Effects of Erythropoietin on Cerebral Vascular Dysfunction and Anemia in Traumatic Brain Injury

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1.1 Study Title
Effects of Erythropoietin on Cerebral Vascular Dysfunction and Anemia in Traumatic Brain Injury

1.2 Objectives
The primary objective of this study is to determine the effect of early administration of recombinant human erythropoietin (rhEpo) on long-term neurological outcome after severe traumatic brain injury (TBI). The hypothesis to be tested is that the early administration of Epo improves global neurological outcome (assessed by Disability Rating Scale [DRS] and Glasgow Outcome Scale [GOS]) at 6 months post-injury.

The secondary objectives are:
1. To study the acute cerebrovascular effects of rhEpo administration.
2. To study the role of anemia of critical illness in determining brain oxygenation and cerebral hemodynamics.
3. To study the complications associated with transfusion of blood products in patients with severe TBI.
4. To study the effect of rhEpo administration in reducing the need for blood transfusion after TBI.
5. To study the natural history of Epo and EpoR expression by the injured brain.

1.3 Design and Outcomes
The overall design of the study is a randomized clinical trial using a factorial (2 x 2) design with administration of rhEpo and transfusion threshold as the two factors that will be randomly assigned. The study will examine the cerebrovascular effects of rhEpo administration and the effects of rhEpo administration on hemoglobin concentration, as well as the effects of both factors on brain oxygenation, the need for blood transfusion, on systemic complications, and on neurological outcome.

1.4 Interventions and Duration
Patients will be randomly assigned to one of four treatment groups:

<table>
<thead>
<tr>
<th>Treatment with rhEpo</th>
<th>Treatment with Placebo</th>
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<tr>
<td>Transfusion trigger of &lt; 10 g/dl</td>
<td>Transfusion trigger of &lt; 10 g/dl</td>
</tr>
<tr>
<td>Transfusion trigger of &lt; 7 g/dl</td>
<td>Transfusion trigger of &lt; 7 g/dl</td>
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Patients randomized to “Treatment with rhEpo” will receive rhEpo administration 500 IU/kg within 6 hours of admission, then weekly x 2 additional doses while they remain in the ICU. Patients randomized to “Treatment with Placebo” will receive an equal volume of saline IV within 6 hours of admission, then weekly x 2 additional doses while they remain in the ICU.

Patients randomized to 'Transfusion trigger < 10g/dl' will follow the general management guideline that hemoglobin concentrations should be maintained at least 10g/dl with transfusion of packed RBC's, if necessary, during the acute post-injury recovery period. Patients randomized to 'Transfusion trigger < 7g/dl' will have hemoglobin concentrations maintained at least 7g/dl with transfusion of packed RBC's, if necessary, during the acute post-injury recovery period.

In all other respects, management during the acute post-injury phase will follow the same standardized management protocol for TBI patients (Appendix II).
1.5 Sample Size and Population

Approximately 200 patients with severe traumatic brain injury will be studied.
I. Study Objectives
   A. Primary Objective
      1. The specific aim of this study is to determine whether early administration of recombinant human erythropoietin (rhEpo) will improve the long-term neurological outcome of individuals sustaining severe traumatic brain injury (TBI). In addition, the acute effects of rhEpo on cerebral hemodynamics in the injured brain and the natural history of Epo and erythropoietin receptor (EpoR), a member of the cytokine receptor superfamily, will be examined.
      2. The primary hypothesis of the study is that early administration of rhEpo will improve global neurologic outcome in patients with severe TBI at six months post-injury. Early administration is defined as within six hours of injury. Global neurologic outcome will be assessed using the Glasgow Outcome Scale (GOS) and the Disability Rating Scale (DRS). The primary outcome measure is the GOS at 6 months.
   B. Secondary Objectives: There are five specific areas for which secondary hypotheses have been generated for this study.
      1. The acute cerebrovascular effects of rhEpo administration
         Hypotheses:
         a. rhEpo administration will increase cerebrospinal fluid (CSF) and microdialysate levels of Epo
         b. rhEpo administration will increase CSF and microdialysate levels of nitrate and nitrite (NOx), the end-products of metabolism of nitric oxide, which is known to play a key role in the regulation of cerebral blood flow
         c. rhEpo administration will:
            - improve pressure autoregulation of cerebral blood flow (CBF), an intrinsic phenomenon in the brain that maintains CBF when changes in the systemic blood pressure occur,
            - increase CBF, and
            - increase the cerebral metabolic rate of oxygen (CMRO₂) as a result of increased oxygen availability in injured brain cells
      2. The role of anemia associated with critical illness in determining brain oxygenation and cerebral hemodynamics
         Hypotheses:
         a. When the hemoglobin trigger level for transfusion is set at 7g/dl (current evidence-based recommendation for critically ill patients), the brain tissue partial pressure of oxygen (PₜO₂) will be lower, adjusted for arterial PₐO₂, than when the transfusion trigger is set at 10g/dl.
         b. When the hemoglobin trigger level for transfusion is set at 7g/dl (current evidence-based recommendation), cerebral blood flow (CBF) and intracranial pressure (ICP) will be higher than when the transfusion trigger is set at 10g/dl.
         c. When the hemoglobin trigger level for transfusion is set at 7g/dl (current evidence-based recommendation), pressure autoregulation of CBF will be significantly more impaired, due to dilation of cerebral blood vessels, than when the transfusion trigger is set at 10g/dl.
         d. When the hemoglobin trigger level for transfusion is set at 7g/dl (current evidence-based recommendation), transfusion of packed red blood cells (PRBCs) will increase PₜO₂, adjusted for arterial PₐO₂, lower CBF, lower ICP, and improve pressure autoregulation.
3. The types and severity of complications associated with transfusion of blood products in patients with severe TBI

**Hypotheses:**

a. Patients transfused at a hemoglobin trigger level of 7g/dl will have a lower incidence of pulmonary edema and adult respiratory distress syndrome (ARDS).

b. Patients transfused at a hemoglobin trigger level of 7g/dl will have a lower incidence of infections.

4. The effect of rhEpo administration in reducing the need for blood transfusion after TBI

**Hypothesis:**

a. Patients assigned to the rhEpo treatment group will not require as many blood transfusions as patients assigned to the control group.

5. The natural history of Epo and EpoR expression by the injured brain.

**Hypotheses:**

a. Levels of Epo in the cerebral spinal fluid (CSF) and microdialysate fluid of TBI patients will be higher than the levels found in normal control subjects, from whom brain tissue has been removed for therapeutic reasons in non-trauma neurosurgical procedures.

b. Expression of Epo by the injured brain will occur as a function of injury severity – more severe injuries (GCS 3-5) will elicit more expression of Epo than less severe injuries (GCS 6-8).

c. The maximum expression of Epo in CSF and microdialysate fluid will be detected three to four days after brain injury.

d. Levels of Epo found in microdialysate fluid will be highest when the microdialysis probe is placed in close proximity to an evolving cerebral contusion and will be decreased if the probe is placed distant to the contusion.

e. Examination of contused brain tissue, removed as part of the standard surgical treatment for TBI patients, will find both Epo and EpoR.

II. **Background**

A. **Rationale**

The brain receives 20% of the cardiac output and is almost entirely dependent on oxygen for its metabolic processes; therefore, any degree of hypoxia puts injured neurons at risk. A therapy that can improve oxygen delivery to the injured brain may offer potential benefit to patients with severe traumatic brain injuries (TBI). In addition, trauma patients, including those with TBI, commonly develop anemia during the acute recovery period. The presence of anemia subsequently requires the injured brain to maintain a higher cerebral blood flow (CBF) to achieve the same level of oxygen delivery as would be provided with a normal hemoglobin level.

The quest for an agent that could protect the injured brain from secondary insults such as hypoxia and hypotension has been a driving force in brain injury research in the last 20 years, based on the premise that protection of injured but not destroyed neurons would permit damaged cells to recover and thus contribute to improved neurologic outcome. During this time, there have been a number of clinical trials testing agents with properties believed to arrest or inhibit pathophysiologic processes occurring in the injured brain. Promising compounds that were subjected to phase III clinical trials were tromethamine (THAM), nimodipine, tirilizad mesylate, and polyethylene glycol-conjugated superoxide dismutase (PEG-SOD). All of these trials, however, failed to demonstrate a significant effect on patient outcome (1).
Recombinant human erythropoietin (rhEpo) has been shown to have potent neuroprotective effects after experimental brain injury (2), in addition to its more widely recognized effect of increasing hemoglobin levels. In current practice, Epo is given to stimulate erythropoiesis and increase hemoglobin concentration in a variety of conditions that cause anemia, including chronic renal failure and cancer. In critically ill patients, administration of Epo reduces the need for transfusion of blood; however, Epo is not widely used for this purpose, because of its high cost and because it has not yet been shown to improve outcome (3).

The neuroprotection provided by rhEpo appears to be related to its ability to improve intracranial hemodynamics and cerebrovascular function. TBI directly induces a spectrum of cerebrovascular dysfunction, ranging from impaired pressure autoregulation of cerebral blood flow (CBF) to severe global ischemia. The cerebrovascular dysfunction caused by trauma may prevent adequate increases in CBF, the normal compensatory mechanism for a reduced oxygen-carrying capacity. Both of these factors – cerebrovascular dysfunction and anemia – have been associated with adverse effects on cognitive and functional outcomes of patients with severe TBI. Thus, based on current known physiology, the administration of rhEpo has the potential to improve cerebral hemodynamics and cerebrovascular function which should then improve neurologic outcome.

Epo has also been observed to be expressed in the brain after traumatic and other types of brain injury, including stroke and hypoxia (4,5,6,7). Activation of EpoR by administration of Epo and other molecules with Epo-like activity following experimental traumatic brain injury (TBI) has shown marked neuroprotective effects, significantly reducing contusion volume, preserving hippocampal neurons, and improving neurobehavioral performance. A number of actions of Epo may contribute to this neuroprotection, including anti-apoptotic effects, vascular, and anti-inflammatory effects; however, these processes are not yet well understood, and further research into the natural history of the expression and function of both Epo and EpoR is needed, as part of the required understanding to begin to use these agents in a therapeutic manner.

B. Supporting Data

1. **Normal Physiologic Role of Epo**  
   Epo is a hematopoietic growth factor, and the binding of Epo to the Epo Receptor (EpoR), a member of the cytokine receptor superfamily, controls the terminal maturation of red blood cells. In the human, Epo is produced by peritubular cells in the kidneys of the adult and in hepatocytes in the fetus. Small amounts of extra-renal Epo are produced by the liver in adult human subjects. Epo acts primarily to rescue erythroid cells from apoptosis (programmed cell death) to increase their survival. Epo also acts synergistically with several growth factors (stem cell factor [SCF], granulocyte / macrophage colony-stimulating factor [GM-CSF], interleukin 3 [IL-3], and insulin-like growth factor 1 [IGF-1]) to cause maturation and proliferation of erythroid progenitor cells (primarily colony-forming unit-E). Other effects of Epo include a hematocrit-independent, vasoconstriction-dependent hypertension, increased endothelin production, upregulation of tissue renin, change in vascular tissue prostaglandin production, stimulation of angiogenesis, and stimulation of endothelial and vascular smooth muscle cell proliferation.

2. **Epo Expression in the Normal and Injured Brain**  
   Until recently Epo was thought to be produced exclusively in fetal liver and in adult kidney. In 1995, mRNA encoding of both Epo and EpoR in the mouse brain were reported (8). Hypoxia induced a 20-fold increase in mRNA coding for Epo but not EpoR. Major Epo binding sites were observed in the hippocampus, internal capsule, cortex, and midbrain areas. Subsequently Epo was identified in human brain at autopsy (5) and in CSF of patients with TBI (4).
Epo is expressed basally in neurons and astrocytes (5). Following permanent focal cerebral ischemia, postischemic Epo expression has been localized specifically to endothelial cells (1 day), microglia/macrophage-like cells (3 days), and reactive astrocytes (7 days after occlusion). EpoR expression always preceded that of Epo for each cell type (9). Similar findings have been observed in human autopsy studies using immunohistochemical techniques (7). In normal brain, weak Epo/EpoR immunoreactivity was mainly neuronal. In fresh infarcts, Epo immunoreactivity appeared in vascular endothelium, and EpoR was seen in microvessels and neuronal fibers. In older infarcts reactive astrocytes exhibited Epo/EpoR immunoreactivity. Acute hypoxic brain damage was associated with vascular Epo expression, and older hypoxic damage with Epo/EpoR immunoreactivity in reactive astrocytes.

Under normal conditions, Epo production is mediated by decreased oxygen (O\textsubscript{2}) delivery to oxygen sensors [reviewed in (10)]. Hypoxic stimulation causes production of hypoxia-inducible factor (HIF-1), which is the major factor for transcriptional activation of the EPO gene (11). However, HIF-1 is also found in cells that do not express Epo and is part of a more widespread O\textsubscript{2}\textsuperscript{-}sensing mechanism providing transcriptional regulation of numerous genes, which include vascular endothelial growth factor (VEGF) and glycolytic enzymes (12).

3. Neuroprotective Mechanisms and Effects of Epo Administration

a. Evidence of Neuroprotection with Epo Administration in Experimental Models - Epo has been shown to have neuroprotective effects against a variety of types of experimental neural injury in a variety of species. In rats, Epo has reduced hypoxic/ischemic injury (13), decreased apoptotic neuronal loss after middle cerebral artery occlusion (14), reduced infarct volume after focal brain ischemia (2), prevented the loss of autoregulation in a subarachnoid hemorrhage (SAH) model (15), and prevented loss of motor neurons following sciatic nerve transection (16). In mice, preischemia Epo administration reduced infarct volume (9) and prevented glutamate toxicity in vitro (17) and reduced neurotoxicity in - 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP)-induced parkinsonism. In gerbils, intraventricular Epo improved neurobehavioral outcome and reduced neuronal loss in a global ischemia model (18). In rabbits, Epo has been shown to reduce neurologic deficits in a spinal cord ischemia model (19) and to reduce cortical neuron loss (20) and reduce vasoconstriction (21) in SAH models.

b. Mechanisms of Neuroprotection by Epo Administration In experimental studies, the neuroprotective effects of Epo administration appear to be independent of any systemic effects. Epo has neuroprotective effects in vitro, where confounding systemic mechanisms do not exist (17). However, this does not mean that the systemic effects of Epo administration might not have important independent effects on outcome, especially the long-term outcome following TBI. The mechanism of the neuroprotective action of Epo administration is not fully understood, but multiple potentially beneficial effects have been identified.

1) Systemic vascular effect Epo has a pressor effect which could preserve better perfusion of the brain in focal and incomplete ischemia models (22).

2) Cerebral vascular effect via NO production The effect of Epo administration on NO production has been variable from study to study, but a number of studies suggest that NO production is increased after Epo administration.

a) Increased NO Numerous studies suggest that Epo administration upregulates NOS or increases NO production (23) or dilates vessels in a manner that suggests NO production by endothelium (24). In physiological
circumstances where endogenous Epo production is increased, such as in athletes training at high altitudes, production of NO is also increased (25). Finally, in some pathological conditions, Epo administration has been found to dilate cerebral vessels. In an SAH model, Epo reversed the vasoconstriction that occurred in intracranial vessels (21). A single dose of rhEPO given peripherally has been shown to preserve autoregulation of CBF (15).

b) Decreased NO - Chronic administration (1 week) of Epo caused attenuated depressor responses to endothelium-dependent vasodilators that may have suggested inhibition of NOS activity (26). Some studies have suggested that Epo inhibits eNOS protein expression (27) and reduces NO concentration in the brain after ischemia (28).

c) No change in NO – Some studies suggest that Epo administration does not alter NO synthesis (29).

3) Anti-apoptotic effects  A number of studies implicate Epo activities in apoptosis pathways. In a global ischemia model in gerbils, expression of Bcl-xL was markedly increased in the hippocampus of animals given Epo intraventricularly (30). Activation of neuronal EpoRs prevented apoptosis induced by NMDA (N-methyl-d-aspartate) or NO through activation of NF-kappaB by the JAK2 kinase (31). Studies involving free radical-induced injury in cerebral microvascular endothelial cells showed that constitutive Epo is present in endothelial cells but is insufficient to prevent cellular injury. Signaling through the EpoR, however, remains biologically responsive enough to exogenous Epo administration to offer significant protection against nitric oxide-induced injury. Exogenous Epo maintains both genomic DNA integrity and cellular membrane asymmetry through parallel pathways that prevent the induction of apoptotic-protease activating factor 1 (Apaf-1) and preserve mitochondrial membrane potential in conjunction with enhanced Bcl-xL expression. Consistent with the modulation of Apaf-1 and the release of cytochrome c, Epo also inhibits the activation of caspase-9 and caspase-3-like activities (32). Through pathways that involve the initial activation of protein kinase B, Epo maintains mitochondrial membrane potential. Subsequently, Epo inhibits caspase 8-, caspase 1-, and caspase 3-like activities linked to cytochrome c release through mechanisms that are independent from the mitogen-activated protein (MAP) kinase systems of p38 and c-Jun N-terminal kinase (JNK) (33).

4) Anti-inflammatory effect  Studies by Brines et al (2) noted that the inflammatory response to traumatic injury and to ischemia was markedly reduced in Epo-treated animals. More recent studies have shown that Epo inhibits activation of microglia, possibly by reducing phosphatidylserine exposure (34).

c. Pharmacology of Epo Neuroprotection  Recombinant human erythropoietin (rhEpo) is a 165 amino acid glycoprotein with a molecular weight of 30,400 daltons manufactured by recombinant DNA technology. It is produced by mammalian cells into which the human erythropoietin gene has been introduced and contains the identical amino acid sequence of isolated natural erythropoietin (35). When administered, it produces the same effects as endogenous erythropoietin (36).

1) Crossing the Blood Brain Barrier: Such a large molecule would not be expected to cross the blood brain barrier, and some studies measuring CSF levels of Epo after administration of rhEpo in human neonates who had suffered hypoxic injury suggest that it does not (4). However, in experimental models, immunohistochemical studies suggest that Epo administered systemically is transported into the brain even in uninjured animals (2).
a) In these studies, at 5 hrs after 5000 IU/kg of Epo was administered IP, labeled Epo was found surrounding capillaries and extending into the brain parenchyma a distance 3-4 times that of the thickness of the capillary wall.

b) At 17 hrs after Epo administration, labeled Epo was found localized to scattered neurons. In addition, measurements of Epo in CSF of rats demonstrate a 100 mU/ml increase Epo at 30 minutes after administration of Epo 5000 IU/kg IP (2). These investigators proposed that there is an active translocation of Epo across the blood brain barrier.

c) In the pilot trial of rhEpo in patients with stroke, CSF levels of Epo were 60-100 x higher in the rhEpo treated patients than in the placebo-treated patients (37).

2) Neuroprotective Dosage Levels

Neuroprotective doses for Epo in most of the experimental studies range from 500-5000 IU/kg (38). In a spinal cord ischemia model, a dose of 800 IU/kg was equivalent to or slightly better than 1000 IU/kg (19). In a middle cerebral artery stroke model, doses of Epo between 450 IU/kg and 1000 IU/kg were effective at reducing infarct volume, while doses below 450 IU/kg were not effective (2).

3) Time Window

Epo administration as late as 6 hours after ischemia or trauma has been shown to be neuroprotective. After 6 hours, however, the neuroprotective effect is markedly reduced (2). A similar time window for in vitro neuroprotection studies has been observed (33,32,39). We have also confirmed this 6hr time window in our rat cortical impact injury model of TBI (see summary of data in Appendix I).

d. Current Clinical Use of Epo

rhEpo, has been used in patients with anemia due to chronic renal failure (CRF), including those on and not on dialysis(40,41,42,36,43,44,45,46,47,48,49,77,78), HIV-infected patients treated with zidovudine(50,51), and adult and pediatric cancer patients receiving chemotherapy(52,53). In addition, it has also been used for elective orthopedic(54,55,56,79) surgical patients in order to reduce the need for allogenic blood transfusions. Adverse events associated with rhEpo administration include thrombotic events, hypertension, seizures, pure red cell aplasia, progression of malignant tumors, and increased mortality.

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<th>Adverse Event</th>
<th>Population and Effects</th>
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<tr>
<td>Thrombosis</td>
<td>- Dialysis patients during procedure may require increased heparin to prevent clotting of the artificial kidney (35)</td>
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<td>- Dialysis patients with ischemic heart disease or congestive heart failure (35)</td>
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<td>- CRF patients where hemoglobin 13-15 g/dl was targeted (77)</td>
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<tr>
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<td>- Orthopedic patients treated pre-surgery to reduce need for transfusions (79)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>- Uncontrolled hypertension is a contraindication for use</td>
</tr>
<tr>
<td></td>
<td>- Up to 80% of patients with CRF may have hypertension(57), and approximately 25% of patients on dialysis may require initiation or increases in hypertensive therapy (35)</td>
</tr>
<tr>
<td>Seizures</td>
<td>- CRF patients (35)</td>
</tr>
<tr>
<td>Pure Red Cell Aplasia</td>
<td>- CRF patients (35)</td>
</tr>
<tr>
<td>Increased Mortality</td>
<td>- Dialysis patients with clinically evident heart disease(58)</td>
</tr>
<tr>
<td></td>
<td>- CRF patients where hemoglobin &gt;13.5 g/dl was targeted (76)</td>
</tr>
</tbody>
</table>
It is noteworthy that these adverse events, listed in Table 1 above, occurred primarily in patients with significant medical disease, most notably chronic renal failure, HIV, and cancer. The proposed population for study in this application will be patients with severe brain injuries. This population is usually young and relatively healthy.

1) Use of rhEpo on Patients with Neurologic Conditions. A safety study and a pilot efficacy study have been completed for high-dose administration of Epo in patients with stroke (37). In the safety study, 13 patients received rhEpo intravenously (33,000 IU/50 ml/30 min) once daily for the first 3 days after stroke. No safety issues were identified. In the double-blind randomized pilot trial, 40 patients received either rhEpo or saline within 5 hrs of onset of symptoms, and the plasma concentration of erythropoietin was increased to 5148+1095 mU/ml, compared to 19+3 mU/ml in the placebo-treated patients. A strong trend for improvement in neurological outcome at 1 month post-stroke was observed in the rhEpo-treated group. A multicenter study of rhEpo administration in stroke is currently ongoing in Germany. In another recent clinical study of 1302 critically ill patients reported that treatment with rhEpo 40,000 IU subcutaneously on day 3 and weekly x 3 doses reduced the need for allogenic blood transfusion and also increased hemoglobin concentration (3). No adverse events were reported.

2) Confounding Systemic Effects of Epo in Humans. One systemic effect that might be an important issue is the stimulation of erythropoiesis and subsequent increase in hemoglobin concentration, which could potentially improve cerebral oxygen delivery. Most of the in vivo neuroprotection studies have been conducted over an acute time period, where this effect would be minimal. In addition, asialoerythropoietin, a short-lived Epo preparation produced by completely removing the sialic acids that delay clearance of Epo in vivo, has equal neuroprotective effects to Epo but does not stimulate erythropoiesis (60). For any study involving administration of Epo after trauma, the effect on hemoglobin concentration and the need for transfusion of blood products would be an important confounding issue.

III. Study Design

This study is a randomized clinical trial using a factorial (2 x 2) design. Administration of rhEpo and the hemoglobin level for transfusion threshold are the two factors (i.e. independent variables) in the design that will be randomly assigned. Randomized blocking will be used. The primary outcome variable (i.e. dependent variable) will be neurologic outcome, as measured by the Glasgow Outcome Scale (GOS), at six months after injury. Disability rating scale (DRS) at six months post-injury will be a secondary outcome measure. In addition, the study will examine the cerebrovascular effects of rhEpo administration and the effects of rhEpo administration on hemoglobin concentration, as well as the effects of both factors on brain oxygenation, the need for blood transfusion, and on systemic complications.

A. Patient Assignment to Treatment Groups

After enrollment, patients will be randomly assigned to one of four treatment groups, using two variables -- Epo treatment and Transfusion Trigger Level -- as shown in Table 2, below:
### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Transfusion Trigger &lt; 7g/dl</th>
<th>Transfusion Trigger &lt; 10g/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epo Treatment</strong></td>
<td>Group 1: Treatment with rhEpo, Transfusion trigger &lt;7g/dl</td>
<td>Group 3: Treatment with rhEpo, Transfusion trigger &lt;10g/dl</td>
</tr>
<tr>
<td><strong>No Epo Treatment</strong></td>
<td>Group 2: No Epo treatment, Transfusion trigger &lt;7g/dl</td>
<td>Group 4: No Epo treatment, Transfusion trigger &lt;10g/dl</td>
</tr>
</tbody>
</table>

#### B. Rationale for the Factorial (2X2) Design

The design uses two variables – Epo treatment and transfusion trigger level – to assign patients into one of four treatment groups. This is necessary because there are two major treatment effects anticipated from Epo, neuroprotection and hematopoiesis, and it is necessary to be able to analyze the data to detect the impact of each of these variables on the study dependent variable, neurologic outcome.

1. **Potential Confounding with Systemic Administration**  
   Epo has been shown to be neuroprotective in vitro, where confounding systemic effects are not present. It is likely, however, that systemic Epo administration to TBI patients will produce both a direct effect on the injured brain (i.e. neuroprotection – the goal of the study) and at least one systemic effect, stimulation of erythropoiesis with subsequent elevation of serum hemoglobin levels. As this increase in hemoglobin and associated increase in oxygen-carrying capacity could conceivably produce an improvement in neurologic outcome without the occurrence of neuroprotection, it is necessary to examine the impact of both of these effects of Epo separately and systematically.

2. **Anticipated Hematopoietic Effects**  
   The effects of rhEpo administration on erythropoiesis will probably not alter hemoglobin concentration during the first few days after injury. From the pilot stroke trial of rhEpo, where patients were given 33,000 IU of rhEpo daily for three days, there were no significant differences in hemoglobin concentration between the rhEpo and placebo-treated patients during the first three days (37). After the first three days, however, we expect to see an overall higher hemoglobin concentration and/or a lower need for transfusion of blood in the patients that receive rhEpo. As the duration of ICU care and hospitalization for severe TBI patients is usually at least a week and can be as long as several weeks, it is almost certain that the hematopoietic effects of rhEpo will be detectable, and so must be accounted for in the study design.

#### C. Selection of the Transfusion Trigger Levels

The optimal hemoglobin concentration for a patient with a severe traumatic brain injury is unknown.

