact information for Drs Petroni, Lujan and Lora

December 29, 2008
Revised Randomization procedure

December 30, 2008
Removed FIM
Changed Hopkins Verbal Learning Test – Revised to Spanish Verbal Learning Test
Changed the name from Serious Adverse Event Form to Serious Adverse Event Form and/or Possibly Related to Study Intervention – Initial Report and Follow-up Forms
Remove Randomization Form (it is now included in the Screening Form)
Add a fax number for Dr. Freddy Sandi Lora

January 8, 2009
Alterations to treatment protocols
Since the first DSMB meeting, a number of areas of uncertainty among the study teams have come to light. This was particularly during the start-up phase, where the protocols came into direct clinical applications. Although the Standard Protocol represented the three centres’ approach to managing TBI prior to this study, it actually is a concatenation of management strategies from each centre and its execution requires modification at each location. As well, on-site observations of clinical care revealed aspects of the protocols that didn’t fit as well as possible with the realities of management in Bolivia. For instance, the quality of the midazolam available for sedation appeared variable, a situation that apparently is within the limits of their medical experience (and not within ours in the US). This prompted altering the sedation protocols to allow the use of low dose barbiturates which are commonly used in Latin America and appear to have more consistent quality. We have separated out the two protocols to facilitate their clarity and availability at the bedside. Their availability as stand alone protocols sections makes them more user-friendly. In doing this, we have inserted the basic management sections (prior to divergence of the two study protocols) into each section.
A lot of attention has been paid to clarifying the steps and their application within both treatment approaches. Both protocols have been extensively reformatted, with increased explanatory text. Where this is definitely new, it has been bolded in the accompanying documents.
We have added the use of tonicity to both protocols in following hyperosmotic treatment since serum BUN values are much less clinically available. We also allowed the checking of these values to be acceptable at 24 hour intervals (versus the 12 hour intervals initially specified) as the shorter interval is not reasonable within their clinical world.
We corrected a typographic error in describing the target values. Previously, the SaO2 and PaO2 values had been mixed (eg SaO2 > 60 mm Hg).
We added a section regarding the management of patients following decompressive craniectomy, as this was unclear at all three centres. It specifies continuing the pre-operative management plans and getting a follow-up CT scan. Altering the treatment will depend on the appearance of the CT and
the clinical examination in the Standard Approach, supplemented by post-operative ICP data in the Monitored Approach. In some patients, they are concerned that post-operative ICP monitoring may not be possible. We have described approaches to avoid this but have also outlined a management plan to use if such obtains (similar to the Standard Approach).

Since neuroworsening represents a new “stand alone” concept, we have greatly expanded this section and included it within each protocol. For the Monitoring Group, we have re-stated the necessity of responding to intracranial hypertension within 5 minutes and that such responses should be reflected in the TIL (which we will use as an internal QA check for our monthly reports). We have clarified the protocol for using ventricular drainage when a ventriculostomy is in place. Since these patients will have initially been monitored using an intraparenchymal device, we have requested that this be kept (whenever possible) and used to transduce the ICP.

We have added a section on contraindicated treatments (from the TBI Guidelines).

**February 5-27, 2009**
- Added in AE section (inadvertently removed in last revision)
- Changed data entry from 2 to 4 weeks of receipt
- Updated ‘Relatedness of adverse event to the intervention’
- Changed names of 2 outcome forms
- Revised administrative forms
- Updated randomization procedure
- Added more detail on protocol deviations and violations
- Added intention to treat section
- Added Mini-Mental State Examination
- Revised references
- Cleaned up the formatting for Study Intervention
- Revised treatment protocol for ICP monitoring group

**June 8th – June 16th, 2009**
- Further specify inclusion/exclusion criteria
- Change phenytoin from 7-30 days to 7 – 28 days
- Revised the treatment protocol for the ICP monitoring group
- Changed who would receive Serious Adverse Event reports at the UW
- Changed who would receive Protocol Deviation & Violation form at the UW
- Update Dr. Silvia Lujan’s email address

**October 26-27, 2009**
- Inclusion of Tarija site
- Modification of mild hyperventilation section of the Standard (Non-Monitored) Therapy group

**November, 2009 – February, 2010**
- Inclusion of Espejo site
- Inclusion of 3 figures explaining the treatment protocol for the non ICP group
- Modification of figures depicting study sites
- Further specification of scores used in the composite measure
- Update the references
August 2010 – July 2012
Added Hospital Vernaza to list of sites
Corrected various typos
Dropped Wechsler Memory Scale III Spatial Span August 2010
Dropped Disability Rating Scale Feeding, Toileting, Grooming, Level of Functioning and Employability subtests January 2011
Revised composite score to reflect these changes and to clarify age, sex and education adjustment for neuropsychological measures; to clarify subcomposites July 2012
SAE procedures were corrected July 2012
**All changes during this time period were made prior to database lock and breaking of the blind.**