1. **Current Transfusion Practices in Critical Care**  
   Current practice for blood transfusion level in all types of critically ill patients varies widely. A meta-analysis of transfusion guidelines in critical care units found that transfusion triggers varied primarily between 7 and 10 g/dl (61). The average hemoglobin concentration prior to transfusion in the CRIT study of 4892 critically ill patients cared for at 213 hospitals between 2000 and 2001 was 8.6±1.7 g/dl (62). A follow-up survey of critical care physicians regarding transfusion thresholds in several different clinical situations has recently been reported (63), in which 63% of physicians indicated that they had adopted a 7g/dl threshold for transfusion trauma patients. This was a significantly higher proportion of physicians than in 1993.

2. **Stable vs. Unstable Patients**  
   For stable patients, critical care physicians have generally adopted the lower transfusion threshold of 7g/dl to reduce the risk of transfusion-related complications. However, for critically ill patients with potential organ ischemia, especially
of brain or myocardium, there is still considerable controversy over the risk/benefit of this practice. Recent large retrospective studies in patient groups with multiple trauma (64), cardiac surgery (65), and acute coronary syndromes (66) have shown blood transfusions to be an independent predictor of mortality. Each of these studies has recommended either directly in the paper or in an accompanying editorial that prospective, randomized trials are needed to define the appropriate transfusion threshold in these subgroups of patients. It seems clear that there is considerable equipoise for a randomized trial of transfusion thresholds in these subgroups of critically ill patients.

3. Selection of a Transfusion Trigger for this Trial Based on these and other studies, we have set the lower conservative end transfusion trigger to be 7g/dl and selected 10g/dl as the higher level to initiate transfusion. If we use current evidence-based recommendations and choose a transfusion trigger of 7g/dl for all patients in our proposed trial, it would minimize the risk of transfusion-related complications. However, with the transfusion trigger set at this lower level, failure to find a neuroprotective effect with rhEpo administration might be attributable to secondary injury of the brain caused by accepting a hemoglobin concentration that is too low.

On the other hand, if we follow the brain-oriented practice and choose a transfusion trigger of 10g/dl for all patients in our proposed trial, which would theoretically optimize cerebral O₂ delivery, then a better outcome with rhEpo administration might be partially explained by a reduction in the need for blood transfusion, and so a reduction in transfusion-associated complications, to maintain the targeted hemoglobin concentration. The proposed design gives us the best chance to examine the overall neuroprotective effects of rhEpo and the interactions of rhEpo and hemoglobin concentration, blood transfusion, and transfusion-associated complications on outcome.

IV. Selection and Enrollment of Subjects The population of interest for this trial is patients that have sustained a severe traumatic brain injury, as evidenced by the initial post-resuscitation Glasgow Coma Score (GCS) but with limited systemic trauma, as categorized by the Abbreviated Injury Score (67) (AIS).

A. Inclusion Criteria
1. Blunt trauma mechanism of brain injury
2. Glasgow Coma Score – motor ≤ 5 (not following commands) on the post-resuscitation neurologic exam
3. Available for enrollment and administration of study drug within 6 hours of injury

B. Exclusion Criteria
1. Penetrating trauma (i.e. gun shot wounds)
2. GCS = 3 and bilateral fixed and dilated pupils
3. Pregnant
4. AIS score ≥ 5 for any body part except brain
5. severe pre-existing chronic disease
6. uncontrolled hypertension, defined as MAP > 130mmHg despite antihypertensive treatment
7. known hypersensitivity to mammalian cell-derived products or human albumin
8. currently taking anticoagulants

C. Study Enrollment Procedures
1. Identification of Potential Subjects Dr. Gopinath, the attending neurosurgeon for all TBI patients, or Dr. Robertson, medical director of the Neuro ICU at Ben Taub General Hospital, or UT Neurosurgery or the Neurosurgery Research Team will notify the on-call
research personnel about potential subjects for the study. The research personnel will confirm that the patients are eligible, and then try to locate relatives for informed consent.

2. Potential Subjects Not Enrolled in the Study A log list will be kept of all patients who are screened for the study. If a patient is found to be ineligible for the study, the reason will be recorded in the log. If a patient is eligible for the study, but relatives cannot be located or do not wish to participate in the study, this information will be recorded in the log. Basic demographic information (age, gender, race/ethnicity) and information about the nature and severity of the brain injury will also be recorded for these patients. No identifiers will be kept on any of these patients who do not participate in the study.

3. Informed Consent Procedures Patients enrolled in this study will be unable to give informed consent for the studies because they are unconscious from the severe TBI. In addition, legally authorized representatives are not commonly available during the first few hours after injury. Because of the need to administer the study drug as soon as possible after injury, most patients will be enrolled in this study under the emergency consent exception. This process will involve the following:

   a. We will try to contact relatives of the patient for the first 3 hours after injury. We will work with the social worker in the EC to find any identifying information available with the patient, and to call all phone numbers identified as possible relatives at least once, leaving messages when possible. If family arrives at the hospital within 3 hours after injury, one of the investigators or their research associates will approach the family member, describe the study, and ask if they would like to participate in the study. If they agree to participate, this will be documented by having the appropriate relative sign an IRB-approved informed consent form, and the patient will be enrolled in the study. For determining the appropriate relative to sign the informed consent, we will use the definition of LAR that is practiced at the individual hospital. At Ben Taub General Hospital, this is the available family member that is highest in the following order of priority: spouse, adult child, parent, adult sibling, grandparent, adult grandchild. The highest priority relative may choose to transfer this right to another eligible relative. At Memorial Hermann Hospital, only the highest priority relative, even if that person is not immediately available, is able to give informed consent for research, and this right cannot be transferred to another relative.

   b. If we are able to contact relatives by phone within the first 3 hours, but they are not able to get to the hospital quickly then we will describe the study to the relative by phone following the narrative that is in Appendix IX. If they are agreeable, we will enroll the patient in the study using the emergency consent exception. When the family arrives at the hospital, we will discuss the study with them again and have them sign the consent form to continue participation in the study.

   c. If no family is located within the first 3 hours then we will enroll the patient using the emergency exception. If relatives not qualified to be LAR are located within the first 3 hours, the study will be explained to them, and we will enroll the patient using the emergency consent exception if these relatives have no objection. The circumstances of the enrollment will be described in a progress note in the patient’s chart and research records. When family is subsequently found, we will inform them about the study and allow them the opportunity to continue to participate. If they agree, we will have them sign the consent form to continue participation in the study.

   d. It is possible that a patient might be enrolled in the study using the emergency exception from informed consent, and then die prior to locating the family. If this should happen and any relatives are subsequently identified, they will be informed about the patient’s participation in the study.
e. We will summarize these events for the IRB at the time of each annual review.
f. At Ben Taub, the original copy of the consent form will be placed in the patient’s medical record, as required by hospital’s policy. A copy of the consent form will also be kept in a locked file cabinet in Dr. Robertson’s offices, and a copy will also be given to the relative signing the form. At UTHSC-H/MHH the original consent will be kept with study documents and copies will be placed on the chart. A note will be placed in the chart indicating that the patient has been enrolled in the study. A study registration form (Appendix VI) will be filled out for the patient and faxed to the Harris County Hospital District business office (713-873-2278), as required by hospital policy.
g. It is unlikely that any of the patients will recover sufficiently during the acute intervention period to give informed consent for research. However, many of the patients will recover during the 6 month follow-up period. At each of the follow-up visits (3 months and 6 months), the neuropsychology technicians, under the supervision of Dr. Hannay, will assess the patient’s level of functioning. If they have recovered sufficiently to give informed consent, the study will be explained to them and they will be asked to sign a consent form for the follow-up assessments.

4. Operational Procedure  Randomization lists with the four groups (See Table 2, page 18) will be prepared by Dr. Barbara Tilley, the study statistician, and kept in each hospital’s research pharmacy. When a patient is enrolled in the study, the research personnel will call the research pharmacy with the patient’s weight. The pharmacist will select the next unassigned treatment on the appropriate list, and prepare the assigned drug treatment. The pharmacist will also tell the research personnel what the assigned transfusion trigger level is, and this information will be recorded and also put on a label on the front of the patients chart.

V. Study Interventions  The primary study intervention is the administration of rhEpo; however, several additional management and treatment variables will be carefully factored into and controlled in the overall study protocol. In addition to the administration of rhEpo, these variables include: 1) administration of blood transfusions, as indicated by the transfusion trigger level, 2) concomitant interventions specific to this protocol, and 3) standard management of patients with TBI management of blood pressure, intracranial pressure, and cerebral perfusion pressure.

A. Interventions, Administration, and Duration

1. Administration of rhEpo
2. Administration of blood transfusions, as indicated by transfusion trigger level of hemoglobin
3. Concomitant protocol interventions
4. Standard management of patients with TBI management of blood pressure, intracranial pressure, and cerebral perfusion pressure

B. Handling of Study Interventions

1. Administration of rhEpo
   a. Dosage and administration
      1) Patients assigned to one of the “Treatment with Epo” groups (See Table 2, page 18) will receive 500 IU/kg intravenous bolus infusion over two minutes of rhEpo (Epogen®, Amgen, Inc., Thousand Oaks, CA), within 6 hours of injury. Two additional doses will be given, one per week for the next two weeks, while the patient remains in the ICU.
      2) Patients randomized to one of the “Treatment with Placebo” groups will receive an equal volume of normal saline, administered according to the same schedule.
3) All investigators and clinical personnel will be blinded to the treatment group administration of rhEpo.

4) The hospital’s pharmacy will purchase and store rhEpo for use in this study. The pharmacist will prepare the assigned treatment drug dose from a standardized order sheet (Appendix X).
   a) The dose of rhEpo (500 IU/kg) will be drawn into a syringe and provided to the NICU for administration by the nursing staff.
   b) The placebo dose of normal saline will also be dispensed by the pharmacist in a similar manner.
   c) The dosage forms of both the rhEpo and the placebo saline will be prepared so that it is undetectable as which one is given (i.e. blinded).
   d) All study personnel will remain blinded to the Epo study drug assignment.

b. Dose modification protocol for Epo

1) In the event that patients experience an increased hemoglobin level from the first rhEpo dose, it will be necessary to modify the protocol for the subsequent two weekly doses. The first dose of Epo is given primarily for neuroprotection, and would not be modified because of hemoglobin concentration.

2) However, the subsequent two doses at weekly intervals could potentially increase hemoglobin concentration excessively, and therefore the following dose modification rule will be used for these later two doses:
   a) If the hemoglobin concentration is >12g/dl or the rate of rise of hemoglobin is >1.0g/dl over 2 weeks (not due to transfusion), then dose will be held.

3) Transfusion during acute bleeding: In patients who are actively bleeding, as may occur in the early post-injury period, hemodynamic instability may also be used as an indication for transfusion therapy in both transfusion trigger arms.

2. Administration of blood transfusions, as indicated by transfusion trigger level of hemoglobin

a. Patients randomized to 'Transfusion trigger < 7g/dl' will have hemoglobin concentrations maintained at least 7g/dl with transfusion of packed red blood cells (PRBCs), whenever the patient’s hemoglobin level is found to be less than 7g/dl, during the acute post-injury recovery period (i.e., until ICP monitoring and ventilatory support are no longer required).

b. Patients randomized to 'Transfusion trigger < 10g/dl' will have hemoglobin concentrations maintained at least 10g/dl with transfusion of packed red blood cells (PRBCs), whenever the patient’s hemoglobin level is found to be less than 10g/dl, during the acute post-injury recovery period (i.e., until ICP monitoring and ventilatory support are no longer required).

c. In patients who are actively bleeding, as may occur in the early post-injury period, hemodynamic instability may also be used as an indication for transfusion therapy in both transfusion trigger arms.

d. All transfusions will be performed in keeping with the hospital’s standards of care for the administration of blood and blood products.

e. It is not possible for investigators or clinical personnel to be blinded to the patients’ assignment to transfusion trigger group. However, personnel conducting outcome assessments will be blinded to all treatment assignments.

C. Concomitant Interventions

1. Concomitant protocol interventions: All patients in the trial will be supplemented with folate (1mg po/NG or IV daily) and iron sulfate (300-325mg po/NG tid) as a part of the standard management protocol to be certain that any anemia that might develop is not due to nutritional deficiencies.
2. **Standard management of patients with TBI**
   
a. All patients enrolled in this study will be cared for in the NICU at Ben Taub, or the NTICU and possibly the STICU at MHH, during the acute post-injury period.

b. Management will follow a detailed standard protocol ([Appendix II](#)) which conforms to the Guidelines for the Management of Severe Head Injury(68) and also capitalizes on the unique experience and capabilities of the neuro ICUs. Briefly summarized here, our management protocol includes:

c. Intubation and ventilation with $P_{a}O_2$ maintained at or near 100 mm Hg and $P_{a}CO_2$ maintained between 35-40 mm Hg

d. Management of fluid volume status to keep mean arterial pressure > 80 mm Hg

e. CT scanning and xenon-CT cerebral blood flow studies on admission

f. Evacuation of mass lesions, when present

g. Monitoring of intracranial pressure (ICP), cerebral perfusion pressure (CPP), brain tissue oxygenation ($P_{bt}O_2$), and systemic jugular venous oxygenation ($S_{jv}O_2$)

h. Placement of a microdialysis catheter

i. Sedation with morphine

j. Management of elevated ICP – goal ICP < 20 mm Hg
   
a) Neuromuscular blockade
   
b) Drainage of CSF
   
c) Administration of mannitol/hypertonic saline
   
d) Hyperventilation to a $P_{a}CO_2$ 25-30 mm Hg if $S_{jv}O_2$ remains > 55%
   
e) Barbiturate coma
   
f) Decompressive craniectomy

k. Management of decreased CPP - goal CPP > 60 mmHg
   
a) Treat ICP if > 20 mm Hg
   
b) Fluid resuscitation
   
c) Dopamine/norepinephrine/phenylephrine/hormonal replacement dose vasopressin
   
d) Milrinone or dobutamine as indicated for low cardiac output states

l. Nutritional support starting within 48 hours of injury to supply 140% of estimated resting energy expenditure

**D. Adherence Assessment**  Protocol adherence will be monitored through the following mechanisms:

1. **Daily clinical supervision**: All the investigators will also be involved in the clinical care of these patients on a daily basis, and matters of protocol compliance and treatment adherence will be integrated into NICU rounds and other patient care activities, as appropriate.

**VI. Clinical and Laboratory Evaluations**

**A. Schedule of Evaluations**

see [Table 3](#) on next page
Table 3. Schedule of Evaluations

<table>
<thead>
<tr>
<th>Timing of Test</th>
<th>Part of Standard Management?</th>
<th>Day 0/1</th>
<th>Day 2</th>
<th>Days 3-4</th>
<th>Day 5</th>
<th>Days 6-8</th>
<th>Day 9</th>
<th>Day 10</th>
<th>Days 11-15</th>
<th>Day 16</th>
<th>Days 17-29</th>
<th>Day 30 or D/C</th>
<th>3 Mo</th>
<th>6 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening Tests:</strong></td>
<td></td>
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<tr>
<td>Neurological/general examination</td>
<td>at admission</td>
<td>yes</td>
<td>X/-</td>
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<tr>
<td>CT scan of head and other organ systems as indicated by injury</td>
<td>at admission</td>
<td>yes</td>
<td>X/-</td>
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<tr>
<td>Hct/Hgb</td>
<td>at admission</td>
<td>yes</td>
<td>X/-</td>
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<tr>
<td>BUN/creatinine/electrolytes</td>
<td>at admission</td>
<td>yes</td>
<td>X/-</td>
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<td>liver function tests</td>
<td>at admission</td>
<td>yes</td>
<td>X/-</td>
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<tr>
<td>ABGs</td>
<td>at admission</td>
<td>yes</td>
<td>X/-</td>
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<td>Chest x-ray</td>
<td>at admission</td>
<td>yes</td>
<td>X/-</td>
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<tr>
<td><strong>Randomization:</strong></td>
<td>after informed consent</td>
<td>for study</td>
<td>X/-</td>
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<td>Informed Consent:</td>
<td>after screening</td>
<td>for study</td>
<td>X/-</td>
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<tr>
<td><strong>Treatments and Physiological Monitoring of Treatments:</strong></td>
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<tr>
<td><strong>Study drug</strong> (rhEpo 500IU/kg or placebo) IV over 2 minutes</td>
<td>within 6hr of injury, and then qwk x 2 while still in ICU</td>
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<tr>
<td><strong>Evaluate for possible study drug dose modification</strong></td>
<td>days 9 and 16 before giving dose of study drug</td>
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<tr>
<td>Vital Signs [EKG, HR, Temperature, BP, Spo₂, +ICP, +ETCO₂, +SjvO₂, +PbtO₂]</td>
<td>continuously monitored on bedside monitor, recorded q1h plus q15min during study drug administration</td>
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<tr>
<td>Noninvasive cerebral hemodynamics [mcaFV, FVol, ARI, THRR, CO₂R]</td>
<td>qd days 1-10</td>
<td>for study</td>
<td>X/X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>O₂ reactivity test</td>
<td>qd x 10d while PbtO₂ is being monitored</td>
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<tr>
<td>Arterial, jugular venous blood for blood gases, serum for Epo, nitrate/nitrite</td>
<td>within 30 min before and at 1hr after study drug administration on day 1</td>
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<tr>
<td>CSF for Epo, nitrate/nitrite</td>
<td>within 30 min before and at 1hr after study drug administration on day 1</td>
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<tr>
<td>Dialysate for Epo, nitrate/nitrite (sample collected)</td>
<td>within 30 min before and at 1hr after study drug administration on day 1</td>
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<td>Procedure</td>
<td>Frequency</td>
<td>Notes</td>
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<tr>
<td>Serum, CSF, and dialysate for Epo, nitrate/nitrite, and inflammatory markers</td>
<td>qd x 10d while still in ICU for study</td>
<td>-/X X X X X X X X x</td>
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<tr>
<td>xenon CT CBF, CMRO₂</td>
<td>within 12 hr of injury, at 48±2hr and 120±4 hr after injury</td>
<td>yes</td>
<td>-/X X x</td>
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<tr>
<td>Freeze and save any contused brain tissue debrided at surgery and not needed for pathology</td>
<td>any surgery done for study</td>
<td>X/X X X X X X X X X X</td>
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<tr>
<td><strong>Apply assigned transfusion trigger guidelines</strong></td>
<td>during acute post-injury period (days 1-10 or until not requiring ICP monitoring and ventilatory support)</td>
<td>transfusion is standard management-randomization to transfusion trigger is part of study</td>
<td>X/X X X X X X X</td>
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<tr>
<td>Hct/Hgb</td>
<td>before and 1hr after any blood transfusions that are given during days 1-30</td>
<td>yes</td>
<td>X/X X X X X X X X X x</td>
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<tr>
<td>Hct/Hgb</td>
<td>qd x 10d, then qwk while in ICU, at 30d or hospital discharge</td>
<td>yes</td>
<td>X/X X X X X X X X X</td>
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<tr>
<td>Vital Signs (EKG, HR, Temperature, BP, SpO₂, +ICP, +ETCO₂, +SjvO₂, +PbtO₂)</td>
<td>continuously monitored on bedside monitor, recorded q1h plus q15min any blood transfusions that are given days 1-30</td>
<td>yes</td>
<td>X/X X X X X X X X X X</td>
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<tr>
<td>Noninvasive cerebral hemodynamics (mcaFV, FVol, ARI, THR, CO₂R, O₂R)</td>
<td>within 30 min before and at 1hr after any blood transfusions that are given during days 1-5</td>
<td>for study</td>
<td>X/X X X X X</td>
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<tr>
<td>Record detailed information about blood transfusions</td>
<td>any occurrence during first 30 days or to hospital discharge</td>
<td>for study</td>
<td>X/X X X X X X X X X</td>
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<tr>
<td>Record SOFA score qd and detailed information about any infections that occur</td>
<td>qd (SOFA) and any occurrence (infections) during first 30 days or to hospital discharge</td>
<td>for study</td>
<td>-/X X X X X X X X X X</td>
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<tr>
<td>ABG, PaO₂/FiO₂</td>
<td>at admission and qd while ventilated</td>
<td>yes</td>
<td>X/X X X X X X X X X</td>
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<tr>
<td>Chest x-ray</td>
<td>at admission and qd while ventilated</td>
<td>yes</td>
<td>X/X X X X X X X X</td>
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<tr>
<td>Record detailed information about ARDS that occurs</td>
<td>any occurrence during first 30 days or to hospital discharge</td>
<td>for study</td>
<td>X/X X X X X X X</td>
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Notes:
- X: Yes
- : No
## Timing of Test

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<thead>
<tr>
<th>Test</th>
<th>Part of Standard Management?</th>
<th>Day 0/1</th>
<th>Day 2</th>
<th>Days 3-4</th>
<th>Day 5</th>
<th>Days 6-8</th>
<th>Day 9</th>
<th>Day 10</th>
<th>Days 11-15</th>
<th>Day 16</th>
<th>Days 17-29</th>
<th>Day 30 or D/C</th>
<th>3 Mo</th>
<th>6 Mo</th>
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<tr>
<td><strong>General Monitoring:</strong></td>
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<tr>
<td>Vital Signs (EKG, HR, Temperature, BP, SpO₂)</td>
<td>yes</td>
<td>X/X</td>
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<td>BUN/creatinine/electrolytes</td>
<td>yes</td>
<td>X/X</td>
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<td>Liver function tests</td>
<td>yes</td>
<td>X/-</td>
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<td><strong>Long-Term Outcome:</strong></td>
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<td>GOAT</td>
<td>Daily until score ≥ 76 (or patient DC), 3, 6 mo</td>
<td>-/X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>GOS</td>
<td>at 3 and 6 mo</td>
<td>for study</td>
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<td>DRS</td>
<td>at 3 and 6 mo</td>
<td>for study</td>
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<td>Neuropsych battery</td>
<td>at 3 and 6 mo</td>
<td>for study</td>
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B. Timing of Evaluations

1. Pre-randomization evaluations
   a. Screening:
      1) The screening tests that will be done to determine eligibility in the study are those
         which are normally done as a part of the emergency department work-up of a
         patient with a severe TBI, including:
         a) a neurological/general examination,
         b) a CT scan of head (required) and other organ systems as indicated by the
            injury,
         c) hematocrit and hemoglobin (Hct/Hgb),
         d) blood urea nitrogen (BUN) and creatinine,
         e) serum electrolytes,
         f) liver function tests,
         g) arterial blood gases (ABGs),
         h) chest x-ray
         i) body weight
      2) Screening activities done specifically and exclusively for this study will include:
         a) Comparing clinical data obtained from the routine evaluation (above) with the
            study inclusion and exclusion criteria
         b) Determining the time period from injury to hospital arrival to determine
            whether the patient falls within the time line for study eligibility
         c) Identifying family members and their potential availability to provide informed
            consent
   b. Pre-entry:
      1) Family members will be approached regarding the patient’s participation in the
         study only after they have been informed about the patient’s medical condition
      2) Informed consent must be obtained within the 6 hour time window for study
         enrollment and administration of study drug
   c. Entry:
      1) The on-call research personnel will verify that enrollment has occurred within the
         6 hour time window.
      2) The on-call research personnel will notify the research pharmacist of the patient’s
         enrollment
      3) The research pharmacist will verify the time from injury and body weight in order
         to determine the appropriate randomization assignment

2. On-study evaluations
   a. Physiologic monitoring related to administration of study drug/placebo
      1) See Table 3 (page 24) for detailed listings
      2) Continuously monitored and recorded every 15 minutes during study drug
         administration
         a) Vital signs (heart rate, temperature, blood pressure)
         b) MAP, ICP, and CPP
         c) Oxygen saturation (SpO₂)
         d) Jugular venous oxygen saturation (SjvO₂)
         e) Brain tissue oxygen saturation (P₅₀O₂)
      3) Performed daily on hospital days 1-10
         a) Non-invasive cerebral hemodynamics
            i. middle cerebral artery flow dynamics (mcaFV)
            ii. internal carotid artery flow volume (icaFvol)
            iii. autoregulatory index (ARI)
            iv. transient hyperemic response ratio (THRR)
v. **CO₂ reactivity (CO₂R)**

b) Oxygen reactivity test performed once every day that \( P_{\text{a}}O_2 \) is monitored
c) Analysis of arterial, **jugular venous** blood for:
   i. blood gases
   ii. Epo levels
   iii. Nitrate/nitrite levels
   iv. Inflammatory markers
d) Analysis of CSF and **microdialysis fluid**
   i. Epo levels
   ii. Levels of nitrate/nitrite
   iii. Inflammatory markers

4) Performed within 30 minutes before and 1 hour after administration of the study drug on hospital day 1
   a) Analysis of arterial, **jugular venous** blood for
      i. blood gases
      ii. Epo levels
      iii. Nitrate/nitrite levels
      iv. Inflammatory markers
   b) Analysis of CSF and **microdialysis fluid**
      i. Epo levels
      ii. Levels of nitrate/nitrite
      iii. Inflammatory markers

5) Performed during specific time windows after injury
   a) Tests
      i. Stable xenon CT-CBF
      ii. Cerebral metabolic rate of oxygen (CMRO₂)
   b) Times for evaluation
      i. between 1 – 12 hours after injury
      ii. between 46 – 50 hours after injury
      iii. between 116 – 124 hours after injury

6) Performed on surgical specimens
   a) Any brain tissue that is resected and not required for clinical neuropathological analysis will be frozen at -80°C for later analysis of Epo and EpoR.

b. **Physiologic monitoring related to transfusion trigger level**
   1) See Table 3 on page 24

2) Continuously monitored and recorded every 15 minutes during transfusions given in ICU on hospital days 1-30
   a) Vital signs (heart rate, temperature, blood pressure)
   b) MAP
   c) ICP and CPP, if ICP monitor is present
   d) Oxygen saturation (SpO₂)
   e) **Jugular venous oxygen saturation (SjvO₂), if monitor is present**
   f) Brain tissue oxygen saturation (\( P_{\text{a}}O_2 \)), if monitor is present
   g) Oxygen reactivity test performed once every day that \( P_{\text{a}}O_2 \) is monitored

3) Performed within 30 minutes prior to and 1 hour after any blood transfusions given during hospital days 1-5
   a) Non-invasive cerebral hemodynamics
      i. middle cerebral artery flow dynamics (mcaFV)
c. General monitoring

1) Intensive care monitoring
   a) See Table 3 (page 24) for detailed monitoring activities related to administration of study drug and transfusions
   b) Additional ICU monitoring activities
      i. arterial blood gases and PaO₂/FiO₂ measurements daily while on mechanical ventilation
      ii. chest x-ray daily while on mechanical ventilation
      iii. laboratory evaluations daily for 10 days, then weekly while in the ICU, then at hospital day 30 or discharge, whichever is earliest:
         - blood urea nitrogen (BUN)
         - creatinine
         - serum electrolytes
         - hematocrit and hemoglobin
         - liver function test (weekly only)

2) Transfusion monitoring
   a) Record detailed information about blood transfusions including:
      i. Blood product type (i.e. whole blood, packed red blood cells, etc)
      ii. Age of the blood product
      iii. Any transfusion-related reactions

3) Complication monitoring during the first 30 days or until hospital discharge, whichever is first
   a) Record detailed information about any infectious complications (i.e. pneumonia, bacteremia, urinary tract infection, ventriculitis)
   b) Record detailed information about episodes of Adult Respiratory Distress Syndrome (ARDS)
   c) Calculate the Sepsis-related Organ Failure Assessment (SOFA) score, for first 30 days or until hospital discharge (whenever sufficient information is available to calculate score)

3. Intervention discontinuation evaluations
   a. There are no specific evaluations performed at the time of the final dose of study drug.
   b. Patients will be managed according to the study protocol for the duration of their stay in intensive care, which will most likely extend beyond the actual time of study drug administration.

4. Post-intervention evaluations
   a. At the time of hospital discharge, patients will be evaluated for the appropriate level of care and discharge accordingly, with the majority of patients requiring inpatient rehabilitation or some type of extended care facility from historical experience
   b. Evaluation of long-term neurologic outcome will include the following tests:
      1) Galveston Orientation and Amnesia Test (GOAT) daily until the score is = 76 (or hospital discharge) and at 3 and 6 months post-injury
      2) Glasgow Outcome Scale (GOS) score at 3 months and 6 months post-injury
      3) Disability Rating Scale (DRS) score at 3 months and 6 months post-injury
4) Neuropsychology battery of tests (listed in Appendix III) at 3 months and 6 months post-injury
c. For patients who are lost to follow-up at 6 months post-injury, we will search vital statistics databases to determine if we can document that the patient has died.

5. Final evaluations: The 6 month evaluation will be the final evaluation for this study.

6. Pregnancy
   a. Approximately 70% of severe TBI patients are male. Women of childbearing age will have a negative pregnancy test prior to enrolling in the study.
   b. It is highly unlikely that a female subject would become pregnant during the hospitalization portion of this trial.
   c. In the event that a female subject becomes pregnant after hospital discharge but during the 6 month follow-up period, this will be noted in the patient’s study records and reported to the DSMB. There should be no residual effects from the study drug by this point.

C. Special Instructions and Definitions of Evaluations

1. Informed consent
   a. Patients will be unable to provide informed consent due to unconsciousness from their severe brain injury
   b. The procedure for obtaining informed consent is discussed in Section 4.3.c on page 20

2. Documentation of TBI and other clinical conditions
   a. All clinical patient data will be recorded on hospital forms currently in use for day-to-day patient care according to the best clinical judgment of the treating clinicians
   b. Description of the traumatic brain injury will be done using the following standardized assessments:
      1) Glasgow Coma Scale
      2) Clinical neurologic exam
      3) Marshall classification of traumatic brain injury on CT scan (69)
      4) Trauma triage primary and secondary surveys and neurosurgery admission history and physical
   c. Abbreviated Injury Score
      a. Research data will be transcribed/entered onto case report forms, both manual and electronic, designed specifically for this study
      b. Data about medical complications related to specific study hypotheses will be recorded in accordance with definitions (see Appendix VIII) promulgated by the Centers for Disease Control (70), the American College of Chest Physicians/Society of Critical Care Medicine (71), or other recognized expert panels for the following conditions:
         1) Pneumonia (70)
         2) Urinary tract infection (70)
         3) Ventriculitis (70)
         4) Bacteremia (70)
         5) Acute respiratory distress syndrome (72)
         6) Systemic inflammatory response syndrome (SIRS) (71)
         7) Sepsis (71)
         8) Multiple organ dysfunction syndrome (MODS) (71,73)
         9) Septic shock (71)
3. **Medical history**: A medical history will be taken on admission to the hospital, including any past history of neurologic problems or conditions.

4. **Treatment history**: Significant medical treatments that the patient was receiving prior to the injury will be recorded, including prescription medications, alternative and complementary therapies, recreational drug use, and use of alcohol and tobacco.

5. **Concomitant treatments**: Data about the patient’s inpatient care will be recorded including medications administered and neurologic and other major surgical procedures performed.

6. **Study intervention modifications**: See Section 5.2.a.ii on page 22

7. **Clinical assessments**: See Section 6.3.b on page 30 and also Table 3 on page 24

8. **Laboratory evaluations**: See Table 3 on page 24 and Section 6.2 on page 27

9. **Pharmacokinetic studies**: While there will be evaluations of Epo levels in CSF and microdialysate fluid, no true pharmacokinetic studies will be done for this study.

10. **Other laboratory studies**: See Table 3 on page 24 and Section 6.2 on page 27

11. **Additional evaluations**
   a. The stable xenon CT imaging is performed under another IND protocol (IND #62,662). The procedures related to this evaluation are detailed in the manual of procedures for that protocol.
   b. The details of the noninvasive Doppler-based non-invasive evaluations of cerebral hemodynamics (see section 6.2.b.i.c.i on page 27) are described in detail in the manual of procedures.

12. **Questionnaires**: The Disability Rating Scale and Glasgow Outcome Scale structured interviews are validated and widely-used instruments to evaluate outcome from severe brain injury. They are shown in Appendix IV and V, respectively.

13. **Adherence assessments**: See Section 5.4, page 22.

D. **Off-Intervention Requirements**: none

VII. **Management of Adverse Experiences**

A. **Risks Associated with the Protocol**

1. **Standard management of severe TBI**: All procedures used in the management of TBI will follow a detailed standard protocol (Appendix II) which conforms to the Guidelines for the Management of Severe Head Injury(68) and also capitalizes on the unique experience and capabilities of this neuro ICU.

2. **Risks associated with administration of rhEpo**
   a. Known adverse effects of rhEpo administration – see section 2.2.c.iv page 16
   b. Specific risks
      1) **Hypertension**: Although high blood pressure is a potential side effect, it has been noted only rarely in patient groups other than in chronic renal failure patients. In the pilot stroke trial of rhEpo (37), intravenous administration of the
drug in the doses planned for the current study had no significant effect on blood pressure.

2) **Thrombotic events**: An increased incidence of thrombotic events and also an increased mortality has been observed primarily in studies where the target hematocrit was a normal value (i.e. 14-16g/dl for males, 12-14g/dl for females). This risk is minimized in the current study by targeting a lower hematocrit and with the dose modification rules that will be applied to the fourth and fifth doses of Epo.

3. **Risks associated with blood transfusion**: 
   a. Keeping hemoglobin levels greater than 10 g/dl may very well require more transfusions than keeping levels above 7 g/dl, thus increasing the risk for transfusion-related complications including:
      1) transmitted infections (risk of hepatitis B 1:100,000, risk of HIV 1:1,000,000),
      2) immune-related reactions including an increased risk of nosocomial infections (5.2- to 6-fold increased risk)
      2) non-immune-related reactions such as fluid overload and ARDS
   b. Keeping hemoglobin levels greater than 7 g/dl may put the injured brain at risk for hypoxia and decreased CBF
   c. Both levels of hemoglobin (7g/dl vs. 10g/dl) are considered clinically acceptable with some risk and some potential benefit, but it is not known for this subgroup of critically ill patients which level has the best risk-to-benefit ratio.

B. **Event Reporting**

1. **Expected adverse events** (see Appendix VIII for definitions) that will be tracked and reported in summary tables as rates per patient, and rates per patient days:
   a. Severe hypertension
   b. Thrombosis/thrombophlebitis events (deep vein thrombophlebitis, pulmonary embolus, myocardial infarction)
   c. ARDS
   d. Infections (meningitis/ventriculitis, urinary tract infection, pneumonia, bacteremia, MODS, sepsis/SIRS, septic shock)
   e. Brain tissue hypoxia

2. Screenshots of the forms that will be used to document details about these expected serious adverse events are shown in Appendix VIII.

3. TBI patients will also have many serious adverse events related to the severity of their traumatic injury. A checklist of adverse events (see Appendix VIII) will be used daily for the first 30 days post-injury to monitor for these events.

4. All adverse events that involve harm to the subject, that are unexpected and that are related to the study procedures will be reported to the following bodies within 5 working days:
   a. Local Institutional Review Board (IRB)
   b. The FDA
   c. The study medical safety monitor, Dr. Matthew Carrick
   d. The study statistician, Dr. Barbara Tilley and Dr. Jose-Miguel Yaml
   e. The NINDS clinical research project manager, Joanne Odenkirchen, who will forward the information to the Data Safety and Monitoring Board (DSMB) if appropriate
Other serious adverse events will be reported to the safety monitor and the statistician within 5 working days. These adverse events will be recorded in individual patients for the first 6 months post injury.

5. All other adverse events will be summarized every 6 months (approximately every 20 patients) for the DSMB and yearly for the IRB and FDA.

6. Event thresholds that would prompt early review of adverse events are given in a table in Appendix VIII

7. Reporting Adverse Event (AE) Data
   a. Dr. Tilley will prepare 2 sets of reports to facilitate AE monitoring and evaluation
      1) Summary of AEs by time period: a complete summary of the adverse events reported during a particular time period, and the total number of adverse events of each type to date
      2) Patient Specific Reports: demographic and injury description of the patient will be presented, including a time-line documenting the date and time of injury, the time of arrival in the emergency center, the time of arrival in the NICU, the times of all surgeries, the times of all study related procedures and therapies, and the times of all adverse and serious adverse events
         a. All summary and patient-specific AE reports will be presented in A/B/C/D format unless otherwise requested by the DSMB

C. Safety Monitoring
   1. Medical Safety Monitor: Dr. Matthew Carrick, an experienced trauma surgeon, will serve as the Safety Monitor for the study. He will review the medical records of each of the cases enrolled in the study for compliance with the protocol, as well as all of the serious adverse event reports.

   2. Data Safety and Monitoring Board: A Data and Safety Monitoring Board (DSMB) will be assembled for this study.
      a. The members of the DSMB are:
         1) Kyra Becker, MD (Associate Professor of Neurology and Neurological Surgery, University of Washington Medical Center)
         2) Charles F. Contant, PhD (Pfizer Global Research and Development)
         3) Daniel F. Hanley, MD (Jeffrey and Harriet Legum Professor Acute Care Neurology, The Johns Hopkins Medical Institutions)
         4) Geoffrey Manley, MD, PhD (Associate Professor of Neurological Surgery, University of California San Francisco)
         5) Ramon Diaz-Arrastia, MD, PhD (Professor, Department of Neurology, Southwestern Medical School)
      b. The study statistician, Dr. Tilley, will prepare a report set for the DSMB consisting of:
         1) Demographic data
         2) Injury descriptors
         3) Clinical management and protocol compliance data
            a) ICP, CPP, and MAP data summaries
            b) Use of mannitol and vasopressors
            c) Number and types of surgical procedures
            d) Results and timing of non-invasive cerebral hemodynamic evaluations
            e) Results and timing of xenon-CT CBF and CMRO₂
         4) Study treatment data (rhEpo administration status blinded)
VIII. **Criteria for Intervention Discontinuation:** The study intervention will be discontinued in the following circumstances:

A. The dose of Epo may be held for patients that show an elevation in hemoglobin. See section 5.2.a.ii on page 22

IX. **Statistical Analysis Plans**

A. **OVERVIEW**

The statistical analysis plan includes an interim analysis for futility of EPO, interim analyses for EPO safety at each DSMB meeting, and an interim analysis for efficacy of a Trigger. The final analysis will be an EPO futility analysis, a Trigger GOSS analysis, and a Trigger safety analysis. The expected sample sizes at the end of the trial are given in Table 1.

<table>
<thead>
<tr>
<th>Trigger</th>
<th>EPO Dose 1</th>
<th>EPO Dose 2</th>
<th>Concurrent Placebo Dose 1</th>
<th>Concurrent Placebo Dose 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7</td>
<td>18</td>
<td>31 *</td>
<td>19</td>
<td>32 *</td>
</tr>
<tr>
<td>&lt;10</td>
<td>20</td>
<td>31 *</td>
<td>17</td>
<td>32 *</td>
</tr>
<tr>
<td>Total</td>
<td>100 **</td>
<td>100 **</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*For Dose 1 simple randomization was used leading to an imbalance in treatment assignments. For Dose 2, randomization was blocked (block size randomly chosen) and initially stratified by time from injury to ED arrival and later by site (Baylor, Herman). At the DSMB meeting in September, 2010, the DSMB approved eliminating the time-related strata given the limited recruitment into the early strata. Given the numbers in the early strata and Herman strata are so small, strata will be ignored in the analysis.

All patients will be analyzed in the EPO and in the trigger group to which they were assigned regardless of the amount of blood received. Where the Glasgow Outcome Structured Scale (GOSS) is used as an outcome the GOSS will be dichotomized as unfavorable (dead, vegetative, and severely disabled) or favorable (moderately disabled and good recovery).

B. **INTERIM ANALYSIS FOR FUTILITY OF EPO**
One interim analysis for futility of EPO will be conducted using a Bayesian approach appropriate to the futility design. We would not use stochastic curtailment as an interim analytic approach. Even if the EPO drug is futile at an interim stage, there would still be an interest in finishing the study to be able to compare the trigger arms and to obtain as much data as possible to determine if a future Phase III trial should be conducted.

C. INTERIM ANALYSIS OF TRIGGER FOR GOSS

One interim analysis of trigger with GOSS as the outcome will be conducted. This interim analysis will use the O'Brien-Fleming stopping boundary (81) as a guideline for any recommendation of early termination due to overwhelming efficacy (as measured by the GOSS score). In addition, we will compute the conditional power (82) to detect a 20% difference in GOSS and determine if a recommendation to stop for lack of efficacy should be considered.

D. INTERIM SAFETY ANALYSIS

Safety analyses will be presented at each meeting of the DSMB. For all safety analyses of EPO, except tests of interactions, we will use a critical level of 0.001 and will not adjust for multiple comparisons. Except for tests of dose-trigger interactions, primary safety analyses will combine data across EPO dose 1 and 2 and use all placebo patients. If a safety concern is identified we will focus on providing necessary data to assess the consistency of evidence across dose.

1. Testing for a EPO dose x Trigger Interaction

   a. **EPO** - We will test for a trigger (<7, <10) x EPO (EPO dose 1, EPO dose 2, placebo) interaction with respect to the primary EPO outcome, the dichotomized GOSS (unfavorable versus favorable). We will use a log linear model testing at a critical level of 0.20 rather than the traditional 0.1 or 0.05 to increase our ability to detect an interaction. In the presence of an interaction we would determine if the interaction was driven by EPO dose 1 or dose 2 or the two doses combined and this would guide the analyses. In the absence of an interaction we will test for a main effect of EPO and a main effect of Trigger as described below. At the end of the trial, when more data are available, we will test again for an interaction using a 0.1 criterion, whether or not an interaction is detected in this analysis.

   b. **Trigger** - We will test for a trigger (<7, <10) x EPO (EPO dose 1, EPO dose 2, placebo) interaction with respect to the three primary trigger safety outcomes, ARDS, mortality, and infections (all SAEs considered to be infection-related).

2. NO Trigger Dose Interaction Detected

   a. **EPO safety analysis**

      We will compare the EPO and placebo groups on dichotomized GOSS at week 4, 3 months and 6 months using a one-sided two-sample test of proportions. We chose a one-sided test as we are testing the hypothesis that there are more poor outcomes in the EPO arm as compared to placebo. We will compare mortality using time to event analysis and a time to first event analysis for each SAE with deaths censored when they occur.

   b. **Trigger safety analysis**
We will compare the two Trigger groups on the three primary safety outcomes, incidence of ARDS, mortality, and incidence of infections (pneumonia, bacteremia, UTI, and ventriculitis) at each DSMB meeting starting in 2011 using a two sample test of proportions using a uniform critical level of 0.001 (80). Secondary outcomes assessed for safety include the duration of time that PbtO₂ is less than 10 mmHg, duration of time that ICP is greater than 30 mm Hg, and highest ICP treatment score. We will use a two-sided two-sample test of proportions with a uniform critical level of 0.001 for binary variables. For continuous or ordinal variables, we will use either a two-sample t-test or a Wilcoxon rank sum test if the normality assumption is not satisfied with a uniform critical level of 0.001. We chose a two-sided test for Trigger as we would consider a difference in either direction a safety issue.

3. Trigger Dose Interaction Detected

a. Analyses below assume the interaction was not driven by a single dose group. If this is not the case, the analyses below would be modified accordingly.

b. EPO safety analysis

In the presence of a trigger by dose interaction we will conduct the comparisons of EPO and Placebo within trigger category using the same analyses as described above.

c. Trigger safety analysis

If there is an interaction detected for primary trigger outcomes at an interim analysis we will bring this to the attention of the DSMB and will ask the DSMB to determine if further action should be taken. We will also conduct separate comparisons of Trigger <7 to Trigger <10 within EPO dose and within placebo using the same analyses as described above.

4. Other Safety Analyses

We will present adverse events and SAEs and heat maps of laboratory values along with other descriptive tables and figures by EPO Dose 1, EPO Dose 2, and placebo and separately by Trigger <7 and Trigger <10. If a trigger interaction is detected we would present additional data by Dose and Placebo within Trigger group.

If an EPO safety issue arises, we will redo the analysis by two cohorts, EPO Dose 1 versus concurrent placebo (placebos accrued during the time period when Dose 1 was collected) and EPO Dose 2 versus concurrent placebo (accrued during the time period when Dose 2 was collected). Using these separate Dose/Concurrent Placebo cohorts will provide descriptive dose-related information and will protect from the bias introduced by placebo group differences related to changes over time that could be introduced by using the total placebo group. In particular there were changes in the consent procedure that were instituted during the study that may have affected the race/ethnicity distribution, SES, and there may have been other un-measureable changes over time that could affect outcome.

5. DSMB Decisions
The DSMB will consider whether a trigger arm or EPO dose 2 must be stopped for safety at each DSMB meeting. EPO dose 1 was stopped previously. In making any decision the DSMB would consider the p-values as guidelines. If other concerns are generated by the tables, the lack of a p-value <0.001 would not preempt the DSMB from stopping an arm or stopping the trial. Because many comparisons are being made, it is possible to make a Type I error. However, the purpose of the safety analysis is to detect any possible safety concerns and ask the DSMB to assess consistency of evidence.

E. FINAL ANALYSIS OF EPO AT THE END OF THE TRIAL

The numbers of patients randomized in the early strata and in the Hermann site are so small, that analyses will not take this stratification into account. All analyses are by intent to treat with missing values replaced by methods of multiple imputation. For all subjects with a missing GOSS final outcome we will use vital statistics records to assess mortality unless other information is available. For GOSS missing scores could be estimated from the patient’s current level of activity (e.g. death certificate, in nursing home, holding a job, or other information) depending on the extent of information available. Where a value is to be coded based on outside information, an independent observer (Dr. Julia Hannay) familiar with the GOSS, and blinded to treatment assignment, will make the GOSS designation. We will test for an EPO dose x trigger treatment interaction for the primary EPO and trigger outcomes using a critical level of 0.1. If an interaction is detected we would modify the analysis plans below to conduct EPO futility analyses within Trigger category and Trigger analyses within treatment categories. Since we will only conduct these analyses if there is a significant interaction we assume weak protection of alpha and would conduct the analyses within category at p=0.05.

In all the analyses comparisons will be considered separate questions (79) and we will not adjust for multiple comparisons.

1. EPO Futility Analysis

We will test for futility of EPO at the end of the trial unless the trial is stopped prematurely. In the absence of an EPO trigger interaction we will conduct the primary futility analysis comparing EPO 2 to concurrent (or combined) placebo. The futility analysis will be done for the EPO 2 regimen only for two reasons. First, the FDA currently will not allow the use of the higher dose. Secondly, the lower dose (EPO2) may be less effective or the higher dose could be more toxic and including the higher dose could lead to misleading results. As a secondary analysis, we will use logistic regression adjusting for variables unbalanced in randomization, one sided alpha of 0.15. We will also perform a secondary futility analysis using EPO 1.

If analyses must be conducted within trigger category (given the presence of an EPO-trigger interaction) these will be considered separate questions [79] and we will not adjust for multiple comparisons. We will conduct EPO dose 1 and dose 2 versus placebo analyses separately as described above.

Due to the small sample sizes for assessing EPO, we gain power if we combine the two concurrent placebo groups for the futility analyses. We will test if the placebo group using the first dosing regimen is significantly different than the placebo group using the second dosing regimen using a two-sample test of proportions of the dichotomized GOSS using a two-sided alpha = 0.05. The two placebo groups will be combined if no significant difference is found. If a difference is detected we would use the concurrent placebo groups (\(p_{PLC1}, p_{PLC2}\) respectively).
The purpose of the futility analysis is to test the null hypotheses that:

\[ H_0 : p_{EPOi} > p_{PLC} + \Delta \]

\[ H_a : p_{EPOi} \leq p_{PLC} + \Delta \]

where

\[ p_{EPOi} = \text{the proportion expected to have a good GOSS outcome in the treated group} \]

under the dosing regimen (i=1,2 where 1= dose 1 and 2=dose 2)

\[ p_{PLC} = \text{the proportion expected to fail in combined placebo group} \]

\[ \Delta = \text{the increase in good outcomes considered clinically meaningful} \]

\[ p_{EPOi} = p_{PLC} + \Delta = \text{target threshold; if change is less than } p_{PLC} + \Delta, \text{ do not consider} \]

studying the drug in a phase III trial.

We will use a two-sample test of proportions, one-sided alpha = 0.15. Rejecting the null hypotheses implies that it is futile to take the treatment to Phase III. Failing to reject implies that futility could not be detected and given the many other considerations that go into a Phase III trial, a Phase III trial may be worthwhile to conduct. We will use STAT EXACT to do computations of p-values.

2. Sample size and Power

The following table gives the power for the futility analysis with one-sided alpha=0.15, placebo 0.3 versus EPO 0.5. If there is no interaction between dose and trigger for the primary EPO outcome, GOSS favorable versus unfavorable, then all analyses will have sufficient power except for EPO 1 versus concurrent Placebo 1 if the placebo groups cannot be combined. In the presence of an interaction, the futility analyses will be under-powered to detect small differences.

Table 2. Power for EPO futility analysis

<table>
<thead>
<tr>
<th></th>
<th>n1</th>
<th>n2</th>
<th>power</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPO1 Placebo1</td>
<td>38</td>
<td>36</td>
<td>0.69</td>
</tr>
<tr>
<td>All TT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPO1 all Placebo</td>
<td>38</td>
<td>100</td>
<td>0.83</td>
</tr>
<tr>
<td>EPO2 Placebo2</td>
<td>62</td>
<td>64</td>
<td>0.86</td>
</tr>
<tr>
<td>EPO2 all Placebo</td>
<td>62</td>
<td>100</td>
<td>0.91</td>
</tr>
<tr>
<td>&lt;7 TT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPO1 all Placebo</td>
<td>18</td>
<td>51</td>
<td>0.57</td>
</tr>
<tr>
<td>EPO2 Placebo2</td>
<td>31</td>
<td>32</td>
<td>0.63</td>
</tr>
<tr>
<td>EPO2 all Placebo</td>
<td>31</td>
<td>51</td>
<td>0.71</td>
</tr>
<tr>
<td>&lt;10 TT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPO1 Placebo1</td>
<td>20</td>
<td>17</td>
<td>0.45</td>
</tr>
<tr>
<td>EPO1 all Placebo</td>
<td>20</td>
<td>49</td>
<td>0.59</td>
</tr>
<tr>
<td>EPO2 Placebo2</td>
<td>31</td>
<td>32</td>
<td>0.63</td>
</tr>
<tr>
<td>EPO2 all Placebo</td>
<td>31</td>
<td>51</td>
<td>0.71</td>
</tr>
</tbody>
</table>
In addition to assessing futility under these hypotheses, the analysis may help us in determining the sample size for Phase III if a trial is warranted.

F. FINAL ANALYSIS OF TRIGGER AT THE END OF THE TRIAL

The final analyses at the end of the trial will be (1) a comparison of GOSS between trigger <7 versus <10, (2) comparisons of safety outcomes mortality, ARDS, and infections between triggers, and (3) comparisons of secondary safety outcomes. In the presence of a dose*trigger interaction, as for the futility analysis, we will conduct separate safety analyses of trigger within dose category. Since we will only conduct these analyses if there is a significant interaction we assume weak protection of alpha and would conduct the analyses within category at p=0.05

1. Trigger final GOSS analysis

The primary outcome will be the dichotomized GOSS score. We will use a two-sample test of proportions, two-sided alpha = 0.05.

2. Trigger final safety analysis

The three primary safety outcomes for the trigger analysis are mortality, the incidence of ARDS, and the incidence of infections (total number of incidences of pneumonia, bacteremia, UTI, and ventriculitis). Secondary outcomes include the duration of time that PbtO2 is less than 10 mmHg, duration of time that ICP is greater than 30 mm Hg, and highest ICP treatment score.

We will use a two-sample test of proportions, two-sided alpha = 0.05 for the primary outcomes. To test for a difference in the continuous secondary outcomes, we will use either a two-sample t-test or a Wilcoxon rank-sum test if the assumption of normality is not satisfied with a two-sided alpha = 0.05. To test for a difference in the number of events, we will use a two-sample test of proportions with two-sided alpha = 0.05. As a secondary analysis, we will use logistic regression to account for any covariates that may be unbalanced in the groups and related to trigger.

3. Sample size and Power

We expect there to be a favorable GOSS rate of 0.4 in the <7 trigger group (an average of the expected rates for the EPO and placebo groups). Assuming a two-sided test with \( \alpha = 0.05 \), we will have 80% power to detect a 20%, 23%, and 25% difference in GOSS if using EPO and placebo, EPO 2 and all placebo, or EPO 2 and placebo 2, respectively. Concerns about combining dose groups are described under the EPO analysis. Thus combining groups will be carefully considered in light of these concerns to determine if such a combination could provide misleading results. Calculations assume no dose-trigger interaction. If there is a dose*trigger interaction, the sample sizes will depend on whether the two concurrent placebo groups and the two dose groups can be combined.

For the safety outcomes, we expect there to be a mortality rate of 20% in the <7 trigger group. We expect there to be 5% incidence of ARDS in the <7gm/dl trigger group. We also expect there to be a 50% incidence of all infections combined in the <7gm/dl group. We consider the ARDS and infections analyses to be separate questions and will not adjust for multiple comparisons. We assumed a two-sided test with \( \alpha = 0.05 \). Table 3 is provided to assist in interpretation of trial results, given a difference is not detected between trigger groups.
Table 3. Power and effect size for trigger secondary analysis.

<table>
<thead>
<tr>
<th></th>
<th>N TT7</th>
<th>N TT10</th>
<th>Power %</th>
<th>Mortality Δ %</th>
<th>ARDS Δ %</th>
<th>Infections Δ %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epo &amp; Placebo</td>
<td>100</td>
<td>100</td>
<td>90</td>
<td>22</td>
<td>16</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>80</td>
<td>19</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>70</td>
<td>17</td>
<td>12</td>
<td>18</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>60</td>
<td>15</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>Epo2 &amp; all placebo</td>
<td>82</td>
<td>80</td>
<td>90</td>
<td>25</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>80</td>
<td>21</td>
<td>15</td>
<td>23</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>70</td>
<td>19</td>
<td>13</td>
<td>20</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>60</td>
<td>17</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Epo2 &amp; Placebo2</td>
<td>63</td>
<td>63</td>
<td>90</td>
<td>28</td>
<td>21</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>80</td>
<td>25</td>
<td>18</td>
<td>25</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>70</td>
<td>22</td>
<td>16</td>
<td>23</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>60</td>
<td>20</td>
<td>14</td>
<td>20</td>
</tr>
</tbody>
</table>

G. OUTCOME FROM ANALYSES

The final decision to go forward to Phase III with EPO would be based on the FDA, futility analyses, safety, other information collected during the Phase II trial, and resources available in the future (if a Phase III trial appears warranted). The choice of Trigger would be based on the Trigger analyses unless power is reduced substantially by interactions. It is expected that if a Phase III trial is warranted, that a new cohort of patients from multiple sites will be recruited.

NOTE: EAST and STAT EXACT are software packages developed by CYTEC.

X. Data Collection, Site Monitoring, and Adverse Experience Reporting

A. Records to be Kept

1. The clinical data that will be collected and stored in the database consists of the standard clinical information for patients with severe traumatic brain injury, including:
   a. demographic characteristics-age, gender, ethnicity, race, height, weight
   b. past medical history
   c. details about the injury, typically from the EMS report-date/time of injury, mechanism of injury, setting, neuro exam in the field, vital signs in the field, treatment if any given in the field
   d. details about the ER events-date/time of arrival in ER, neuro exam, injury severity score, vital signs, result of any lab that is done (CBC, platelets, PT, PTT, ABGs, alcohol level, tox screen), any treatment given
   e. details about any surgical procedure, including date/time of procedure, type of procedure, anesthetic records (vital signs, lab, treatment)
   f. copies of any CT scans of the brain that are done
   g. copies of any xenon CT CBF measurements that are done
   h. details of the early ICU care-date/time of admission, condition on admission, code status on admission, serial neuro exams, serial vital signs, serial labs, meds that are
given, transfusion of blood products (including age of any PRBCs transfused and any
transfusion-related complications that occur)
i. physiological data collected by the ICU monitoring system (q30sec recording of vital
signs)
j. values for any noninvasive cerebral hemodynamic studies that are performed
k. three summary lists of diagnoses: final diagnoses, ICU admission diagnoses,
   complications
l. details of any catheters that are placed for monitoring in the ICU: type of catheter,
   length of monitoring, results, complications

2. The database containing the clinical information will be kept on the server of the
   neurosurgery local network at Ben Taub General Hospital. The server is owned and
   administrated by Baylor, but is protected by the Hospital District’s firewall. This database
   will receive physiological information from the NICU monitoring system and laboratory
   data from the HCHD system in via an automated process. Other clinical information is
   manually entered by research personnel.

3. Images, such as CT scans, will be digitized (with all identifiers being removed) and kept
   in the database as a binary field.

4. Only members of the neurosurgery research team (co-investigators, data entry
   personnel, and research fellows) will have access to the database via password.

5. Once the final six month outcome exam is obtained and the data checking for data quality
   monitoring purposes has been completed, all patient identifiers will be removed from the
   database. These identifiers will then be kept in a separate file that is accessible only by
   Dr. Robertson and might be used at a later time only if it becomes necessary to contact
   the patient for additional studies or for regulatory purposes.

6. For future approved studies that may use the database and resource samples from this
   trial, limited datasets will be provided to the investigators with only the study number as
   an identifier.

B. Quality Assurance
1. Data Quality: Some procedures are in place which will minimize errors in data entry.
   The database has validity limits on each of the fields and some checks for logical errors
   which reduce typos during data entry. In addition, some of the data is downloaded
   directly from the hospital information system and is checked each day for accuracy as a
   part of the normal morning work rounds of the neurosurgery team. Additional procedures
   will be put into place for this study to check each individual dataset. When a patient’s
   dataset is complete, it will be printed out and checked for completeness and for accuracy
   by a research data manager working under the supervision of Dr. Swank. Any
   corrections that are needed will be made in the database at that time. A final print-out of
   this corrected data will become the permanent record for this patient.

2. Regulatory Compliance: All necessary certifications and approvals for the conduct of this
   research, as required by the study hospital and affiliated university and the study sponsor
   (NINDS) will be completed in a timely manner and kept on file in the study office. This
   will include IRB documentation and reporting, documents for compliance with HIPAA
   requirements, and documentation related to specific study procedures, including
   administration of the study drug.
3. **Protocol Compliance**: see Section 5.4, page 23 and Section 7.1, page 31.

4. **Ethical Standards**:
   a. All investigators and research personnel will complete the required education programs regarding human subjects’ protection and maintain their certification throughout the period of this study.
   b. All investigators and research personnel will comply with ethical standards for obtaining informed consent for research, in accordance with the policies and procedures of the local IRB and the study hospital.
   c. Any observed breach of ethical standards will be reported immediately to the Investigator and to the local IRB or other authority as indicated.

C. **Adverse Experience Reporting**

1. **Adverse event definition**: An adverse event will be considered any untoward medical event, including physical or psychological, experienced by a subject during administration of Epo or for one month after administration of Epo.

2. **Types of AEs**: The types of adverse events are as follows:
   a. Serious: Any untoward medical or psychological occurrence that:
      1) Results in death (occurrence in the absence of chronic underlying disease)
      2) Is life-threatening (the patient was at risk of death at the time of the event)
      3) Requires inpatient hospitalization or prolongs existing hospitalization
      4) Is a permanently disabling experience
      5) Results in the development of cancer
      6) Is a drug overdose
      7) Results in persistent or significant disability/incapacity,
      8) Is a congenital anomaly/birth defect
   b. Important medical events that may not meet the above criteria may be considered a serious adverse event when, based upon appropriate medical judgment they may:
      1) Jeopardize the research subject and
      2) May require medical or surgical intervention to prevent one of the outcomes listed above
   c. Non-serious: Include any event which is not included in the definition of serious adverse event
   d. Unexpected: Any adverse experience that is not identified in nature, severity, or frequency in the risk information described in the general investigation plan, brochure, or elsewhere in the current application, as amended.
   e. Expected: Potential adverse events that have been identified in the human protocol summary submitted to the IRB as likely to occur due to:
      1) Disease
      2) Condition under study
      3) As a result of a known adverse effect of an investigational drug, device, or intervention

3. **Reporting of Adverse Events**: reporting of adverse events is described under section 7.

**Management of Adverse Experiences**

XI. **Human Subjects**

A. **Institutional Review Board (IRB) and Informed Consent**: This protocol and the informed consent document (**Appendix IX**) and any subsequent modifications will be reviewed and approved by the IRB. A signed consent form will be obtained from the subject’s legally
authorized representative or from family (spouse, adult children, parents, siblings, grandparents, adult grandchildren). 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. Also, see Section 4.3.3.c Informed Consent Procedures, page 20.

B. Subject Confidentiality:
1. All subject data recorded in the study database will be recorded there by study identification number and patient identification data.
2. The study database will be password-protected and only investigators and research personnel will have a password.
3. Once the final six month outcome exam is obtained and the data checking for data quality monitoring purposes has been completed, all patient identifiers will be removed from the database. These identifiers will then be kept in a separate file that is accessible only by Dr. Robertson and might be used at a later time only if it becomes necessary to contact the patient for additional studies or for regulatory purposes.
4. All laboratory specimens, evaluation forms, reports, 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. 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.

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

XII. Publication of Research Findings: This group of investigators has an extensive publication and presentation record, and they will continue to do so.

XIII. References


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Appendix I. Detailed Background Information

Erythropoietin (Epo) is a hematopoietic growth factor, and binding of Epo to the erythropoietin receptor (EpoR, a member of the cytokine receptor superfamily), controls the terminal maturation of red blood cells. Epo is given to stimulate erythropoiesis and this treatment increases hemoglobin concentration in a variety of conditions that cause anemia, including chronic renal failure and cancer. In critically ill patients, administration of Epo reduces the need for transfusion of blood but Epo is not widely used for this purpose, because of its high cost and because it has not yet been shown to improve outcome. Reducing the need for blood transfusion by using a lower threshold for transfusing blood in critically ill patients (7g/dl compared to the more conventional 10g/dl) has been shown to improve outcome in critically ill patients. However, allowing hemoglobin concentration to decrease as low as 7g/dl in a patient with severe traumatic brain injury (TBI) has not been systematically studied and could potentially reduce oxygenation in injured areas of the brain and worsen neurological outcome. These issues regarding the appropriate transfusion threshold for critically ill patients, the optimal hemoglobin concentration for the injured brain, and the usefulness of Epo in reducing the need for transfusion as well as the effect of all of these issues on outcome are high priority areas of research in the field of critical care medicine.

Recently, Epo has also been observed to be expressed in the brain after traumatic and other types of brain injury. Activation of EpoR by administration of Epo and other molecules with Epo-like activity following experimental traumatic brain injury (TBI) has marked neuroprotective effects, significantly reducing contusion volume, preserving hippocampal neurons, and improving neurobehavioral performance. A number of actions of Epo may contribute to this neuroprotection, including anti-apoptotic effects, vascular, and anti-inflammatory effects. A safety study and a pilot efficacy study have been completed for administration of Epo in patients with stroke (1), showing a trend for improved neurological outcome at 1 month, and no significant safety issues.

Expression of Epo in the Brain - Epo is a hematopoietic growth factor, and binding of Epo to the EpoR (a member of the cytokine receptor superfamily), controls the terminal maturation of red blood cells. Until recently Epo was thought to be produced exclusively in fetal liver and in adult kidney. In 1995, mRNA encoding both Epo and EpoR in mouse brain were reported (2). Hypoxia induced a 20-fold increase in mRNA coding for Epo but not EpoR. Major Epo binding sites were observed in the hippocampus, internal capsule, cortex, and midbrain areas. Subsequently Epo was identified in human brain at autopsy (3) and in CSF of patients with TBI (4,5).

Cell Types that Produce Epo After TBI - Epo is expressed basally in neurons and astrocytes (3,6). Following permanent focal cerebral ischemia postischemic Epo expression has been localized specifically to endothelial cells (1 day), microglia/macrophage-like cells (3 days), and reactive astrocytes (7 days after occlusion). EpoR expression always preceded that of Epo for each cell type.(7) Similar findings have been observed in human autopsy studies using immunohistochemical techniques (8). In normal brain, weak Epo/EpoR immunoreactivity was mainly neuronal. In fresh infarcts, Epo immunoreactivity appeared in vascular endothelium, and EpoR was seen in microvessels and neuronal fibers. In older infarcts reactive astrocytes exhibited Epo/EpoR immunoreactivity. Acute hypoxic brain damage was associated with vascular Epo expression, and older hypoxic damage with Epo/EpoR immunoreactivity in reactive astrocytes.

Pathways Involved in Epo Expression and EpoR Activation

Regulation of Epo expression by HIF-1 - Under normal conditions, Epo production is mediated by decreased oxygen (O2) delivery to oxygen sensors [reviewed in (9)]. Hypoxic stimulation causes production of hypoxia-inducible factor (HIF-1), which is the major factor for transcriptional activation of the EPO gene (10). However, HIF-1 is also found in cells that do not express Epo and is part of a more widespread O2-sensing mechanism providing transcriptional regulation of numerous genes, which include vascular endothelial growth factor (VEGF) and glycolytic enzymes (11,12). HIF-1 regulates vasculogenesis, is required for embryonic development, elevates glucose uptake by
cells, augments production of glycolytic enzymes, and plays an important role in carcinogenesis (13,14). HIF-1 regulates genes that promote cell survival under ischemia (15).

HIF-1 is composed of two subunits, HIF-1α and HIF-1β, that form a heterodimer (16). Only HIF-1α is regulated by hypoxia. HIF-1α mRNA and protein levels are induced by hypoxia, and HIF-1α protein decays rapidly in the presence of normoxia. Posttranslational regulation of HIF-1α protein accounts for the majority of the hypoxic regulation of this gene (10). Normoxia-induced ubiquitin-mediated degradation of the HIF-1α protein is the major regulator of HIF-1α levels (17).

The targeting and subsequent polyubiquitination of HIF-1α requires von Hippel Lindau protein (VHL), iron, O2 and a unique proline hydroxylase; this complex constitutes the oxygen sensor (18,19,20,21).

**Genes Upregulated by Epo** - In endothelial cell culture experiments using a semiquantitative reverse transcriptase polymerase chain reaction protocol, 8 genes that were upregulated by administration of rhEpo have been described (22). The genes coded for proteins in 4 functional groups:

a. Proteins implicated in the regulation of vascular functions (thrombospondin-1, 20 kDa myosin regulatory light chain; relative increase of rhEpo-induced mRNA levels: 155.2%, P = 0.043; 137.6%, P = 0.046, respectively);
b. Gene products involved in gene transcription and/or translation (c-myc purine-binding transcription factor PuF, tryptophanyl-tRNA synthetase, S19 ribosomal protein; increase of mRNA levels: 126.4%, P = 0.032; 150.9%, P = 0.012; 134.9%, P = 0.038);
c. Subunits of mitochondrial enzymes related to energy transfer (nicotinamide adenine dinucleotide [NADH] dehydrogenase subunit 6, cytochrome C oxidase subunit 1; increase of mRNA concentrations: 141.7%, P = 0.007; 140.3%, P = 0.01); and
d. Regulators of signal transduction (protein tyrosine phosphatase G1, increase of transcript level: 160.3%, P = 0.016).

**Activation of EpoR** - Epo binds to an erythroid progenitor cell surface receptor that includes a p66 chain. It was originally thought that when activated, the p66 protein becomes dimerized. More recent reports suggest that EpoR exists as a preformed dimer, and that Epo binding results in closer association of the two chains and intracellular signaling (23,24). This interaction of Epo with the EpoR results in stimulation of mitogenicity of erythroid cells, erythroid differentiation by induction of erythroid-specific expression of proteins, and prevention of apoptosis of erythroid progenitors [reviewed in (25)]. The cytoplasmic portion of the EpoR contains a positive regulatory domain that interacts with Janus kinase-2 (JAK2) (26). Immediately after Epo binding, JAK2 phosphorylates itself, the EpoR, and other proteins such as signal transducer and activator of transcription 5 (STAT-5)(27).

**Pathways that stimulate erythropoiesis.** The JAK2/STAT-5 signaling plays an essential role in Epo/EpoR-mediated regulation of erythropoiesis (28,29). The EpoR contains a negative regulatory domain at its extreme C-terminus (30) which binds hematopoietic cell phosphatase (HCP, also known as SHP-1) to down-modulate signaling (31). Recruited by EpoR tyrosine Y429, HCP attaches to the cytoplasmic EpoR domain and dephosphorylates JAK2. Mutation of the HCP binding site was shown to lead to prolonged phosphorylation of JAK2/STAT-5 (31,32). Another negative regulator of erythropoiesis, cytokine-inducible SH2 protein-3 (CIS3; also known as SOCS3), binds to the cytoplasmic portion of the EpoR Y401 and suppresses Epo-dependent JAK2/STAT-5 signaling (33,34). Thus, deletion of the C-terminal cytoplasmic portion of EpoR removes negative regulatory elements and results in an increased proliferation of erythroid progenitor cells.

**Pathways that involve neuroprotection.** The pathways involved in neuroprotection are just beginning to be elucidated. At least part of the mechanism of Epo neuroprotection involves cross-talk between EpoR and anti-apoptotic pathways through activation of NF-kappaB by the JAK2 kinase. Epo stimulates JAK2 phosphorylation of I-kappaB, releasing NF-kappaB to translocate into the nucleus and activate transcription of additional genes, some of which may
Neuroprotective genes known to be activated by NF-kappaB include the anti-oxidant enzyme manganese superoxide dismutase and calbindin-D (28k).

**Neuroprotection with Epo Administration in Experimental Models** - Epo has been shown to have neuroprotective effects against a variety of types of experimental brain injury, including the following:

**Experimental cerebral ischemia**
- Hypoxic/ischemic injury in neonatal rats reduced by 1000IU/kg Epo (36)
- Global retinal ischemia caused by increasing intraocular pressure reduced by Epo (37)
- Bilateral carotid occlusion – Epo .5-25IU intraventricularly reduced cognition deficits (38)
- Rat middle cerebral artery (mca) occlusion model-Epo 5000IU/kg reduced apoptotic neuronal loss (39)
- Focal cerebral ischemia in mice-preischemia Epo reduced infarct volume (7)
- Focal brain ischemia in rats-Epo given up to 6 hr post-ischemia reduced infarct volume (40)
- Gerbil global ischemia model-Epo intraventricularly improved neurobehavioral outcome and reduced neuronal loss (41)

**Experimental traumatic brain injury** - Cortical impact injury model-Epo given up to 6hr post-injury reduced contusion volume (40)

**Glutamate neurotoxicity** - Epo prevents glutamate toxicity in vitro (42)

**Toxin induced parkinsonism** - 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP)-induced parkinsonism in mice-Epo administration reduced neurotoxicity (43)

**Spinal cord ischemia** - Rabbit spinal cord ischemia model-Epo reduced neurological deficits (44)

**Spinal cord trauma** - Epo 1000IU/kg reduced neurological deficits following spinal cord injury (SCI)(45)

**Subarachnoid hemorrhage**
- Rabbit subarachnoid hemorrhage (SAH)-Epo 1000IU/kg q8h reduced vasoconstriction/neuronal loss (46)
- Rabbit SAH model-Epo reduced cortical neuron loss (47)
- Rat SAH model-Epo (400IU/kg SC) prevented loss of autoregulation (48)

**Axotomy** - Epo prevented loss of motor neurons following sciatic nerve transection in rats (49)

**Mechanisms of Neuroprotection by Epo Administration** - The mechanism of the neuroprotective action of Epo administration is not fully understood, but multiple potentially beneficial effects have been identified.

**Systemic vascular effect**. Epo has a pressor effect which could preserve better perfusion of the brain in focal and incomplete ischemia models (50,51,52).

**Cerebral vascular effect via NO production**. - The effect of Epo administration on NO production has been variable from study to study, but a number of studies suggest that NO production is increased after Epo administration.

- **Increased NO** - Numerous studies suggest that Epo administration upregulates NOS or increases NO production (51,53,54,55) or dilates vessels in a manner that suggests NO production by endothelium (56,43). In physiological circumstances where endogenous Epo production is increased, such as in athletes training at high altitudes, production of NO is also increased (57). Finally, in some pathological conditions, Epo administration has been found to dilate cerebral vessels. In an SAH model, Epo reversed the vasoconstriction that occurred in intracranial vessels (46). A single dose of rhEPO given peripherally has been shown to preserve autoregulation of CBF (48).

- **Decreased NO** - Chronic administration (1 week) of Epo caused attenuated depressor responses to endothelium-dependent vasodilators that may have suggested inhibition of
NOS activity (58). Some studies have suggested that Epo inhibits eNOS protein expression (59) and reduces NO concentration in the brain after ischemia (60).

- **No change in NO** – Some studies suggest that Epo administration does not alter NO synthesis (61,62).

**Anti-apoptotic effects** – a number of studies implicate Epo activities in apoptosis pathways.

- In a global ischemia model in gerbils, expression of Bcl-xL was markedly increased in the hippocampus of animals given Epo intraventricularly (63).
- Activation of neuronal EpoRs prevented apoptosis induced by NMDA (N-methyl-d-aspartate) or NO through activation of NF-kappaB by the JAK2 kinase (35)
- Studies involving free radical-induced injury in cerebral microvascular endothelial cells showed that constitutive Epo is present in endothelial cells but is insufficient to prevent cellular injury. Signaling through the EpoR, however, remains biologically responsive enough to exogenous Epo administration to offer significant protection against nitric oxide-induced injury.
  - Exogenous Epo maintains both genomic DNA integrity and cellular membrane asymmetry through parallel pathways that prevent the induction of apoptotic-protease-activating factor 1 (Apaf-1) and preserve mitochondrial membrane potential in conjunction with enhanced Bcl-xL expression. Consistent with the modulation of Apaf-1 and the release of cytochrome c, Epo also inhibits the activation of caspase-9 and caspase-3-like activities (64).
- Through pathways that involve the initial activation of protein kinase B, Epo maintains mitochondrial membrane potential. Subsequently, Epo inhibits caspase 8-, caspase 1-, and caspase 3-like activities linked to cytochrome c release through mechanisms that are independent from the mitogen-activated protein (MAP) kinase systems of p38 and c-Jun N-terminal kinase (JNK)(65).

**Anti-inflammatory effect** - Studies by Brines et al (40) noted that the inflammatory response to traumatic injury and to ischemia was markedly reduced in Epo-treated animals. More recent studies have shown that Epo inhibits activation of microglia, possibly by reducing phosphatidylserine exposure (66,67).

**Pharmacology of Epo Neuroprotection**

**Pharmacology and Available Preparations of Epo** - In the human, Epo is produced by peritubular cells in the kidneys of the adult and in hepatocytes in the fetus. Small amounts of extra-renal Epo are produced by the liver in adult human subjects. Epo acts primarily to rescue erythroid cells from apoptosis (programmed cell death) to increase their survival. Epo acts synergistically with several growth factors (stem cell factor [SCF], granulocyte / macrophage colony-stimulating factor [GM-CSF], interleukin 3 [IL-3], and insulin-like growth factor 1 [IGF-1]) to cause maturation and proliferation of erythroid progenitor cells (primarily colony-forming unit-E). Other effects of Epo include a hematocrit-independent, vasoconstriction-dependent hypertension, increased endothelin production, upregulation of tissue renin, change in vascular tissue prostaglandin production, stimulation of angiogenesis, and stimulation of endothelial and vascular smooth muscle cell proliferation.

  - Recombinant human Epo (rhEpo) is currently being used to treat patients with anemia associated with chronic renal failure, AIDS patients with anemia due to treatment with zidovudine, nonmyeloid malignancies in patients treated with chemotherapeutic agents, perioperative surgical patients, and autologous blood donation.
  - A novel erythropoiesis-stimulating factor (Novel Erythropoiesis Stimulating Protein [NESP] or darbEpoetin) has been synthesized, and when compared with rhEpo, NESP has a higher carbohydrate content (52% vs 40%), a longer plasma half-life, an amino acid sequence that differs from that of native human Epo at five positions, and has been reported to maintain hemoglobin levels just as effectively in patients with chronic renal failure as rhEpo despite less frequent dosing (68).

**Does Systemically Administered Epo Cross the Blood Brain Barrier?** - Epo is a 30,400-dalton glycoprotein. Such a large molecule would not be expected to cross the blood brain.
barrier, and some studies measuring CSF levels of Epo after administration of rhEpo in human neonates who had suffered hypoxic injury suggest that it does not (4). However, in experimental models, immunohistochemical studies suggest that Epo administered systemically is transported into the brain even in uninjured animals (40). In these studies, at 5 hrs after 5000 IU/kg of Epo was administered IP, labeled Epo was found surrounding capillaries and extending into the brain parenchyma a distance 3-4 times that of the thickness of the capillary wall. At 17 hrs after Epo administration, labeled Epo was found localized to scattered neurons. In addition, measurements of Epo in CSF of rats demonstrate a 100 mU/ml increase Epo at 30 minutes after administration of Epo 5000 IU/kg IP (40). These investigators proposed that there is an active translocation of Epo across the blood brain barrier. In the pilot trial of rhEpo in patients with stroke, CSF levels of Epo were 60-100 x higher in the rhEpo treated patients than in the placebo-treated patients (1).

**Neuroprotection Doses of Epo in Experimental Models** - Neuroprotective doses for Epo in most of the experimental studies range from 500-5000 IU/kg (45). In a spinal cord ischemia model, a dose of 800 IU/kg was equivalent to or slightly better than 1000 IU/kg (44). In a mca stroke model, doses of Epo between 450 IU/kg and 1000 IU/kg were effective at reducing infarct volume, while doses below 450 IU/kg were not effective (40).

**Neuroprotection Time Window for Epo in Experimental Models** - Epo administration as late as 6hr after ischemia or trauma have been neuroprotective. After 6hr, the neuroprotective effect is markedly reduced (40). A similar time window for in vitro neuroprotection studies has been observed. We have confirmed this 6hr time window in our rat cortical impact injury model (Cherian, et al.-submitted).

Briefly, 67 rats underwent a controlled cortical impact injury (3mm deformation, velocity 5m/sec) while anesthetized with isoflurane. The animals were given saline or erythropoietin (Epo) 5000 units/kg IP at 5min, 1hr, 3hr, 6hr, 9hr, or 12hr post injury. The volume of contused brain, and cell counts of viable neurons in the CA1 and CA3 regions of the hippocampus were assessed at 2 weeks post-injury. The results, which confirm those reported in the mouse TBI model (40), are shown in the figure below.

Results for contusion volume (left) and CA1 neurons (middle) show no significant effect when Epo is given more than 6 hr after injury. For contusion volume, the result with administration of Epo at 6 hr is intermediate between the result obtained with administration at 3 hr and at 9 hr. For CA1 neurons, the results are similar with administration at 3 and 6 hr post-injury.

The mean contusion volume was significantly reduced (p<.05 adjusted for multiple comparisons by Dunnett’s test), compared to the animals treated with saline, when the Epo was given 5min, 1hr, 3hr, and 6hr post-injury. With administration at 9 and 12 hr post-injury, the mean contusion volume was close to that found in the saline-treated animals. Administration of Epo at 6 hr post-injury provided a mean contusion volume that was intermediate between the results obtained with 1hr and 3hr administration and with results obtained with 9 and 12 hr administration of Epo but was still significantly different from the saline-treated animals.
The mean neuron density in the CA1 area of the hippocampus was significantly increased when Epo was administered at 1hr, 3hr, and 6hr after controlled cortical impact injury in rats. Unlike the contusion volumes, for the CA1 neuron preservation administration of Epo at 6 hr post-injury had an effect equal to administration of Epo at 3 hr post-injury. The comparison of neuron density in the CA3 area of the hippocampus followed the same pattern as the CA1 data and was significant (p=.011), but no individual group was significantly different from the control group, when adjusted for multiple comparisons (Dunnett’s test).

The experimental data which we now have in a standard TBI model using histological endpoints suggest that the optimal neuroprotective effect occurs if Epo is administered within 3 hr of injury, although there still maybe some neuroprotection, especially for hippocampal neuronal preservation, if Epo is administered within 6 hr of injury. Beyond 6 hr post-injury, there is no significant neuroprotective effect with Epo administration in this TBI model.

**Human Studies of High Dose rhEpo**

- **Epo Neuroprotection in Stroke** - A safety study and a pilot efficacy study have been completed for high-dose administration of Epo in patients with stroke (1). In the safety study, 13 patients received rhEpo intravenously (33,000 IU/50 ml/30 min) once daily for the first 3 days after stroke. No safety issues were identified. In the double-blind randomized pilot trial, 40 patients received either rhEpo or saline within 5 hrs of onset of symptoms, and the plasma concentration of erythropoietin was increased to 5148±1095 mU/ml, compared to 19±3 mU/ml in the placebo-treated patients. A strong trend for improvement in neurological outcome at 1 month post-stroke was observed in the rhEpo-treated group. A multicenter study of rhEpo administration in stroke is currently ongoing in Germany.

- **Epo Treatment of Critical Illness Anemia** - A recent clinical study of 1302 critically ill patients reported that treatment with rhEpo 40,000 IU subcutaneously on day 3 and weekly x 3 doses reduced the need for allogenic blood transfusion and also increased hemoglobin concentration (69). No adverse events were reported.

**Adverse Events Associated with Administration of rhEpo**

Adverse events associated with rhEpo administration include thrombotic events, hypertension, seizures, pure red cell aplasia, and increased mortality (http://www.epogen.com/professional/resources/prescribing_information/pi.jsp). Almost all of the reported adverse events have been observed in patients with chronic renal failure.

**Systemic Effects of Epo Administration** - In experimental studies, the neuroprotective effects of Epo administration appear to be independent of any systemic effects. Epo has neuroprotective effects in vitro, where confounding systemic mechanisms do not exist (42). However, this does not mean that the systemic effects of Epo administration might not have important independent effects on outcome, especially the long-term outcome following TBI.

One systemic effect that might be an important issue is the stimulation of erythropoiesis and subsequent increase in hemoglobin concentration, which could potentially improve cerebral oxygen delivery. Most of the in vivo neuroprotection studies have been conducted over an acute time period, where this effect would be minimal. In addition, asialoerythropoietin, a short-lived Epo preparation produced by completely removing the sialic acids that delay clearance of Epo in vivo, has equal neuroprotective effects to Epo but does not stimulate erythropoiesis (70). For any study involving administration of Epo after trauma, the effect on hemoglobin concentration and the need for transfusion of blood products would be an important confounding issue.

**Interaction of the Effects of Anemia of Critical Illness and Transfusion of Blood on Outcome**

**Anemia After Trauma** - Anemia in severe trauma is the result of a complex interaction of bleeding, blunted Epo response to low hemoglobin concentrations, inflammatory mediators, and a hypoferremic state (71). An estimated 40-50% of all critically ill patients receive a transfusion
of blood products. The incidence is probably even higher in trauma patients. Sixty percent of our severe TBI patients require transfusion at least one unit of packed red blood cells (PRBCs).

**Blood Transfusions in the Critically Ill Patient** - The role of transfusion of blood products in determining outcome in the critically ill patient has recently been emphasized, and it remains a topic of continued investigation in the critical care field. The known consequences of allogenic RBC transfusions include:

1. Transfusion-transmitted infections
   a. Risk of hepatitis B 1:100,000
   b. Risk of HIV 1:1,000,000
   c. Recently, cases of West Nile virus have been reported.

2. Immune-related reactions (acute or delayed hemolytic reactions; febrile, allergic, and anaphylactic reactions; and graft-versus-host disease)
   a. A meta-analysis of risk of post-operative bacterial infections concluded that allogeneic blood transfusion is associated with a 3.45-fold increased risk of infection (5.263 increased risk in trauma-only studies). (72)
   b. A retrospective study of 1717 patients admitted to a medical/surgical/trauma intensive care unit (ICU) found that patients who received blood transfusions had a 6-fold increase in the incidence of nosocomial infections compared to patients who did not receive blood transfusions (73).

3. Nonimmune-related reactions (fluid overload, hypothermia, electrolyte toxicity, and iron overload)
   a. Rate of pulmonary edema higher (10.7% vs 5.3%) in patients in liberal transfusion group compared to the restricted transfusion group (74).

   A multicenter randomized controlled trial of a restricted (trigger 7g/dl) vs. a liberal (trigger 10g/dl) transfusion policy demonstrated that critically ill patients tolerate a much lower hematocrit than was previously thought and do not benefit by transfusion to a more normal hematocrit (74). In this study, patients randomized to the restrictive transfusion group had a 42% reduced probability of receiving a blood transfusion, a 0.93-unit reduction in the volume of blood transfused, and a 5.6% reduction in the overall average hematocrit. The mortality rate during hospitalization was significantly lower in the restrictive transfusion group (22.3% vs. 28.1%, p=0.05). However, this study also suggested that there may be subgroups of critically ill patients, such as those with acute myocardial infarction or unstable angina, who do not tolerate a low hemoglobin concentration and for whom blood transfusions seem to provide more benefit than risk. For trauma patients, in general, blood transfusion during the first 24hrs has been observed to result in a three-fold increased risk of death that is independent of injury severity (75). This study in trauma patients was not a randomized trial, and it is not entirely clear that the need for blood transfusion may not simply be an additional marker of the severity of injury. In summary, it is not known if patients with severe TBI may be another important exception to the findings of the study by Hebert et al. (74) or if TBI patients are currently being unnecessarily transfused and placed at risk for transfusion-related complications.

**Optimal Hemoglobin Concentration for the Injured Brain** - The optimal hemoglobin concentration for the traumatically injured brain is not known. The traditional teaching in neurocritical care is that a hemoglobin concentration of approximately 10g/dl provides the optimal balance between blood viscosity, which is directly related to the hemoglobin concentration, and the oxygen content of the blood, which is determined by the hemoglobin concentration and the pO2 of the blood. At hemoglobin concentrations < 10g/dl, the increase in CBF induced by the lower viscosity does not completely compensate for the reduction in oxygen content, and the overall oxygen delivery can be reduced. Some experimental studies confirm that oxygen delivery and oxygen consumption are greatest when hematocrit is approximately 30% (76). However, some reports from patients with ischemic cerebrovascular disease suggest that cerebral oxygen delivery was optimal when hematocrit was normal (77).
**Effects of Hemoglobin Concentration on Cerebral Hemodynamics** - In hemodialysis (HD) patients with chronic anemia, regional CBF (rCBF), regional oxygen extraction fraction (rOEF), and regional cerebral metabolic rate of oxygen (rCMRO₂) were measured before and after a 10% increase in hematocrit was induced by administration of rhEPO (78). Before rhEPO administration, the hemispheric rCMRO₂ in HD patients was lower than that in control subjects, averaging 1.48±0.09 ml/100g/min, and both rCBF and rOEF were significantly greater than in control subjects, being 40±3ml/100g/min for rCBF and 49±1% for rOEF. After treatment with rhEPO, hematocrit rose significantly from 21±1 to 31±1%. There were significant reductions in both the hemispheric rCBF to 32±1 ml/100g/min and rOEF to 42±1%. However, the hemispheric rCMRO₂ remained low at 1.58±0.06 ml/100g/min even after rhEPO treatment. Others have reported similar hemodynamic changes upon treatment of chronic anemia (79,80,81). Using this cerebral hemodynamic information to describe the relationship between CBF and hematocrit, it was extrapolated that the highest oxygen delivery would be provided when the hematocrit was 35.2% (82).

**Effects of Hemoglobin Concentration on Cerebral Metabolism/Neuropsych-ological Testing** – Some studies from patients with anemia due to chronic renal failure have suggested that neuropsychological functioning is improved when hemoglobin concentration is normal. Auditory evoked potentials were improved when anemia was corrected with rhEpo administration (83). Improvements in performance on the Wechsler Adult Intelligence Test were observed when anemia was corrected with rhEpo administration (81).

**Effects of Hemoglobin Concentration on Intracranial Pressure** - Anecdotal cases are reported of patients with severe anemia presenting with symptoms of raised intracranial pressure and signs of papilledema, which resolve with treatment of the anemia (84,85). The mechanism is thought to be related to the marked increase in CBF that is required to maintain cerebral O₂ delivery when anemia is severe.

**Effects of Hemoglobin Concentration on Neurological Outcome** - In a focal ischemia model, a hematocrit of 30% resulted in the smallest infarct volume (86). Little information is available on the effect of hemoglobin concentration on outcome from experimental TBI.

**Current Practice for Transfusion Trigger** – Current practice for blood transfusion level in critically ill patients varies widely. A meta-analysis of transfusion guidelines in critical care units found that transfusion triggers varied primarily between 7 and 10 g/dl (87). The CRIT study (88) of 4892 critically ill patients cared for at 213 hospitals between 2000 and 2001 found no change in transfusion practice following the report of the randomized trial by Hebert (74). The average hemoglobin concentration prior to transfusion in the CRIT study was 8.6±1.7 g/dl (88).

A follow-up survey of critical care physicians regarding transfusion thresholds in several different clinical situations has recently been reported (89). For trauma patients, 63% of physicians indicated that they had adopted a 7g/dl threshold for transfusion. This was a significantly higher proportion of physicians than in 1993. For post-operative acute myocardial infarction, only 3% of physicians answered that they used a 7g/dl transfusion threshold.

For stable patients, there has been a general adoption by critical care physicians of the lower transfusion threshold to reduce the risk of transfusion-related complications. However, for critically ill patients with potential organ ischemia (especially of brain or myocardium), there is still considerable controversy over the risk/benefit of this practice. Recent large retrospective studies in the disorders of multiple trauma (75,90), cardiac surgery (91), and acute coronary syndromes (92) have shown blood transfusions to be an independent predictor of mortality. Each of these studies has recommended either directly in the paper or in an accompanying editorial that prospective, randomized trials are needed to define the appropriate transfusion threshold in these subgroups of patients. It seems clear that there is considerable equipoise for a randomized trial of transfusion thresholds in these subgroups of critically ill patients.

References for Appendix I


Appendix II  Standardized Management Protocol for Severe TBI Patients

1. On admission to the hospital, patients will be intubated to protect their airway and ventilated to maintain a pO₂ ~ 100 mm Hg and pCO₂ 35-40 mm Hg. Patients will be resuscitated as necessary to increase MAP to > 80 mm Hg. After hemodynamic stabilization, the patient will be taken for a CT scan and xenon-CT CBF measurement. If an intracranial hematoma is identified on the admission CT scan, the guidelines for Surgical Management of Traumatic Brain Injury, which have been formulated by the Brain Trauma Foundation, will be followed for decisions about surgical evacuation. Following surgical evacuation of a hematoma, the bone flap will be replaced unless massive brain swelling prohibits this. An ICP monitor, SjvO₂ catheter, PbtO₂ catheter, and microdialysis catheter will be placed, either in the OR or upon return to the ICU. If there is no surgical hematoma, the patient will be taken directly to ICU, where an ICP monitor, SjvO₂ catheter, PbtO₂ catheter, and microdialysis catheter will be placed. The conventions used for placement of the various catheters will be as follows: for global measures (SjvO₂) – place on side of dominant jugular venous flow; for local measures (PbtO₂, microdialysis) – place in an area of injured, but not necrotic, cortex observed at surgery and/or on CT scan, or place in right frontal cortex if the injury is diffuse.

2. The following measures will be used as a routine in all patients:

3. Sedation: morphine 10 mg/hr IV prn.

4. Head elevation: 15-30°; keep head straight to avoid compression of jugular veins.

5. Maintenance IV fluids: usually normal saline; keep electrolytes normal.

6. Keep hemoglobin concentration at or above assigned level, sodium concentration 140-155 mEq/L, glucose concentration < 180 mg/dl.
   a. Maintain MAP > 80 mm Hg, CPP > 60 mm Hg, SjvO₂ > 50%.
   b. Ventilatory support to maintain PaO₂ ~100mmHg, PaCO₂ 35-40mmHg
   c. Provide nutritional support, usually enteral, within 48 hr of injury to supply 140% of estimated Resting Energy Expenditure.

7. The following measures will be used to treat intracranial hypertension, defined as ICP > 20 mm Hg. The goal will be to keep ICP ≤ 20 mm Hg. If appropriate, repeat CT scan to rule out delayed mass lesions.
   a. Sedation: morphine 10 mg/hr.
   b. Neuromuscular blockade, titrated to one twitch on train-of-four testing.
   c. CSF drainage: 10 drops prn.
   d. Mannitol: 0.25-1 gm/kg IV q2-6hr prn or hypertonic saline
   e. Hyperventilation to pCO₂ 25-30 mm Hg if SjvO₂ remains > 55%.
   f. Barbiturate coma if refractory to above treatment and MAP > 80 mm Hg without large doses of pressors.
   g. For intracranial hypertension refractory to barbiturate coma or when barbiturate coma is contraindicated because of hypotension or other reasons, decompressive craniectomy may be used.

8. The following measures will be used to treat a reduced CPP, defined as CPP < 60 mm Hg.
   a. Treat increased ICP if > 20 mm Hg.
   b. Fluid resuscitation to increase CVP to 8 mm Hg or PWP to 12 mm Hg.
   c. Dopamine, norepinephrine, phenylephrine and/or hormonal replacement dose vasopressin titrated to keep MAP ≥ 80 mm Hg and CPP ≥ 60 mm Hg, if hypotensive after fluid resuscitation.
   d. Milrinone or dobutamine may be used as indicated for low cardiac output states.
### Appendix III: Neuropsychological/Behavioral Assessment of Outcome After TBI

<table>
<thead>
<tr>
<th>Domain</th>
<th>Measurement Instruments</th>
<th>Test Settinga</th>
<th>Sourceb</th>
<th>Time of Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global Outcome</td>
<td>Glasgow Outcome Scale</td>
<td>Tel</td>
<td>P, SO, O</td>
<td>3, 6 mos</td>
</tr>
<tr>
<td></td>
<td>Disability Rating Scale</td>
<td>Tel</td>
<td>P</td>
<td>3, 6 mos</td>
</tr>
<tr>
<td>Orientation and Amnesia</td>
<td>Galveston Orientation and Amnesia Test</td>
<td>Tel</td>
<td>P</td>
<td>Daily until score ≥ 76 (or patient DC), 3, 6 mos</td>
</tr>
<tr>
<td>Functional Independence</td>
<td>Functional Independence Measure</td>
<td>Tel</td>
<td>P, SO, O</td>
<td>3, 6 mos</td>
</tr>
<tr>
<td>Behavioral/Emotional/</td>
<td>N.Y.U. Head Injury Family Interview</td>
<td>Tel</td>
<td>P &amp; SO</td>
<td>3, 6 mos</td>
</tr>
<tr>
<td>Psychosocial</td>
<td></td>
<td></td>
<td>or O</td>
<td></td>
</tr>
<tr>
<td>Awareness</td>
<td>Awareness Questionnaire</td>
<td>Tel</td>
<td>P &amp; SO</td>
<td>3, 6 mos</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>or O</td>
<td></td>
</tr>
<tr>
<td>Community Reintegration</td>
<td>Craig Handicap and Reporting Technique</td>
<td>Tel</td>
<td>P or SO</td>
<td>3, 6 mos</td>
</tr>
<tr>
<td>Environmental Barriers and</td>
<td>Craig Hospital Inventory of Environmental Factors^d</td>
<td>Tel</td>
<td>P</td>
<td>3, 6 mos</td>
</tr>
<tr>
<td>Facilitators</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of Life</td>
<td>Satisfaction With Life Scale</td>
<td>Tel</td>
<td>P</td>
<td>3, 6 mos</td>
</tr>
<tr>
<td>Neuropsychological</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focused Attention: Auditory</td>
<td>WAIS III Digit Span Forward</td>
<td>Tel</td>
<td>P</td>
<td>3, 6 mos</td>
</tr>
<tr>
<td>Divided Attention: Auditory</td>
<td>WAIS III Digit Span Backward</td>
<td>Tel</td>
<td>P</td>
<td>3, 6 mos</td>
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<td>Neurobehavioral Rating Scale – Arousal Item</td>
<td>Tel</td>
<td>P</td>
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<tr>
<td>Focused Attention: Visual</td>
<td>Trail Making Test A</td>
<td>IP</td>
<td>P</td>
<td>3, 6 mos</td>
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<tr>
<td>Divided Attention: Visual</td>
<td>Trail Making Test B</td>
<td>IP</td>
<td>P</td>
<td>3, 6 mos</td>
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<tr>
<td>Vigilance</td>
<td>Connor’s Continuous Performance Test II</td>
<td>IP</td>
<td>P</td>
<td>3, 6 mos</td>
</tr>
<tr>
<td>Information Processing</td>
<td>Paced Auditory Serial Addition Test</td>
<td>Tel</td>
<td>P</td>
<td>3, 6 mos</td>
</tr>
<tr>
<td>Speed &amp; Working Memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal Learning &amp; Memory</td>
<td>Selective Reminding Test</td>
<td>Tel</td>
<td>P</td>
<td>3, 6 mos</td>
</tr>
<tr>
<td>Visual Learning &amp; Memory</td>
<td>Rey-Osterrieth Complex Figure Test (memory)</td>
<td>IP</td>
<td>P</td>
<td>3, 6 mos</td>
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<tr>
<td>Language</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Word Fluency</td>
<td>Controlled Oral Word Association Test</td>
<td>Tel</td>
<td>P</td>
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<tr>
<td>Auditory Comprehension</td>
<td>Token Test</td>
<td>IP</td>
<td>P</td>
<td>3, 6 mos</td>
</tr>
<tr>
<td>Naming to Confrontation</td>
<td>Visual Naming Test</td>
<td>IP</td>
<td>P</td>
<td>3, 6 mos</td>
</tr>
<tr>
<td>Social Communication</td>
<td>Profile of Functional Impairment in Communication</td>
<td>IP</td>
<td>P</td>
<td>3, 6 mos</td>
</tr>
<tr>
<td>Visuoperceptual/Visuospatial</td>
<td>Rey-Osterrieth Complex Figure Test (copy)</td>
<td>IP</td>
<td>P</td>
<td>3, 6 mos</td>
</tr>
<tr>
<td>Visuoconstructive</td>
<td>Visual Discrimination Test</td>
<td>IP</td>
<td>P</td>
<td>3, 6 mos</td>
</tr>
<tr>
<td>Motor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fine Motor Speed</td>
<td>Finger Tapping Test</td>
<td>IP</td>
<td>P</td>
<td>3, 6 mos</td>
</tr>
<tr>
<td>Fine Motor Coordination</td>
<td>Grooved Pegboard</td>
<td>IP</td>
<td>P</td>
<td>3, 6 mos</td>
</tr>
<tr>
<td>Executive Function</td>
<td>Color Word Interference Test</td>
<td>IP</td>
<td>P</td>
<td>3, 6 mos</td>
</tr>
<tr>
<td></td>
<td>Tower of London</td>
<td>IP</td>
<td>P</td>
<td>3, 6 mos</td>
</tr>
</tbody>
</table>

*a Test Setting: Telephone (Tel) or In person (IP); *b Source of Information: Patient (P), Significant Other (SO) or Other (O; nurse, PT, OT, ST); *c First GOAT administered once GCS motor score = 6 for 2 days; *d Short Form
# Appendix IV. Disability Rating Scale Form

## Disability Rating Scale (DRS)

### Arousalability, Awareness, & Responsivity

<table>
<thead>
<tr>
<th>Eye Opening</th>
<th>Communication Ability</th>
<th>Motor Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Spontaneous</td>
<td>0 Oriented</td>
<td>0 Obeying</td>
</tr>
<tr>
<td>1 To Speech</td>
<td>1 Confused</td>
<td>1 Localizing</td>
</tr>
<tr>
<td>2 To Pain</td>
<td>2 Inappropriate</td>
<td>2 Withdrawing</td>
</tr>
<tr>
<td>3 None</td>
<td>3 Incomprehensible</td>
<td>3 Flexing</td>
</tr>
<tr>
<td></td>
<td>4 None</td>
<td>4 Extending</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 None</td>
</tr>
</tbody>
</table>

### Cognitive Ability for Self Care Activities

- **Knows how and when to feed, toilet or groom self**
- **Toileting**
  - 0.0 Complete
  - 0.5
  - 1.0 Partial
  - 1.5
  - 2.0 Minimal
  - 2.5
  - 3.0 None
- **Grooming**
  - 0.0 Complete
  - 0.5
  - 1.0 Partial
  - 1.5
  - 2.0 Minimal
  - 2.5
  - 3.0 None

### Dependence on Others

- **Physical & cognitive disability**
  - 0.0 Completely Independent
  - 0.5
  - 1.0 Independent in special environment
  - 1.5
  - 2.0 Mildly Dependent-Limited assistance
    - Non-resident helper
  - 2.5
  - 3.0 Moderately Dependent-moderate assist
    - Person in home
  - 3.5
  - 4.0 Markedly Dependent
    - Assistance with all major activities, all times
  - 4.5
  - 5.0 Totally Dependent
    - 24 hour nursing care

### Psychosocial Adaptability

- **Employability**
  - As full time worker, homemaker, student
  - 0.0 Not Restricted
  - 0.5
  - 1.0 Selected jobs, competitive
  - 1.5
  - 2.0 Sheltered workshop, Noncompete.
  - 2.5
  - 3.0 Not Employable

## Total Score (sum all scores) ______

Revised 2/99 San Jose Valley Medical Center
Appendix V. Glasgow Coma Score Structured Interview

STRUCTURED INTERVIEWS FOR THE GOS AND GOSE

Glasgow Outcome Scale

<table>
<thead>
<tr>
<th>Patient's name:</th>
<th>Date of interview:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of Birth:</td>
<td>Date of injury:</td>
</tr>
<tr>
<td>Gender: M/F</td>
<td></td>
</tr>
<tr>
<td>Age at injury:</td>
<td>Interval post-injury:</td>
</tr>
<tr>
<td>Respondent: Patient alone</td>
<td>Relative/ friend/ carer alone</td>
</tr>
<tr>
<td>Interviewer:</td>
<td></td>
</tr>
</tbody>
</table>

CONSCIOUSNESS

1. Is the head injured person able to obey simple commands, or say any words?  
   1 = No (VS)  
   2 = Yes

Anyone who shows ability to obey even simple commands, or utter any word or communicate specifically in any other way is no longer considered to be in the vegetative state. Eye movements are not reliable evidence of meaningful responsiveness. Corroboration with nursing staff. Confirmation of VS requires full assessment as in the Royal College of Physician Guidelines.

INDEPENDENCE IN THE HOME

2a Is the assistance of another person at home essential every day for some activities of daily living?  
   1 = No  
   2 = Yes (SD)

For a 'No' answer they should be able to look after themselves at home for 24 hours if necessary, though they need not actually look after themselves. Independence includes the ability to plan for and carry out the following activities: getting washed, putting on clean clothes without prompting, preparing food for themselves, dealing with callers, and handling minor domestic chores. The person should be able to carry out activities without needing prompting or reminding, and should be capable of being left alone overnight.

INDEPENDENCE OUTSIDE THE HOME

3a Are they able to shop without assistance?  
   1 = No (SD)  
   2 = Yes

This includes being able to plan what to buy, take care of money themselves, and behave appropriately in public. They need not normally shop, but must be able to do so.

4a Are they able to travel locally without assistance?  
   1 = No (SD)  
   2 = Yes

They may drive or use public transport to get around. Ability to use a taxi is sufficient, provided the person can phone for it themselves and instruct the driver.
WORK

5a Are they currently able to work to their previous capacity?

1 = No (MD)
2 = Yes (GR)

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

SOCIAL & LEISURE ACTIVITIES

6a Are they able to resume regular social and leisure activities outside home?

1 = No - Go to 6b
2 = Yes (GR)

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

6b What is the extent of restriction on their social and leisure activities?
   a) Participate a bit less: at least half as often as before injury.
   b) Participate much less or unable to participate

1 = a (GR)
2 = b (MD)

FAMILY & FRIENDSHIPS

7a Have there been psychological problems which have resulted in ongoing family disruption or disruption to friendships?

1 = No (GR)
2 = Yes - Go to 7b

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

7b What has been the extent of disruption or strain?
   a) Occasional - less than weekly
   b) Frequent or constant - once a week or more

1 = a (GR)
2 = b (MD)

Epilepsy:
Since the injury has the head injured person had any epileptic fits? No / Yes
Have they been told that they are currently at risk of developing epilepsy? No / Yes

What is the most important factor in outcome?
Effects of head injury ______ Effects of illness or injury to another part of the body ______ A mixture of these ______

Scoring: The patient's overall rating is based on the lowest outcome category indicated on the scale. Refer to Guidelines for further information concerning administration and scoring.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dead</td>
</tr>
<tr>
<td>2</td>
<td>Vegetative State (VS)</td>
</tr>
<tr>
<td>3</td>
<td>Severe Disability (SD)</td>
</tr>
<tr>
<td>4</td>
<td>Moderate Disability (MD)</td>
</tr>
<tr>
<td>5</td>
<td>Good Recovery (GR)</td>
</tr>
</tbody>
</table>

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### Glasgow Outcome Scale - Extended

**Patient's name:** ____________________________  **Date of interview:** ____________

**Date of Birth:** ____________  **Date of injury:** ____________  **Gender:** M / F

**Age at injury:** ____________  **Interval post-injury:** ____________

**Respondent:** Patient alone __  Relative/ friend/ carer alone __  Patient + relative/ friend/ carer __

**Interviewer:** ____________________________

#### CONSCIOUSNESS

1. Is the head injured person able to obey simple commands, or say any words?
   - 1 = No (VS)
   - 2 = Yes

Anyone who shows ability to obey even simple commands, or utter any word or communicate specifically in any other way is no longer considered to be in the vegetative state. Eye movements are not reliable evidence of meaningful responsiveness. Corroborate with nursing staff. Confirmation of VS requires full assessment as in the Royal College of Physician Guidelines.

#### INDEPENDENCE IN THE HOME

2a Is the assistance of another person at home essential every day for some activities of daily living?
   - 1 = No
   - 2 = Yes

For a 'No' answer they should be able to look after themselves at home for 24 hours if necessary, though they need not actually look after themselves. Independence includes the ability to plan for and carry out the following activities: getting washed, putting on clean clothes without prompting, preparing food for themselves, dealing with callers, and handling minor domestic crises. The person should be able to carry out activities without needing prompting or reminding, and should be capable of being left alone overnight.

2b Do they need frequent help or someone to be around at home most of the time?
   - 1 = No (Upper SD)
   - 2 = Yes (Lower SD)

For a 'No' answer they should be able to look after themselves at home for up to 8 hours during the day if necessary, though they need not actually look after themselves.

#### INDEPENDENCE OUTSIDE THE HOME

3a Are they able to shop without assistance?
   - 1 = No (Upper SD)
   - 2 = Yes

This includes being able to plan what to buy, take care of money themselves, and behave appropriately in public. They need not normally shop, but must be able to do so.

4a Are they able to travel locally without assistance?
   - 1 = No (Upper SD)
   - 2 = Yes

They may drive or use public transport to get around. Ability to use a taxi is sufficient, provided the person can phone for it themselves and instruct the driver.
### WORK
5a Are they currently able to work to their previous capacity?  
- 1 = No  
- 2 = Yes  

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

5b How restricted are they?  
- a) Reduced work capacity.  
- b) Able to work only in a sheltered workshop or non-competitive job, or currently unable to work.  
- 1 = a (Upper MD)  
- 2 = b (Lower MD)

### SOCIAL & LEISURE ACTIVITIES
6a Are they able to resume regular social and leisure activities outside home?  
- 1 = No  
- 2 = Yes  

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

6b What is the extent of restriction on their social and leisure activities?  
- a) Participate a bit less: at least half as often as before injury.  
- b) Participate much less: less than half as often.  
- c) Unable to participate: rarely, if ever, take part.  
- 1 = a (Lower GR)  
- 2 = b (Upper MD)  
- 3 = c (Lower MD)

### FAMILY & FRIENDSHIPS
7a Have there been psychological problems which have resulted in ongoing family disruption or disruptions to friendships?  
- 1 = No  
- 2 = Yes  

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

7b What has been the extent of disruption or strain?  
- a) Occasional - less than weekly  
- b) Frequent - once a week or more, but tolerable.  
- c) Constant - daily and intolerable.  
- 1 = a (Lower GR)  
- 2 = b (Upper MD)  
- 3 = c (Lower MD)

### RETURN TO NORMAL LIFE
8a Are there any other current problems relating to the injury which affect daily life?  
- 1 = No (Upper GR)  
- 2 = Yes (Lower GR)  

Other typical problems reported after head injury: headaches, dizziness, tiredness, sensitivity to noise or light, slowness, memory failures, and concentration problems.
Epilepsy:
Since the injury has the head injured person had any epileptic fits? No / Yes
Have they been told that they are currently at risk of developing epilepsy? No / Yes

What is the most important factor in outcome? Effects of head injury ___ Effects of illness or injury to another part of the body ___ A mixture of these ___

Scoring: The patient’s overall rating is based on the lowest outcome category indicated on the scale. Refer to Guidelines for further information concerning administration and scoring.

1. Dead
2. Vegetative State (VS)
3. Lower Severe Disability (Lower SD)
4. Upper Severe Disability (Upper SD)
5. Lower Moderate Disability (Lower MD)
6. Upper Moderate Disability (Upper MD)
7. Lower Good Recovery (Lower GR)
8. Upper Good Recovery (Upper GR)

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Appendix VI. **HCHD patient registration form.**

---

**HARRIS COUNTY HOSPITAL DISTRICT**  
**RESEARCH PATIENT REGISTRATION FORM**

**General Information:** This form is to be completed by research personnel and faxed to the Benefits Coordinator in the Pre-Registration Office @ 713.440.1102.

| CONTACT INFORMATION  
(For person completing the form) |
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name:</strong></td>
</tr>
</tbody>
</table>
| **Phone:** 713-873-2795  
**Fax:** 713-798-8063  
**Email:** |
| **Location:** RTGH  
□ LBIGH  
□ QM  
□ CHP: |

| CLINIC/UNIT LOCATION  
(Enter unit name or clinic specialty and contact name, phone and email address) |
|---|
| **Unit Name/Clinic Specialty:** 4C NICU/Department of Neurosurgery  
**Clinic Contact:** Athena Baldwin PA  
**Phone:** 713-873-2795  
**Email:** abbalwd@bcm.edu |

| SCHOOL AFFILIATION:  
□ UTSHC-Houston  
□ BCM  
□ Other: |

| RESEARCH STUDY ACCOUNT  
(This information is needed at the initial set-up) |
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Protocol Number:</strong></td>
</tr>
<tr>
<td><strong>Billing Address:</strong></td>
</tr>
</tbody>
</table>
| **Phone:** 713-873-2794  
**Fax:** 713-798-8063  
**Email:** |

| Administrative Contact:  
**Sharon Barnes** |

| PI Name: Claudia Robertson, MD |

| PATIENT REGISTRATION FOR RESEARCH ACCOUNT  
(This information is needed for each patient enrolled in the study)  
(Missing information will delay your ability to implement the protocol) |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Patient Name:</strong></td>
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<tr>
<td><strong>MRN:</strong></td>
</tr>
<tr>
<td><strong>SSN:</strong></td>
</tr>
<tr>
<td><strong>Date of Birth:</strong></td>
</tr>
<tr>
<td><strong>Race:</strong></td>
</tr>
</tbody>
</table>
| □ Male  
□ Female |

<table>
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<tr>
<th>Billing Address:</th>
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<tbody>
<tr>
<td><strong>Mother’s Name:</strong></td>
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<th>Date Submitted:</th>
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<tbody>
<tr>
<td><strong>Enrollment Date:</strong></td>
</tr>
<tr>
<td><strong>Length of Time on Study:</strong></td>
</tr>
</tbody>
</table>

| PATIENT REGISTRATION USE ONLY  
(Date Received: Received By: Date Entered: Entered By:)|
Appendix VII. The Sepsis-related Organ Failure Assessment (SOFA) Score

The Sepsis-related Organ Failure Assessment (SOFA) score is a score for evaluating multiorgan failure in intensive care patients with the sepsis syndrome. It is intended to be easy to calculate and to describe the sequence of complications in a critically ill patient rather than to predict outcome. It was developed by the Working Group on Sepsis-related Problems of the European Society of Intensive Care Medicine.

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>respiration</td>
<td>PaO₂ to FIO₂ ratio</td>
</tr>
<tr>
<td>coagulation</td>
<td>platelet count</td>
</tr>
<tr>
<td>liver</td>
<td>serum bilirubin</td>
</tr>
<tr>
<td>cardiovascular</td>
<td>hypotension</td>
</tr>
<tr>
<td>central nervous</td>
<td>Glasgow coma score</td>
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<tr>
<td>system</td>
<td>serum creatinine or urine output</td>
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</table>

<table>
<thead>
<tr>
<th>Measure</th>
<th>Finding</th>
<th>Points</th>
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</thead>
<tbody>
<tr>
<td>PaO₂ to FIO₂ ratio</td>
<td>&gt;= 400 mm Hg</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>300 – 399 mm Hg</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>200 – 299 mm Hg</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>100 – 199 mm Hg</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>&lt; 100 mm Hg</td>
<td>4</td>
</tr>
<tr>
<td>platelet count</td>
<td>&gt;= 150,000 per µL</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>100,000 to 149,999 per µL</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>50,000 to 99,999 per µL</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>20,000 to 49,999 per µL</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>&lt; 20,000 per µL</td>
<td>4</td>
</tr>
<tr>
<td>serum bilirubin</td>
<td>&lt; 1.2 mg/dL</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1.2 – 1.9 mg/dL</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2.0 – 5.9 mg/dL</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>6.0 – 11.9 mg/dL</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>&gt;= 12.0 mg/dL</td>
<td>4</td>
</tr>
<tr>
<td>hypotension</td>
<td>MAP &gt;= 70 mm Hg</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>MAP &lt; 70 mm Hg, no pressor agents used</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>dobutamine, any dose</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>dopamine &lt;= 5 µg per kg per min</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>dopamine &gt; 5 to 15 µg per kg per min</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>dopamine &gt; 15 µg per kg per min</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>epinephrine &lt;= 0.1 µg per kg per min</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>epinephrine &gt; 0.1 µg per kg per min</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>norepinephrine &lt;= 0.1 µg per kg per min</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>norepinephrine &gt; 0.1 µg per kg per min</td>
<td>4</td>
</tr>
<tr>
<td>Glasgow coma score</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>13 - 14</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>10 - 12</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>6 - 9</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>3 - 5</td>
<td>4</td>
</tr>
<tr>
<td>serum creatinine or urine output</td>
<td>serum creatinine &lt; 1.2 mg/dL</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>serum creatinine 1.2 – 1.9 mg/dL</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>serum creatinine 2.0 – 3.4 mg/dL</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>serum creatinine 3.5 – 4.9 mg/dL</td>
<td>3</td>
</tr>
</tbody>
</table>
urine output 200 - 499 mL per day 3
serum creatinine > 5.0 mg/dL 4
urine output < 200 mL per day 4

where:
• PaO₂ is in mm Hg and FIO₂ in percent from 0.21 to 1.00.
• Adrenergic agents as administered for at least 1 hour with doses in µg per kg per min.
• A score of 0 indicates normal and a score of 4 indicates most abnormal.
• Data can be collected and the score calculated daily during the course of the admission.

mean systemic arterial pressure (MAP) in mm Hg =
= ((systolic systemic arterial pressure in mm Hg) + (2 * (diastolic systemic arterial pressure in mm Hg))) / 3

total SOFA score =
= SUM(points for all 6 measures)

Interpretation:
• minimum total score: 0
• maximum total score: 24
• The higher the organ score, the greater the organ dysfunction.
• The higher the total score, the greater the multiorgan dysfunction.

<table>
<thead>
<tr>
<th>Organ System</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>respiratory</td>
<td>20%</td>
<td>27%</td>
<td>32%</td>
<td>46%</td>
<td>64%</td>
</tr>
<tr>
<td>cardiovascular</td>
<td>22%</td>
<td>32%</td>
<td>55%</td>
<td>55%</td>
<td>55%</td>
</tr>
<tr>
<td>coagulation</td>
<td>35%</td>
<td>35%</td>
<td>35%</td>
<td>64%</td>
<td>64%</td>
</tr>
<tr>
<td>CNS</td>
<td>26%</td>
<td>35%</td>
<td>46%</td>
<td>56%</td>
<td>70%</td>
</tr>
<tr>
<td>liver</td>
<td>32%</td>
<td>34%</td>
<td>50%</td>
<td>53%</td>
<td>56%</td>
</tr>
<tr>
<td>renal</td>
<td>25%</td>
<td>40%</td>
<td>46%</td>
<td>56%</td>
<td>64%</td>
</tr>
</tbody>
</table>

in 1,643 patients from the ENAS study, estimated from Figure 2, page 709

References:

For the Epo study, the SOFA score should be calculated on all days 1 – 30 where this is possible, but at minimum on days 1-5, day 9, day 16, day 23, and day 30 as long as the patient remains hospitalized. There should always be information available for blood pressure and for GCS. On days where a BMP is available, but ABGs, platelet count, and/or bilirubin values are not available, use the following guidelines to assume values for these that are missing:
- If the patient is no longer ventilated, and SpO₂ > 93%, assume that the respiratory score is 0.
- If the last platelet count measured was normal, and there is no clinical evidence that this has changed, assume that the coagulation score is 0.
- If the last bilirubin was normal and there is no clinical evidence that this has changed, assume that the liver score is 0.
Appendix VIII. Definitions of Expected Adverse Events, Expected Incidence in TBI Patients, and Thresholds for Early Referral to DSMB

Definitions (Left) and Screen-Shots of Forms (Right) to Document Expected Adverse Events:

**Pneumonia (1):** A new or progressive chest x-ray finding of infiltrate, consolidation, cavitation, or pleural effusion, plus any of the following:
- New onset of purulent sputum or change in character of sputum
- Isolation of organism from blood culture
- Isolation of pathogen from specimen obtained by transtracheal aspiration, bronchial brushing, or biopsy
- Isolation of virus or detection of viral antigen in respiratory secretions
- Diagnostic single antibody titer (IgM) or fourfold increase in paired serum samples (IgG) for pathogen
- Histopathological evidence of pneumonia

**Urinary tract infection (1):** must meet at least one of the following criteria:
- At least one of the following signs or symptoms with no other recognized cause: fever (≥38°C), urgency, frequency, dysuria, or suprapubic tenderness and patient has a positive urine culture, that is, ≥10^5 microorganisms per cm^3 or urine with no more than two species of microorganisms OR
- At least two of the following signs or symptoms with no other recognized cause: fever (>38°C), urgency, frequency, dysuria, or suprapubic tenderness and at least one of the following:
  - Positive dipstick for leukocyte esterase and/or nitrate
  - Pyuria (urine specimen with >10 WBC/mm^3 or >3 WBC/high power field of unspun urine) organisms seen on Gram stain of unspun urine at least two urine cultures with repeated isolation of the same uropathogen (gram-negative bacteria or S. saprophyticus) with ≥10^5 colonies/ml in nonvoided specimens
  - ≤10^7 colonies/ml of a single uropathogen (gram-negative bacteria or S. saprophyticus) in a patient being treated with an effective antimicrobial agent for a urinary tract infection
  - Physician diagnosis of a urinary tract infection
  - Physician institutes appropriate therapy for a urinary tract infection
SIRS (Systemic Inflammatory Response Syndrome) (3):
The complex findings that result from a systemic activation of the innate immune response, regardless of the cause. SIRS is considered to be present when patients have all four of the following:
Temperature >38°C or <36°C
Heart rate >90 beats/min
Hyperventilation, with respiratory rate >20 breaths/min or PaCO₂ < 32 mm Hg
WBC > 12,000 or < 4000 or >10% immature forms

ARDS: (Adult Respiratory Distress Syndrome):
Pulmonary edema caused by increased pulmonary capillary permeability, not by increased pulmonary hydrostatic pressure (i.e., in the absence of left heart failure). The criteria developed by consensus conference (2) include:
Bilateral infiltrates on chest x-ray
Hypoxia (PaO₂/FiO₂ < 200)
Normal PWP or no clinical findings of left heart failure on physical exam

Bacteremia: The finding of a positive blood culture of a pathogenic organism.

Sepsis (3): SIRS plus infection.
**MODS** (Multiple Organ Dysfunction Syndrome) (3): Sepsis with organ dysfunction. The peak SOFA (Sepsis-related Organ Failure Assessment) score (4,5) during the hospitalization will be used to describe this condition.

**Septic shock** (3): Sepsis with arterial hypotension despite adequate fluid resuscitation.

**Brain tissue hypoxia**  PbtO$_2$ < 10 mmHg for at least 1 hour
**Deep venous thrombophlebitis (DVT)**: The clinical findings of a swollen, tender, erythematous extremity or of fever plus diagnostic findings on duplex Doppler ultrasound or on venography.

**Pulmonary embolus (PE)**: One or more of the following clinical findings:
- dyspnea, tachypnea
- pleuritic chest pain
- hemoptysis
- syncope
- hypoxia
- EKG changes of right heart strain (RBBB, right axis deviation, S1Q3T3 pattern)

plus a high probability lung scan or a positive CT angiogram or pulmonary angiogram or pathological findings of a PE

**Acute myocardial infarction (acute MI)**: One of the following biochemical markers of myocardial injury:
- typical rise and fall of troponin
- rapid rise and fall of CK-MB

and at least one of the following clinical findings:
- chest pain x 30 minutes without relief from nitrates
- development of pathological q waves on EKG
- new ST elevation (>1mm) in 2 contiguous leads
- new ST elevation (>2mm) in precordial leads
- new LBBB
- EKG changes of posterior infarction (ST depression of 2mm in V1V2)

or pathological findings of an acute MI

**Severe hypertension**: MAP > 130 mmHg for at least 1 hour despite anti-hypertensive treatment
# Incidence of Expected Adverse Events in TBI Patients in Past Studies

## Historical Data from Ben Taub NICU

<table>
<thead>
<tr>
<th>Study</th>
<th>CPP Trial</th>
<th>CBF Regulation Study</th>
<th>On-going eNOS SNP Study</th>
<th>Total Group</th>
<th>Hypo</th>
<th>Normo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>192</td>
<td>304</td>
<td>35</td>
<td>531</td>
<td>199</td>
<td>193</td>
</tr>
<tr>
<td>Average ICU Stay (days)</td>
<td>20.98</td>
<td>20.1</td>
<td>18.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average Hospital Stay (days)</td>
<td>34.91</td>
<td>35.48</td>
<td>29.97</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ventriculitis</td>
<td>8 (4.2%)</td>
<td>11 (3.6%)</td>
<td>3 (8.6%)</td>
<td>22 (4.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UTI</td>
<td>5 (2.6%)</td>
<td>20 (6.6%)</td>
<td>2 (5.6%)</td>
<td>27 (5.1%)</td>
<td>26%</td>
<td>23%</td>
</tr>
<tr>
<td>pneumonia</td>
<td>47 (24.4%)</td>
<td>69 (22.7%)</td>
<td>14 (40%)</td>
<td>130 (24.5%)</td>
<td>69%</td>
<td>63%</td>
</tr>
<tr>
<td>bacteremia</td>
<td>18 (9.4%)</td>
<td>24 (7.9%)</td>
<td>1 (2.9%)</td>
<td>43 (8.1%)</td>
<td>17%</td>
<td>18%</td>
</tr>
<tr>
<td>MODS</td>
<td>1 (0.5%)</td>
<td>2 (0.7%)</td>
<td>0</td>
<td>3 (0.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sepsis/SIRS</td>
<td>7 (3.6%)</td>
<td>4 (1.3%)</td>
<td>0</td>
<td>11 (2.1%)</td>
<td>15%</td>
<td>11%</td>
</tr>
<tr>
<td>septic shock</td>
<td>3 (1.6%)</td>
<td>3 (1.0%)</td>
<td>0</td>
<td>6 (1.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>severe hypertension</td>
<td>6 (3.1%)</td>
<td>0</td>
<td>1 (2.9%)</td>
<td>7 (1.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombotic events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td>1 (0.5%)</td>
<td>2 (0.7%)</td>
<td>1 (2.9%)</td>
<td>4 (0.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pulmonary embolus</td>
<td>0</td>
<td>1 (0.3%)</td>
<td>0</td>
<td>1 (0.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>acute MI</td>
<td>2 (1.0%)</td>
<td>1 (0.3%)</td>
<td>0</td>
<td>3 (0.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARDS</td>
<td>13 (6.8%)</td>
<td>9 (3.0%)</td>
<td>3 (8.6%)</td>
<td>25 (4.7%)</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Brain tissue hypoxia</td>
<td>79/176</td>
<td>16/35</td>
<td>95/211</td>
<td>(44.9%)</td>
<td>(45.7%)</td>
<td>(45%)</td>
</tr>
</tbody>
</table>

The table above shows the incidence of the expected adverse events during past studies at Ben Taub, and the incidence of some of these complications in the NABISH I trial.

Using this past data, we will develop 95% confidence limits for the occurrence of such events. If the number of adverse events in any category exceeds these limits, the data will be referred to the DSMB early. Adverse events will also be referred to the DSMB early if a treatment difference in the incidence of any serious adverse event reaches a p value < 0.2.
CHECKLIST OF ADVERSE EVENTS THAT WILL BE USED TO TRACK PATIENTS:

Items in red are the expected adverse events that will be documented in detail and tracked for the first 30 days post-injury (or until ICU discharge [whichever is earlier]).

<table>
<thead>
<tr>
<th>IDNo:</th>
<th>Date:</th>
<th>Day:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>TBI-RELATED ADVERSE EVENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS Complications:</td>
</tr>
<tr>
<td>intracranial hypertension</td>
</tr>
<tr>
<td>delayed hematoma</td>
</tr>
<tr>
<td>enlargement of hematoma</td>
</tr>
<tr>
<td>stroke</td>
</tr>
<tr>
<td>CSF leak</td>
</tr>
<tr>
<td>seizure</td>
</tr>
<tr>
<td>hydrocephalus</td>
</tr>
<tr>
<td>brain tissue hypoxia (pH&lt;7.0)</td>
</tr>
<tr>
<td>vasospasm</td>
</tr>
<tr>
<td>death</td>
</tr>
<tr>
<td>other CNS</td>
</tr>
<tr>
<td>Metabolic Complications:</td>
</tr>
<tr>
<td>diabetes insipidus</td>
</tr>
<tr>
<td>hyperglycemia (glucose&gt;300)</td>
</tr>
<tr>
<td>diabetic ketoacidosis</td>
</tr>
<tr>
<td>hypoglycemia (glucose&lt;50)</td>
</tr>
<tr>
<td>severe fever (temp&gt;105)</td>
</tr>
<tr>
<td>hypothermia (temp&lt;96)</td>
</tr>
<tr>
<td>other metabolic</td>
</tr>
<tr>
<td>Cardiac Complications:</td>
</tr>
<tr>
<td>cardiac arrest</td>
</tr>
<tr>
<td>atrial arrhythmia</td>
</tr>
<tr>
<td>ventricular arrhythmia</td>
</tr>
<tr>
<td>pulmonary edema (cardiac)</td>
</tr>
<tr>
<td>hypertension (MAP&gt;130)</td>
</tr>
<tr>
<td>hypotension (MAP&lt;60)</td>
</tr>
<tr>
<td>DVT</td>
</tr>
<tr>
<td>pulmonary embolus</td>
</tr>
<tr>
<td>acute MI</td>
</tr>
<tr>
<td>other cardiac</td>
</tr>
<tr>
<td>Renal Complications:</td>
</tr>
<tr>
<td>acute renal failure</td>
</tr>
<tr>
<td>severe metabolic acidosis (pH&lt;7.2)</td>
</tr>
<tr>
<td>hypocalcemia (Ca&lt;7.0)</td>
</tr>
<tr>
<td>hypomagnesemia (Mg&lt;1.0)</td>
</tr>
<tr>
<td>hypophosphatemia (P0&lt;1.5)</td>
</tr>
<tr>
<td>hyperkalemia (K&gt;6.0)</td>
</tr>
<tr>
<td>hypokalemia (K&lt;2.5)</td>
</tr>
<tr>
<td>hypernatremia (Na&gt;155)</td>
</tr>
<tr>
<td>hyponatremia (Na&lt;130)</td>
</tr>
<tr>
<td>hematuria</td>
</tr>
<tr>
<td>other renal</td>
</tr>
</tbody>
</table>

| Hematologic Complications: |
| anemia (Hgb<9)             |
| coagulopathy (INR>1.3)     |
| DIC                         |
| thrombocytopenia (<100,000) |
| neutropenia (WBC<500)      |
| other hematologic           |
| Respiratory Complications: |
| airway obstruction         |
| atelectasis                 |
| pleural effusion            |
| pneumothorax                |
| ARDS (noncardiac)           |
| epistaxis                   |
| hemoptysis                  |
| other respiratory           |
| GI Complications:           |
| acute liver failure         |
| hepatitis                   |
| pancreatitis                |
| gastric obstruction         |
| C. difficile colitis        |
| GI bleeding-upper           |
| GI bleeding-lower           |
| ileus                       |
| cholestasis                 |
| abdominal abscess           |
| other GI                    |
| Infectious Complications:   |
| ventriculitis               |
| pneumonia                   |
| cellulitis                  |
| UTI                         |
| peritonitis                 |
| bacteremia                  |
| SIRS                        |
| sepsis                      |
| MODS                        |
| septic shock                |
| other infection             |

References for Appendix VIII

Appendix IX. Consent forms and narrative for phone contact

CONSENT FORM
Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals
Consent form for Patients Enrolled by Prospective Written Consent

H-20405- EFFECT OF ERYTHROPOIETIN ON VASCULAR DYSFUNCTION IN HUMAN TBI

Background
Erythropoietin (Epo) is a hormone that is made by the kidneys and causes the body to make new of red blood cells. Epo is usually given in patients to treat anemia (low red blood cell count) caused by chronic kidney disease or cancer. Epo is FDA approved for this purpose.

Epo has also been given in very sick trauma patients who have anemia, where it reduces the number of blood transfusions that are needed. However, Epo is not approved for this use.

Epo is also made in the brain after injury. In animal models of traumatic brain injury, the brain's production of Epo has numerous beneficial effects, and results in improved recovery of brain function. Because Epo may have beneficial effects for both the injured brain and for the anemia that may occur in very sick trauma patients, we are studying the effects of giving Epo to patients with severe traumatic brain injury.

This research study is sponsored by National Institutes of Health

Purpose
Once Epo is administered we will look at:
1. The amounts of Epo in the brain.
2. How the brain injury reacts to early administration.
3. How the brain system recovers and functions.
4. The red blood cell counts and the need for a transfusion.

Procedures
The research will be conducted at the following location(s): Baylor College of Medicine, HCHD: Harris County Hospital District Ben Taub, Memorial Hermann Hospital System, UT: Health Science Center - Houston.

The standard management of severe brain injury tries to reduce brain swelling and maintain a normal pressure inside the brain, as well as keeping an adequate blood flow to the brain. Several types of monitors may be placed in the brain to help guide this treatment.

The research study that you are being asked to participate in has two parts that are not part of this standard management: the treatment and the monitoring of the effects of the treatment. The treatment part of the study will last for the time that you will require treatment in the ICU for your brain injury (usually 1-2 weeks), and the monitoring part of the study will last for up to 6 months after your brain injury.

Treatment Part of the Research:
For the treatment part of the research study, you will be randomly assigned (like flipping a coin) to one of the following four treatment groups:

1. Epo 500 IU/kg will be given IV within 6 hours of your injury, and then weekly x 2 or until you leave the ICU, and you will receive blood transfusion as needed to keep your hemoglobin concentration around 10 g/dl.
2. Epo 500 IU/kg will be given IV within 6 hours of your injury, and then weekly x 2 or until you leave
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Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals
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H-20405 - EFFECT OF ERYTHROPOIETIN ON VASCULAR DYSFUNCTION IN HUMAN TBI

the ICU; and you will receive blood transfusion as needed to keep your hemoglobin concentration around 7 g/dl.
3. Saline will be given IV within 6 hours of your injury, and then weekly x 2 or until you leave the ICU, and you will receive blood transfusion as needed to keep your hemoglobin concentration around 10 g/dl.
4. Saline will be given IV within 6 hours of your injury, and then weekly x 2 or until you leave the ICU, and you will receive blood transfusion as needed to keep your hemoglobin concentration around 7 g/dl.

There are equal chances of being assigned to the four groups. You and your physicians will not know whether you received Epo or saline. All other aspects of your treatment will be the standard management of a patient with severe traumatic brain injury. Folate 1mg every day and iron sulfate 300mg three times a day will be given to all patients.

Monitoring Part of the Research:
For the monitoring part of the research study, most of the information that is recorded to determine the effect of the treatment will be obtained from monitors and tests that are normally done as a part of the standard treatment of a patient with a severe head injury. The tests and information that are recorded include the following:
1. Vital signs, including the results of all monitors that are needed for treatment of your brain injury.
2. Red blood cell count - This test will be done daily for 10 days, and then weekly while in the ICU, and then at hospital discharge. If a blood transfusion is given, then this test will be done before and 1 hour after the transfusion.
3. Blood tests of kidney function - These tests will be done daily for 10 days, and then weekly while in the ICU, and then at hospital discharge.
4. Blood tests of liver function - This test will be done on day 1, 9, 16, and 23, and then at hospital discharge.
5. Arterial blood gases - This test will be done daily for 10 days or until you no longer need mechanical ventilation.
6. Chest x-ray - The test will be done daily for 10 days or until you no longer need mechanical ventilation.
7. Xenon CT scan - This test gives a picture of the amount of blood flow to the brain and will be done on admission and on day 2 and day 5 after admission.
8. Details of any blood transfusions that are given and of any complications that occur during recovery from your brain injury will be recorded.

In addition, the following additional tests are done specifically for the purpose of this research study:
1. Samples of the fluids listed below will be collected daily for the first 10 days after injury, before and after the first 3 doses of the study drug, and before and after any blood transfusions that are given. The levels of Epo, inflammatory markers, and nitrate/nitrate concentrations will be measured in these samples.
   a. Blood samples - A total of 15 tablespoons will be drawn for these samples.
   b. Samples of fluid from catheters used to monitor pressure and chemistry in the brain - A small amount of cerebrospinal fluid (CSF) is removed and discarded whenever the pressure in the brain becomes elevated. As much as 300 ml CSF per day can be removed with this treatment. An additional 2-3 ml per day will be removed and saved for this study. Any fluid removed from
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H-20405- EFFECT OF ERYTHROPOIETIN ON VASCULAR DYSFUNCTION IN HUMAN TBI

microdialysis catheter to measure the chemistry of the brain that is left over after these tests are done will be saved for this study.

2. Blood flow and reactivity of blood vessels in the brain will be measured using transcranial Doppler, which is a noninvasive test that uses sound waves to see the arteries supplying blood flow to the brain. These measurements will be done daily for 10 days, before and after the first 3 doses of the study drug, and before and after any blood transfusions that are given.

3. If you require surgery for brain injury, any contused brain tissue that is removed and not needed for neuropathological examination will be collected and saved for analysis of Epo levels.

4. Recovery from your brain injury will be measured at discharge from the hospital and at 3 and 6 months after the injury by asking you questions about how well you are able to do everyday activities and if you have been able to return to work or school.

The results of the blood and other samples that are collected specifically for this research study will not be recorded in your medical record, and will not be available to you or to the physicians caring for you. All of the samples collected for this study will be used only for the purposes of this study, and any samples remaining after these studies are complete will be discarded. If you should decide to withdraw from the study, any samples that have not been used will be destroyed. Results that have already been obtained from the samples will be kept, but any identifiers connecting you to these results will be destroyed.

You can see and get a copy of your research related health information. Your research doctor may be able to provide you with part of your information while the study is in progress and the rest of your information at the end of the study.

Potential Risks and Discomforts
Epo is the only drug that is not part of the standard management of patients with severe traumatic brain injury. In clinical studies, diarrhea, edema, fever, vomiting, shortness of breath, tingling, and upper respiratory infection occurred more often with Epo than placebo. Although high blood pressure is a potential side effect of Epo, this has been rarely noted except in patients with kidney failure.

In the doses given in this TBI study, the major complication that has been reported with Epo treatment is an increased risk of blood clots in the legs. This complication has been reported in a study of orthopedic surgery patients and in a large trial of critically ill patients who were given Epo to improve their blood count and to reduce the number of blood transfusions needed. Despite this increased risk of blood clots, the mortality was significantly reduced with Epo in the critically ill trauma patients, from 8.7 to 3.5%.

More serious complications have been reported in studies where higher doses of Epo have been given. In patients with kidney failure, where Epo was given chronically to increase the blood count to levels greater than 12gm/dl, an increase in risk of cardiovascular complications and death occurred. In another trial where Epo was given to patients with stroke to try to improve neurological outcome, a higher mortality rate and a higher rate of bleeding within the brain occurred in the patients treated with Epo. To minimize these risks, this study in TBI patients does not include patients with chronic kidney failure or significant cardiac disease, does not try to increase the blood count to greater than 10gm/dl, and uses the lowest possible dose of Epo.
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The 2 different levels for transfusion (less than 7gm/dl and less than 10gm/dl) are both within the ranges of levels that are commonly used in the critically ill patient. The risk of transfusing to keep the blood count at least 10gm/dl, which is our current practice, is that it is likely that more blood transfusions will be required, and therefore there is a greater risk of complications. These potential complications include infections transmitted in the blood (risk of hepatitis B 1:100,000, risk of HIV 1:1,000,000), an increased risk of hospital-acquired infections (5.2- to 8-fold increased risk), and fluid in the lungs. The risk of transfusing to keep the blood count above the lower value of 7gm/dl is that the injured brain may not be able to increase blood flow enough to compensate for the lower arterial oxygen content, and this could result in reduced oxygen being delivered to the brain. There is no specific information available regarding the level of this risk. Both practices are clinically acceptable and have some risk and some benefit, but it is not known for this subgroup of critically ill patients which has the best risk-to-benefit ratio.

Blood, CSF, and microdialysate samples will be collected specifically for the purposes of this study, but the catheters required to obtain these samples will already be in place as a part of the standard monitoring of such critically ill patients. Therefore the additional increase in risk of obtaining these specimens is minimal. The transcranial Doppler tests of blood vessel reactivity are performed using noninvasive methods and do not pose any significant risks.

In addition to the physiological studies, information regarding demographic characteristics, details about the nature and severity of the injury, and details about the hospital course will be collected. The risk of collecting this data is a small risk of breach of confidentiality.

Study staff will update you in a timely way on any new information that may affect your decision to stay in the study.

Potential Benefits
The benefits of participating in this study may be: The treatment with Epo could result in brain protection and a better neurological outcome. The treatment with Epo could reduce the need for blood transfusions and could increase the red blood cell count. Maintaining a blood count of at least 10gm/dl could improve cerebral oxygen delivery. Maintaining a blood count of at least 7gm/dl could reduce the number of transfusion related complications.

In addition, the benefits to society and to future brain-injured patients might be knowledge about whether Epo is protective after traumatic brain injury and about the optimal red blood cell count to maintain in the brain-injured patient. However, you may receive no benefit from participating.

Alternatives
The following alternative procedures or treatments are available if you choose not to participate in this study: you will receive the standard management for a patient with severe traumatic brain injury.

Subject Costs and Payments
You will not be asked to pay any costs related to this research.
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You will not be paid for taking part in this study.

Subject’s Rights
Your signature on this consent form means that you have received the information about this study and that you agree to volunteer for this research study.

You will be given a copy of this signed form to keep. You are not giving up any of your rights by signing this form. Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study.

If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights.

Your Health Information
We may be collecting health information that could be linked to you (protected health information). This protected health information might have your name, address, social security number or something else that identifies you attached to it. Federal law wants us to get your permission to use your protected health information for this study. Your signature on this form means that you give us permission to use your protected health information for this research study.

If you decide to take part in the study, your protected health information will not be given out except as allowed by law or as described in this form. Everyone working with your protected health information will work to keep this information private. The results of the data from the study may be published. However, you will not be identified by name.

People who give medical care and ensure quality from the institutions where the research is being done, the sponsor(s) listed in the sections above, representatives of the sponsor, agents of the Food and Drug Administration, and regulatory agencies such as the U.S. Department of Health and Human Services will be allowed to look at sections of your medical and research records related to this study. Because of the need for the investigator and study staff to release information to these parties, complete privacy cannot be guaranteed.

The people listed above will be able to access your information for as long as they need to, even after the study is completed.

If you decide to stop taking part in the study or if you are removed from the study, you may decide that you no longer allow protected health information that identifies you to be used in this research study. Contact the study staff to tell them of this decision, and they will give you an address so that you can inform the investigator in writing. The investigator will honor your decision unless not being able to use your identifiable health information would affect the safety or quality of the research study.
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The investigator, CLAUDIA SUE ROBERTSON, and/or someone he/she appoints in his/her place will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury related to the research, you may speak with a member of the study staff: CLAUDIA SUE ROBERTSON or SHANKAR GOPINATH at 713-798-4686 during the day and after hours.

Members of the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (IRB) can also answer your questions and concerns about your rights as a research subject. The IRB office number is (713) 798-6970. Call the IRB office if you would like to speak to a person independent of the investigator and research staff for complaints about the research, if you cannot reach the research staff, or if you wish to talk to someone other than the research staff.

In the event of injury resulting from this research, Baylor College of Medicine, and/or the Harris County Hospital District Ben Taub General Hospital, are not able to offer financial compensation nor to absorb the costs of medical treatment. However, necessary facilities, emergency treatment and professional services will be available to you, just as they are to the general community.

If your child is the one invited to take part in this study you are signing to give your permission. Each child may agree to take part in a study at his or her own level of understanding. When you sign this you also note that your child understands and agrees to take part in this study according to his or her understanding.

Please print your child’s name here ____________________________

Last Amendment: 1/8/2010  Approved from December 22, 2010 to December 21, 2011  Chair Initiate: J. K.
CONSENT FORM
Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals
Consent form for Patients Enrolled by Prospective Written Consent

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Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

Subject ____________________________ Date ____________________________

Legally Authorized Representative ____________________________ Date ____________________________
Parent or Guardian

Legally Authorized Representative - Adult ____________________________ Date ____________________________

Investigator or Designee Obtaining Consent ____________________________ Date ____________________________

Witness (if applicable) ____________________________ Date ____________________________

Translator (if applicable) ____________________________ Date ____________________________

Harris County Hospital District
Protocol number: H-20405
Approval Date: 1-20-11
Expiration Date: 12-21-11

Last Amendment: 1/8/2010
Approved from December 22, 2010 to December 21, 2011 Chair Initiate: J. K.
CONSENT FORM
Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals
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H-20405- EFFECT OF ERYTHROPOIETIN ON VASCULAR DYSFUNCTION IN HUMAN TBI

Background
This form will describe a study of a drug called erythropoietin (Epo) that we are conducting in patients who have had a severe brain injury. Epo is a hormone that is made by the kidneys. Epo causes the body to make new red blood cells. Epo is given in patients to treat anemia (low blood count) caused by chronic kidney disease or cancer. Epo is FDA-approved for this purpose.

Epo has also been given to very sick trauma patients who have anemia. Epo reduces the number of blood transfusions that are needed. However, Epo is not yet approved for this use.

Epo is also made in the brain after injury. In animal models of traumatic brain injury, the brain's production of Epo has numerous beneficial effects, and results in improved recovery of brain function. Because Epo may have beneficial effects for both the injured brain and for the anemia that may occur in very sick trauma patients, we are studying the effects of giving Epo to patients with severe traumatic brain injury.

Normally with this type of study, we ask for permission from patients to be in the study. Yet, we cannot ask these patients because of their medical state. To be helpful for the injured brain, Epo must be started as soon as possible after injury. We will ask permission only if we can find an individual, a legally authorized representative (LAR), who is able to make a decision on behalf of the patient. The LAR can be a spouse, family member or lawyer.

Yet, we know that it is rare to locate a LAR within the first few hours after patient admission. If we cannot find a LAR in time, the patient will be entered into the study without consent. We are doing this under a government rule that allows this so that we can learn more about Epo and better treat future patients. The patients that are included in this study may also benefit.

You or your relative were entered in this study, and had some or all of the procedures described later in this form. This form will detail these procedures that were done or will be done in the future as a part of the study. You may choose to continue to participate in the study or you may withdraw from the study.

This research study is sponsored by National Institutes of Health

Purpose
Once Epo is administered we will look at:
1. The amounts of Epo in the brain.
2. How the brain injury reacts to early administration.
3. How the brain system recovers and functions.
4. The red blood cell counts and the need for a transfusion.

Procedures
The research will be conducted at the following location(s): Baylor College of Medicine, HCHD: Harris County Hospital District Ben Taub, Memorial Hermann Hospital System, UT: Health Science Center - Houston.

The standard management of severe brain injury tries to reduce brain swelling and maintain a
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normal pressure inside the brain, as well as keeping an adequate blood flow to the brain. Several types of monitors may be placed in the brain to help guide this treatment.

The research study that you are participating in has two parts that are not part of this standard management: the treatment and the monitoring of the effects of the treatment. The treatment part of the study will last for the time that you will require treatment in the ICU for your brain injury (usually 1-2 weeks), and the monitoring part of the study will last for up to 6 months after your brain injury.

Treatment Part of the Research:
For the treatment part of the research study, you were randomly assigned (like flipping a coin) to one of the following four treatment groups:

1. Epo 500 IU/kg will be given IV within 6 hours of your injury, and then weekly x 2 or until you leave the ICU; and you will receive blood transfusion as needed to keep your hemoglobin concentration around 10 gm/dl.
2. Epo 500 IU/kg will be given IV daily within 6 hours of your injury, and then weekly x 2 or until you leave the ICU; and you will receive blood transfusion as needed to keep your hemoglobin concentration around 7 gm/dl.
3. Saline will be given IV daily within 6 hours of your injury, and then weekly x 2 or until you leave the ICU, and you will receive blood transfusion as needed to keep your hemoglobin concentration around 10 gm/dl.
4. Saline will be given IV daily within 6 hours of your injury, and then weekly x 2 or until you leave the ICU, and you will receive blood transfusion as needed to keep your hemoglobin concentration around 7 gm/dl.

There are equal chances of being assigned to the four groups. You and your physicians will not know whether you received Epo or saline. All other aspects of your treatment will be the standard management of a patient with severe traumatic brain injury. Folate 1mg every day and iron sulfate 300mg three times a day will be given to all patients.

Monitoring Part of the Research:
For the monitoring part of the research study, most of the information that is recorded to determine the effect of the treatment will be obtained from monitors and tests that are normally done as a part of the standard treatment of a patient with a severe head injury. The tests and information that are recorded include the following:

1. Vital signs, including the results of all monitors that are needed for treatment of your brain injury.
2. Red blood cell count - This test will be done daily for 10 days, and then weekly while in the ICU, and then at hospital discharge. If a blood transfusion is given, then this test will be done before and 1 hour after the transfusion.
3. Blood tests of kidney function - These tests will be done daily for 10 days, and then weekly while in the ICU, and then at hospital discharge.
4. Blood tests of liver function - This test will be done on day 1, 9, 16, and 23 then at hospital discharge.
5. Arterial blood gases - This test will be done daily for 10 days or until you no longer need mechanical ventilation.
6. Chest x-ray - The test will be done daily for 10 days or until you no longer need mechanical
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ventilation.
7. Xenon CT scan - This test gives a picture of the amount of blood flow to the brain and will be
done on admission and on day 2 and day 5 after admission.
8. Details of any blood transfusions that are given and of any complications that occur during
recovery from your brain injury will be recorded.

In addition, the following additional tests are done specifically for the purpose of this research study:
1. Samples of the fluids listed below will be collected daily for the first 10 days after injury, before
and after the first 3 doses of the study drug, and before and after any blood transfusions that are
given. The levels of Epo, inflammatory markers, and nitrate/nitrate concentrations will be measured
in these samples.
a. Blood samples - A total of 15 tablespoons will be drawn for these samples.
b. Samples of fluid from catheters used to monitor pressure and chemistry in the brain - A small
amount of cerebrospinal fluid (CSF) is removed and discarded whenever the pressure in the brain
becomes elevated. As much as 300 ml CSF per day can be removed with this treatment. An
additional 2-3 ml per day will removed and saved for this study. Any fluid removed from
microdialysis catheter to measure the chemistry of the brain that is left over after these tests are
done will be saved for this study.
2. Blood flow and reactivity of blood vessels in the brain will be measured using transcranial
Doppler, which is a noninvasive test that uses sound waves to see the arteries supplying blood flow
to the brain. These measurements will be done daily for 10 days, before and after the first 3 doses
of the study drug, and before and after any blood transfusions that are given.
3. If you require surgery for brain injury, any contused brain tissue that is removed and not needed
for neuropathological examination will be collected and saved for analysis of Epo levels.
4. Recovery from your brain injury will be measured at discharge from the hospital and at 3 and 6
months after the injury by asking you questions about how well you are able to do everyday
activities and if you have been able to return to work or school.

The results of the blood and other samples that are collected specifically for this research study will
not be recorded in your medical record, and will not be available to you or to the physicians caring
for you. All of the samples collected for this study will be used only for the purposes of this study,
and any samples remaining after these studies are complete will be discarded. If you should decide
to withdraw from the study, any samples that have not been used will be destroyed. Results that
have already been obtained from the samples will be kept, but any identifiers connecting you to
these results will be destroyed.

You may decide to continue to participate in the study or to withdraw from the study. If you decide
to withdraw from the study, the data that has been collected so far will be kept as a part of the study
but no additional information will be collected.

____ I would like to continue to participate in the study
____ I do not want to continue to participate in the study

You can see and get a copy of your research related health information. Your research doctor may
be able to provide you with part of your information while the study is in progress and the rest of
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Please read this information at the end of the study.

Potential Risks and Discomforts
Epo is the only drug that is not part of the standard management of patients with severe traumatic brain injury. In clinical studies, diarrhea, edema, fever, vomiting, shortness of breath, tingling, and upper respiratory infection occurred more often with Epo than placebo. Although high blood pressure is a potential side effect of Epo, this has been rarely noted except in patients with kidney failure.

In the doses given in this TBI study, the major complication that has been reported with Epo treatment is an increased risk of blood clots in the legs. This complication has been reported in a study of orthopedic surgery patients and in a large trial of critically ill patients who were given Epo to improve their blood count and to reduce the number of blood transfusions needed. Despite this increased risk of blood clots, the mortality was significantly reduced with Epo in the critically ill trauma patients, from 6.7 to 3.5%.

More serious complications have been reported in studies where higher doses of Epo have been given. In patients with kidney failure, where Epo was given chronically to increase the blood count to levels greater than 12gm/dl, an increase in risk of cardiovascular complications and death occurred. In another trial where Epo was given to patients with stroke to try to improve neurological outcome, a higher mortality rate and a higher rate of bleeding within the brain occurred in the patients treated with Epo. To minimize these risks, this study in TBI patients does not include patients with chronic kidney failure or significant cardiac disease, does not try to increase the blood count to greater than 10gm/dl, and uses the lowest possible dose of Epo.

The two different levels for transfusion (less than 7gm/dl and less than 10gm/dl) are both within the range of levels that are commonly used in the critically ill patient. The risk of transfusing to keep the blood count at least 10gm/dl, which is our current practice, is that it is likely that more blood transfusions will be required, and therefore there is a greater risk of complications. These potential complications include infections transmitted in the blood (risk of hepatitis B 1:100,000, risk of HIV 1:1,000,000), an increased risk of hospital-acquired infections (5-2- fold increased risk), and fluid in the lungs. The risk of transfusing to keep the blood count above the lower value of 7gm/dl is that the injured brain may not be able to increase blood flow enough to compensate for the lower arterial oxygen content, and this could result in reduced oxygen being delivered to the brain. There is no specific information available regarding the level of this risk. Both practices are clinically acceptable and have some risk and some benefit, but it is not known for this subgroup of critically ill patients which has the best risk-to-benefit ratio.

Blood, CSF, and microdialysate samples will be collected specifically for the purposes of this study, but the catheters required to obtain these samples will already be in place as a part of the standard monitoring of such critically ill patients. Therefore, the additional increase in risk of obtaining these specimens is minimal. The transcranial Doppler tests of blood vessel reactivity are performed using noninvasive methods and do not pose any significant risks.

In addition to the physiological studies, information regarding demographic characteristics, details about the nature and severity of the injury, and details about the hospital course will be collected.
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The risk of collecting this data is a small risk of breach of confidentiality.

Study staff will update you in a timely way on any new information that may affect your decision to stay in the study.

Potential Benefits
The benefits of participating in this study may be: The treatment with Epo could result in brain protection and a better neurological outcome. The treatment with Epo could reduce the need for blood transfusions and could increase the red blood cell count. Maintaining a blood count of at least 10gm/dl could improve cerebral oxygen delivery. Maintaining a blood count of at least 7gm/dl could reduce the number of transfusion related complications.

In addition, the benefits to society and to future brain-injured patients might be knowledge about whether Epo is protective after traumatic brain injury and about the optimal red blood cell count to maintain in the brain-injured patient. However, you may receive no benefit from participating.

Alternatives
The following alternative procedures or treatments are available if you choose not to participate in this study: you will receive the standard management for a patient with severe traumatic brain injury.

Subject Costs and Payments
You will not be asked to pay any costs related to this research.

You will not be paid for taking part in this study.

Subject’s Rights
Your signature on this consent form means that you have received the information about this study and that you agree to volunteer for this research study.

You will be given a copy of this signed form to keep. You are not giving up any of your rights by signing this form. Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study.

If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights.

Your Health Information
We may be collecting health information that could be linked to you (protected health information). This protected health information might have your name, address, social security number or something else that identifies you attached to it. Federal law wants us to get your permission to use your protected health information for this study. Your signature on this form means that you give us...
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permission to use your protected health information for this research study.

If you decide to take part in the study, your protected health information will not be given out except
as allowed by law or as described in this form. Everyone working with your protected health
information will work to keep this information private. The results of the data from the study may be
published. However, you will not be identified by name.

People who give medical care and ensure quality from the institutions where the research is being
done, the sponsor(s) listed in the sections above, representatives of the sponsor, agents of the
Food and Drug Administration, and regulatory agencies such as the U.S. Department of Health and
Human Services will be allowed to look at sections of your medical and research records related to
this study. Because of the need for the investigator and study staff to release information to these
parties, complete privacy cannot be guaranteed.

The people listed above will be able to access your information for as long as they need to, even
after the study is completed.

If you decide to stop taking part in the study or if you are removed from the study, you may decide
that you no longer allow protected health information that identifies you to be used in this research
study. Contact the study staff to tell them of this decision, and they will give you an address so that
you can inform the investigator in writing. The investigator will honor your decision unless not being
able to use your identifiable health information would affect the safety or quality of the research
study.

The investigator, CLAUDIA SUE ROBERTSON, and/or someone he/she appoints in his/her place
will try to answer all of your questions. If you have questions or concerns at any time, or if you need
to report an injury related to the research, you may speak with a member of the study staff:
CLAUDIA SUE ROBERTSON or SHANKAR GOPINATH at 713-798-6906 during the day and after
hours.

Members of the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals
(IRB) can also answer your questions and concerns about your rights as a research subject. The
IRB office number is (713) 798-6970. Call the IRB office if you would like to speak to a person
independent of the investigator and research staff for complaints about the research, if you cannot
reach the research staff, or if you wish to talk to someone other than the research staff.

In the event of injury resulting from this research, Baylor College of Medicine, and/or the Harris
County Hospital District Ben Taub General Hospital, are not able to offer financial compensation nor
to absorb the costs of medical treatment. However, necessary facilities, emergency treatment and
professional services will be available to you, just as they are to the general community.
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If your child is the one invited to take part in this study you are signing to give your permission. Each child may agree to take part in a study at his or her own level of understanding. When you sign this you also note that your child understands and agrees to take part in this study according to his or her understanding.

Please print your child’s name here ____________________
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Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

Subject ___________________________ Date ___________________________

Legally Authorized Representative
Parent or Guardian ___________________________ Date ___________________________

Legally Authorized Representative - Adult ___________________________ Date ___________________________

Investigator or Designee Obtaining Consent ___________________________ Date ___________________________

Witness (if applicable) ___________________________ Date ___________________________

Translator (if applicable) ___________________________ Date ___________________________

Harris County Hospital District
Protocol number: H-20405
Approval Date: 1-20-11
Expiration Date: 12-21-11

Last Amendment: 1/8/2010
Approved from December 22, 2010 to December 21, 2011 Chair Initials: J. K.
FORMA DE CONSENTIMIENTO
Comité de Revisión Institucional (Institutional Review Board, IRB por sus siglas en inglés) para Baylor College of Medicine e Instituciones Afiliadas.

Forma de Consentimiento Para Pacientes Con Traumatismo craneoencefálico Enrolados por Consentimiento Escrito Prospektivo.

H-20405 – EFECTO DE ERTIPOPOYETINA EN LA DISFUNCIÓN VASCULAR EN LESIÓN TRAUMÁTICA CEREBRAL EN HUMANOS

Antecedentes:
La eritropoietina (Epo) es una hormona que es producida en los riñones. Epo hace que el cuerpo produzca nuevas células sanguíneas rojas. Epo es usualmente administrada en pacientes para tratar la anemia (glóbulos rojos bajos) que es causada por una enfermedad crónica de los riñones o por cáncer. Epo ha sido aprobada por la FDA para estos propósitos

Epo también ha sido administrada en pacientes traumatizados muy enfermos que tienen anemia. Epo reduce el número de transfusiones que son requeridas. Sin embargo, Epo no ha sido aprobada para este uso.

Epo también es producida en el cerebro después de una lesión. En modelos animales de lesión traumática, la producción cerebral de Epo tiene numerosos efectos benéficos, y resulta en una mejor recuperación de la función cerebral. Dado que Epo pudiera tener efectos benéficos tanto para la lesión cerebral y para la anemia que pudiera tomar lugar en pacientes traumatizados muy enfermos, estamos estudiando los efectos de Epo en pacientes con lesión traumática severa.

Este estudio de investigación es patrocinado por el Instituto Nacional De Salud (National Institutes of Health, NIH por sus siglas en inglés).

Propósito
Una vez que la EPO sea administrada prestaremos atención en lo siguiente:
1. Las cantidades de EPO en el cerebro.
2. Como la lesión cerebral reacciona a la administración temprana.
3. Como se recupera y funciona el sistema cerebral.
4. El conteo de glóbulos rojos y la necesidad de transfusión.

Procedimientos:
El estudio será llevado a cabo en los siguientes lugares: Baylor College of Medicine, HCHD: Harris County Hospital District Ben Taub, Memorial Hermann Hospital System, UT: Health Science Center - Houston.

El tratamiento estándar de una lesión cerebral trata de reducir la inflamación cerebral y mantener la presión normal dentro del cerebro, así como mantener un flujo cerebral adecuado. Diferentes tipos de monitores pudieran ser instalados en el cerebro para tratar de guiar esta terapia.
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El estudio de investigación en el que usted está participando tiene dos partes que no son parte del cuidado estándar: el tratamiento y el monitoreo de los efectos del tratamiento. La parte del tratamiento del estudio va a durar el mismo tiempo que el paciente requiera estar en la UCI para manejar su trauma cerebral (usualmente 1-2 semanas) y la parte de la monitorización del estudio durará hasta 6 meses después de la lesión cerebral.

Parte del tratamiento del estudio:
Para la parte del tratamiento del estudio, usted ha sido asignado aleatoriamente (como un volado con una moneda) a uno de los siguientes cuatro grupos de tratamiento:

1. Epo 500 IU/Kg. serán administradas IV (vía intravenosa) dentro de las primeras 6 horas de su lesión, después semanalmente 2 veces o hasta que salga de la UCI (Unidad de Cuidados Intensivos), y usted recibirá transfusión sanguínea como sea necesario para mantener su hemoglobina alrededor de 10gm/dl.

2. Epo 500 IU/Kg. serán administradas IV (vía intravenosa) dentro de las primeras 6 horas de su lesión, después semanalmente 2 veces o hasta que salga de la UCI (Unidad de Cuidados Intensivos), y usted recibirá transfusión sanguínea como sea necesario para mantener su hemoglobina alrededor de 7gm/dl.

3. Solución salina (placebo) será administrada IV (vía intravenosa) dentro de las primeras 6 horas de su lesión, después semanalmente 2 veces o hasta que salga de la UCI (Unidad de Cuidados Intensivos), y usted recibirá transfusión sanguínea como sea necesario para mantener su hemoglobina alrededor de 10gm/dl.

4. Solución salina (placebo) será administrada IV (vía intravenosa) dentro de las primeras 6 horas de su lesión, después semanalmente 2 veces o hasta que salga de la UCI (Unidad de Cuidados Intensivos), y usted recibirá transfusión sanguínea como sea necesario para mantener su hemoglobina alrededor de 7gm/dl.

Habrá las mismas posibilidades de ser asignado a alguno de los cuatro grupos. Usted y sus doctores no sabrán si recibe Epo o salino. Todos los otros aspectos de su tratamiento serán los manejos estándar para el paciente con trauma cerebral severo. 1 mg de folato diario y 325 mg de sulfato de hierro tres veces al día serán dados a todos los pacientes.

Parte de la Monitorización del estudio:
Para la parte de monitorización del estudio, la mayoría de la información que es registrada para determinar el efecto del tratamiento será obtenida de los monitores y pruebas que normalmente
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son hechas como parte del tratamiento estándar con trauma cerebral severo. Las pruebas e información que serán registradas son las siguientes:

1. Signos vitales, incluyendo los resultados de todos los monitores que son requeridos para el tratamiento de su lesión cerebral.
2. Conteo de glóbulos rojos- Esta prueba será realizada diariamente por 10 días, y después semanalemente mientras se encuentre en la UCI, después cuando se le dé de alta. Si una transfusión sanguínea es administrada, entonces esta prueba será realizada antes y una hora después de la transfusión.
3. Pruebas sanguíneas del funcionamiento del riñón- Estas pruebas serán realizadas diariamente por 10 días, y luego semanalemente mientras permanezca en la UCI, y después al momento del alta.
4. Pruebas para valorar el hígado serán hechas los días 1, 9, 16 y 23 y al salir del hospital
5. Gases arteriales serán hechas diariamente por 10 días o hasta que el paciente ya no necesite ventilación mecánica.
6. Radiografía de tórax será hecha diariamente por 10 días o hasta que ya no necesite ventilación mecánica.
7. Tomografía Computarizada con gas xenón, este examen otorga una imagen de la cantidad del flujo sanguíneo hacia el cerebro y será realizada a su admisión, y los días 2 y 5 después de su admisión.
8. Detalles de cualquier transfusión que sean administradas y cualquier complicación que ocurra durante la recuperación de su lesión cerebral serán registradas.

Además, las siguientes pruebas serán realizadas específicamente con el propósito de este estudio:

1. Muestras de fluidos enlistaos abajo serán recolectados diariamente por los primeros 10 días después de la lesión, y después de las primeras 3 dosis de la droga en estudio, y antes y después de cualquier transfusión sea medida. Los niveles de Epo, marcadores de inflamación, y concentración de nitratos/nitratos serán medidos de las siguientes muestras.

   a. Muestra sanguínea – Un total de 15 cucharadas serán recolectadas para estas muestras.
   b. Muestras de fluidos de los catéteres usados para monitorizar la presión y química del cerebro – Un pequeña muestra de líquido cefalorraquideo (LCR) será drenado y desechado cuando la presión del cerebro se eleve. Tanto como 300ml de LCR por día puede ser drenado por este tratamiento. En adición a esto de 2-3ml por día serán drenados y guardados para este estudio. Cualquier otro fluido drenado del catéter de Micromédisis para medir la química del cerebro que sobra después de estas pruebas serán realizadas serán guardadas para este estudio.
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2. Flujo cerebral y reactividad de los vasos sanguíneos en el cerebro será medido usando el Doppler transcraneal, el cual es una prueba no invasiva que utiliza ondas de sonido para ver a las arterias abasteciendo de flujo sanguíneo al cerebro. Estas mediciones serán efectuadas diariamente por 10 días, y antes y después de las primeras 3 dosis de la droga en estudio, y antes y después de cualquier transfusión sanguínea sea administrada.

3. Si usted requiere cirugía cerebral, cualquier tejido lesionado que sea removido y no se necesite para examen neuropatológico será recolectado y guardado para medir niveles de Epo.

4. La recuperación del trauma cerebral será medida al darse de alta del hospital y a los 3 y 6 meses después del trauma le preguntaran acerca de cómo está usted y si puede realizar actividades diarias y se ha regresado a la escuela o el trabajo.

Los resultados de las muestras sanguíneas y otras muestras que sean recolectadas específicamente para este estudio no serán registradas en su expediente médico y no estarán disponibles para usted o para los doctores encargados de usted. Todas las muestras de sangre de este estudio serán solamente para el estudio de investigación y si sobran muestras se desecharan. Si usted decidiera retirarse del estudio, cualquier muestra que no ha sido utilizada se destruirá. Los resultados que ya hayan sido obtenidos serán guardados pero cualquier identificador que lo pudiera reconocer a usted será destruido.

Usted puede ver y obtener una copia de su información de salud ligada al estudio de investigación. Su médico investigador puede proveerle con parte de información mientras el estudio este en progreso y el resto de su información al finalizar el estudio.

Riesgos y Molestias

Epo es el único medicamento que no es parte del manejo normal en pacientes con trauma cerebral severo. En estudios clínicos, diarrea, edema, fiebre, vómito, falta de aire, hormigueo e infecciones respiratorias han ocurrido más comúnmente con Epo que con placebo. Sin embargo, presión arterial alta es un efecto potencial, aunque es raro excepto en pacientes con insuficiencia renal.

En las dosis administradas en este estudio de lesión traumática cerebral, la mayor complicación que ha sido reportada en el tratamiento con Epo es un riesgo incrementado de coágulos sanguíneos en las piernas. Esta complicación ha sido reportada en un estudio de cirugía ortopédica en un estudio grande de pacientes críticamente enfermos que se les administró Epo para mejorar sus niveles de glóbulos rojos en la sangre para reducir el número de transfusiones requeridas. A pesar del riesgo incrementado de formación de coágulos, la mortalidad fue significativamente reducida con Epo en pacientes traumatizados críticamente enfermos del 6.7% al 3.5%.
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Complicaciones más serias han sido reportadas donde se han administrado dosis más altas de Epo. En pacientes con insuficiencia renal donde la Epo fue administrada crónicamente los niveles sanguíneos de glóbulos rojos a más de 12 g/dl ocurrió un incremento en el riesgo de complicaciones cardiovasculares y muerte. En otro estudio donde Epo fue administrado en pacientes con embolia cerebral para tratar de mejorar el resultado neurológico ocurrió una mayor tasa de mortalidad y tasa de sangrado dentro del cerebro en los pacientes que recibieron Epo. Para minimizar estos riesgos, este estudio no incluye pacientes con insuficiencia renal crónica o con enfermedad cardíaca significativa, y no trata de incrementar los glóbulos rojos a una cuenta sanguínea mayor de 10gm/dl, y usa la dosis más baja posible de Epo.

Los dos diferentes niveles de transfusión (menos de 7 g/dl y menos de 10 g/dl) son entre los rangos de niveles que son comúnmente usados en pacientes enfermos críticamente. El riesgo de transfusión para mantener la hemoglobina en niveles de 10 g/dl que es nuestra práctica actual, es que sea necesario más sangre y por lo tanto esta el riesgo de complicaciones relacionadas con la transfusión. Estas complicaciones pueden ser infecciosas (hepatitis B 1:100,000, riesgo de VIH 1:1, 000,000), reacciones inmunes incluyendo el riesgo de infecciones adquiridas en el hospital (5.2 a 6 veces es el riesgo incrementado) y líquido en los pulmones. El riesgo de transfundir para mantener la hemoglobina en concentraciones mayores al valor de 7 g/dl es que el cerebro lesionado no puede ser capaz de aumentar el flujo sanguíneo adecuadamente para compensar el contenido de oxígeno y esto podría resultar en menos oxígeno llevado hacia el cerebro. No existe información específica disponible concerniente a este riesgo. Ambas prácticas son clínicamente aceptables y tienen algo de riesgo y beneficio, pero no se conoce la mejor tasa riesgo-beneficio en este subgrupo de pacientes críticamente enfermos.

Sangre, LCR, y muestras de Microdilisis serán recolectadas específicamente con el propósito del estudio, pero los catéteres requeridos para obtener estas muestras (catéter arterial, ventriculostomía y catéter de Microdilisis) será colocados como parte del monitoreo estándar en dichos pacientes críticos. Entonces el incremento de riesgo para obtener estas muestras es mínimo. Las pruebas con Doppler transcerebral son realizadas usando métodos no invasivos y sin riesgos significativos.

Además de los estudios fisiológicos, la información acerca de las características demográficas, detalles acerca de la naturaleza y severidad del curso hospitalario serán recolectados. El riesgo de colectar estos datos y perder la confidencialidad del paciente es mínimo.

El personal del estudio le estará informando de manera oportuna cualquier información nueva que pueda afectar su decisión de permanecer en el estudio.
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Beneficios Potenciales
Los beneficios al participar en este estudio pueden ser: El tratamiento con Epo puede resultar en protección cerebral y así un mejor resultado neurológico. El tratamiento con Epo puede reducir la necesidad de transfusiones sanguíneas y puede aumentar la concentración de la hemoglobina. Manteniendo la hemoglobina por lo menos 10 g/dl puede incrementar el aporte de oxígeno al cerebro. Mantener la hemoglobina por lo menos a 7gm/dl reduce el número de complicaciones relacionadas con la transfusión.

Además, los beneficios para la sociedad y para futuros pacientes con lesiones cerebrales pueden ser conocimientos acerca de si Epo es protector en la lesión traumática cerebral y acerca de la concentración óptima de hemoglobina que se necesita mantener en pacientes con trauma cerebral. Sin embargo, usted pudiera no recibir beneficio al participar.

Alternativas
Las siguientes alternativas o tratamientos están disponibles si elige no participar en este estudio: usted recibirá el manejo estándar para paciente con lesión cerebral traumática.

Costos y Pagos del Paciente
No hay costos por participar. A Usted no se le pagará por tomar parte en este estudio.

Lesión relacionada a la investigación
El personal de la investigación tratará de reducir, controlar y tratar cualquier complicación que resulte de esta investigación. Si usted es lesionado por este estudio, usted recibirá los cuidados médicos que usted o su seguro tendrá que pagar como si se tratara de cualquier otro cuidado médico.

Derechos del Paciente
Su firma en este consentimiento significa que usted ha recibido la información acerca del estudio y está de acuerdo en participar.

Se le entregará una copia de esta forma firmada. Usted no deja de tener sus derechos al firmar esta forma. Aún después de firmar usted puede cambiar de opinión. Por favor contacte el personal del estudio si decide ya no pertenecer al estudio.

El investigador o el patrocinador pueden decidir retirarlo de ser parte de este estudio en cualquier momento. Usted puede ser removido del estudio por razones relacionadas solo con usted (ejemplo, si usted se muda de ciudad, si no toma su medicamento de investigación, o si tiene una
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Reacción sería al medicamento) o porque el estudio por completo se detuvo. El patrocinador puede detener el estudio en cualquier momento.

Puede haber riesgos y malestares desconocidos. El personal del estudio le informará en cualquier momento cualquier nueva información que afecte su salud, bienestar o decisión.

Si usted se lesionó por causas del estudio, usted recibirá cuidados médicos que usted y su compañía de seguro tendrá que pagar como si fuera otro cuidado médico. A usted no se le pagará por la lesión.

Información sobre su Salud
Podríamos recolectar información de salud que pudiera tener relación con usted. Esta información de salud pudiera tener su nombre, dirección, número de seguro social o algo más que lo identifique. La ley federal quiere que nosotros pidamos permiso para usar su protegida información de salud para el estudio. Si firma en esta forma significa que nos da permiso para usar información de salud protegida en el estudio de investigación.

Si usted decide ser parte del estudio, su información sobre su salud estará protegida y no será expuesta excepto que sea permitido por la ley o como se ha descrito en esta forma. Todos los que trabajen con su información protegida trabajarán para mantener esta información privada. Los resultados de los datos de este estudio pueden ser publicados. Sin embargo, usted no podrá ser identificado con su nombre.

La gente que otorga atención médica y se asegura de calidad de las instituciones donde se realiza la investigación, los patrocinadores, representantes de los patrocinadores, agentes de la Food and Drug Administration (FDA, por sus siglas en inglés) y agencias regulatorias del Departamento de Salud y Servicios Humanos de U.S., les será permitido revisar secciones de su historial médico y de investigación relacionadas con el estudio. Debido a la necesidad del investigador y del personal de dar información a estas personas, privacidad completa no se puede garantizar. La gente enlistada en el párrafo anterior tendrá disponible su información tanto como la necesiten, aún después de que el estudio sea completado.

Si usted decide no ser parte del estudio o si usted es retirado del estudio, usted puede decidir ya no permitir que la información protegida de su salud que lo identifique sea usada en esta investigación. Contacte el personal del estudio para decirles esta decisión, ellos le darán una dirección para que informe por escrito al investigador. El investigador respetará su decisión, a
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menos de que al no estar permitido usar su información afecte la seguridad y calidad del estudio de investigación.

La investigadora CLAUDIA SUE ROBERTSON y/o alguien que ella designe en su lugar podrán responder sus preguntas. Si tiene preguntas o dudas en cualquier momento, o si necesita reportar cualquier incidente relacionado con la investigación, usted puede hablar con un miembro del personal: CLAUDIA ROBERTSON, SHANKAR GOPINATH al número 713 798 4696 durante el día y fuera de horario de oficina.
Miembros del comité de revisión para Baylor College of Medicine y hospitales afiliados también pueden contestar sus preguntas y dudas acerca de los derechos del paciente. El número es 713 798 6970.

En caso de lesión por el estudio, Baylor College of Medicine y/o Harris County Hospital District ben Taub General Hospital no podrán financiar ni absorber costos del tratamiento. Sin embargo, facilidades, tratamientos de urgencia, y servicios profesionales estarán disponibles, como lo están para la población en general.

Si su hijo es uno de los pacientes que se lo solicita entrar al protocolo. Cada niño puede estar de acuerdo en tomar parte del estudio por su propio nivel de entendimiento. Cuando usted firma esto, usted también tomo nota que su hijo entendió y está de acuerdo en participar en el estudio.

Por favor, escribe el nombre del niño aquí: ____________________________
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Al firmar este consentimiento usted indica que ha leído la forma (o se la han leído), que sus preguntas han sido contestadas satisfactoriamente y que usted voluntariamente está de acuerdo en participar en este estudio. Usted recibirá una copia firmada de este consentimiento.

Sujeto

Fecha

Representante Legal Autorizado

Fecha

Padre o Tutor

Representante Legal Autorizado - Adulto

Fecha

Investigador o quien obtiene el consentimiento

Fecha

Testigo (si aplica)

Fecha

Traductor (si aplica)

Fecha

Harris County Hospital District
Protocol number: H-20405
Approval Date: 1-20-11
Expiration Date: 12-21-11

THE INSTITUTIONAL REVIEW BOARD
FOR HUMAN SUBJECT RESEARCH
FOR BAYLOR COLLEGE OF MEDICINE
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AMENDMENT DATE 01/05/2010
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Antecedentes:
Esta forma describirá el estudio de una droga llamada Eritropoyetina (Epo), que nosotros estamos llevando a cabo en pacientes que han tenido una lesión cerebral severa. Epo es una hormona que es producida en los riñones. Epo hace que el cuerpo produzca nuevas células sanguíneas. Epo es administrada en pacientes para tratar anemia (glóbulos rojos bajos) causada por una enfermedad crónica de los riñones o cáncer. Epo ha sido aprobada por la Administración de Drogas y Alimentos (Food and Drug Administration, o FDA por sus siglas en inglés) para estos propósitos.

Epo también ha sido administrada en pacientes traumatizados muy enfermos que tienen anemia. Epo reduce el número de transfusiones que son requeridas. Sin embargo, Epo no ha sido aprobado para este uso.

Epo también es producida en el cerebro después de una lesión. En modelos animales de lesión traumática, la producción cerebral de Epo tiene numerosos efectos benéficos, y resulta en una mejor recuperación de la función cerebral. Dado que Epo pudiera tener efectos beneficios tanto para la lesión cerebral y para la anemia que pudiera tomar lugar en pacientes traumatizados muy enfermos, estamos estudiando los efectos de Epo en pacientes con lesión traumática severa.

Normalmente para este tipo de estudio, pedimos el permiso del paciente que será enrolado en el estudio. Sin embargo no podemos realizar esto en estos pacientes debido a su condición médica. Para que sea de ayuda al cerebro lesionado, Epo debe ser administrada tan pronto como sea posible después de la lesión. Nosotros solicitaremos este permiso sólo si podemos encontrar algún individuo, un representante legal autorizado (RLA), que pueda tomar la decisión por el paciente. El RLA pude ser un esposo(a), miembro de la familia o un abogado.

De antemano, nosotros sabemos que es muy raro encontrar a un RLA en las primeras horas después de que el paciente ha sido admitido. Si nosotros no podemos encontrar a un RLA a tiempo, el paciente entrará en nuestro estudio sin consentimiento alguno. Estamos haciendo esto bajo el reglamento del gobierno que permite esto para que así podamos aprender más acerca de EPO y tratar mejor en un futuro a los pacientes. Los pacientes incluidos en este estudio también pudieran beneficiarse.

Usted o su familiar ha sido enrolados en este estudio, y han tenido alguno o todos los procedimientos descritos posteriormente en esta forma. Esta forma detallará estos
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procedimientos que hemos hecho o que se harán en un futuro como parte de este estudio. Usted puede escoger continuar participando en este estudio o retirarse de este estudio.

Este estudio de investigación es patrocinado por el Instituto Nacional De Salud.

Propósito
Una vez que la EPO sea administrada prestaremos atención en lo siguiente:

1. Las cantidades de EPO en el cerebro.
2. Como la lesión cerebral reacciona a la administración temprana.
3. Como se recupera y funciona el sistema cerebral.
4. El conteo de glóbulos rojos y la necesidad de transfusión.

Procedimientos:

El estudio será llevado a cabo en los siguientes lugares: Baylor College of Medicine, HCHD: Harris County Hospital District Ben Taub, Memorial Hermann Hospital System, UT: Health Science Center - Houston.

El tratamiento estándar de una lesión cerebral trata de reducir la inflamación cerebral y mantener la presión normal dentro del cerebro, así como mantener un flujo cerebral adecuado. Diferentes tipos de monitores pudieran ser instalados en el cerebro para tratar de guiar esta terapia.

El estudio de investigación en el que usted está participando tiene dos partes que no son parte del cuidado estándar: el tratamiento y el monitoreo de los efectos del tratamiento. La parte del tratamiento del estudio va a durar el mismo tiempo que el paciente requiera estar en la UCI para manejar su trauma cerebral (usualmente 1-2 semanas) y la parte de la monitorización del estudio durara hasta 6 meses después de la lesión cerebral.

Parte del tratamiento del estudio:
Para la parte del tratamiento del estudio, usted ha sido asignado aleatoriamente (como un volado con una moneda) a uno de los siguientes cuatro grupos de tratamiento:

1. Epo 500 IU/Kg. serán administradas IV (vía intravenosa) dentro de las primeras 6 horas de su lesión, después semanalmente 2 veces o hasta que salgan de la UCI (Unidad de Cuidados Intensivos), y usted recibirá transfusión sanguínea como sea necesario para mantener su hemoglobina alrededor de 10gm/dl.
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2. Epo 500 IU/Kg. serán administradas IV (vía intravenosa) dentro de las primeras 6 horas de su lesión, después semanalmente 2 veces o hasta que salga de la UCI (Unidad de Cuidados Intensivos), y usted recibirá transfusión sanguínea como sea necesario para mantener su hemoglobina alrededor de 7gm/dl.

3. Solución salina (placebo) será administrada IV (vía intravenosa) dentro de las primeras 6 horas de su lesión, después semanalmente 2 veces o hasta que salga de la UCI (Unidad de Cuidados Intensivos), y usted recibirá transfusión sanguínea como sea necesario para mantener su hemoglobina alrededor de 10gm/dl.

4. Solución salina (placebo) será administrada IV (vía intravenosa) dentro de las primeras 6 horas de su lesión, después semanalmente 2 veces o hasta que salga de la UCI (Unidad de Cuidados Intensivos), y usted recibirá transfusión sanguínea como sea necesario para mantener su hemoglobina alrededor de 7gm/dl.

Habrá las mismas posibilidades de ser asignado a alguno de los cuatro grupos. Usted y sus doctores no sabrán si recibe Epo o salino. Todos los otros aspectos de su tratamiento serán los manejos estándar para el paciente con trauma cerebral severo. 1 mg de folato diario y 325 mg de sulfato de hierro tres veces al día serán dados a todos los pacientes.

Parte de la Monitorización del estudio:
Para la parte de monitorización del estudio, la mayoría de la información que es registrada para determinar el efecto del tratamiento será obtenida de los monitores y pruebas que normalmente son hechas como parte del tratamiento estándar con trauma cerebral severo. Las pruebas e información que serán registradas son las siguientes:

1. Signos vitales, incluyendo los resultados de todos los monitores que son requeridos para el tratamiento de su lesión cerebral.

2. Conteo de glóbulos rojos- Esta prueba será realizada diariamente por 10 días, y después semanalmente mientras se encuentre en la UCI, después cuando se le dé de alta. Si una transfusión sanguínea es administrada, entonces esta prueba será realizada antes y una hora después de la transfusión.

3. Pruebas sanguíneas del funcionamiento del riñón- Estas pruebas serán realizadas diariamente por 10 días, y luego semanalmente mientras permanezca en la UCI, y después al momento de alta.

4. Pruebas para valorar el hígado serán hechas los días 1, 5, 9, 16 y 23 y al salir del hospital
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5. Gases arteriales serán hechas diariamente por 10 días o hasta que el paciente ya no necesite ventilación mecánica.
6. Radiografía de tórax será hecha diariamente por 10 días o hasta que ya no necesite ventilación mecánica.
7. Tomografía Computarizada con gas xenón, este examen otorga una imagen de la cantidad del flujo sanguíneo hacia el cerebro y será realizada a su admisión, y los días 2 y 5 después de su admisión.
8. Detalles de cualquier transfusión que sean administradas y cualquier complicación que ocurra durante la recuperación de su lesión cerebral serán registradas.

Además, las siguientes pruebas serán realizadas específicamente con el propósito de este estudio:
1. Muestras de fluidos enlistados abajo serán recolectados diariamente por los primeros 10 días después de la lesión, y después de las primeras 3 dosis de la droga en estudio, y antes y después de cualquier transfusión sea medida. Los niveles de Epo, marcadores de inflamación, y concentración de nitratos/nitritos serán medidos en las siguientes muestras.
   a. Muestra sanguínea – Un total de 15 cucharadas serán recolectadas para estas muestras.
   b. Muestras de fluidos de los catéteres usados para monitorizar la presión y química del cerebro – Un pequeña muestra de líquido cefalorraquídeo (LCR) será drenado y descartado cuando la presión del cerebro se eleve. Tanto como 300ml de LCR por día puede ser drenado por este tratamiento. En adición a esto de 2-3ml por día serán drenados y guardados para este estudio. Cualquier otro fluido drenado del catéter de Microdialisis para medir la química del cerebro que sobren después de estas pruebas serán guardados para este estudio.
2. Flujo cerebral y reactividad de los vasos sanguíneos en el cerebro será medido usando el Doppler transcraneal, el cual es una prueba no invasiva que utiliza ondas de sonido para ver a las arterias abasteciendo de flujo sanguíneo al cerebro. Estas mediciones serán efectuadas diariamente por 10 días, y antes y después de las primeras 3 dosis de la droga en estudio, y antes y después de cualquier transfusión sanguínea sea administrada.
3. Si usted requiere cirugía cerebral, cualquier tejido lesionado que sea removido y no se necesite para examen neuropatológico será recolectado y guardado para medir niveles de Epo.
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4. La recuperación del trauma cerebral será medida al darle de alta del hospital y a los 3 y 6 meses después del trauma le preguntaran acerca de cómo estás usted y si puede realizar actividades diarias y se ha regresado a la escuela o el trabajo.

Los resultados de las muestras sanguíneas y otras muestras que sean recolectadas específicamente para este estudio no serán registradas en su expediente médico y no estarán disponibles para usted o para los doctores encargados de usted. Todas las muestras de sangre de este estudio serán solamente para el estudio de investigación y si sobran muestras se desecharan. Si usted decidiera retirarse del estudio, cualquier muestra que no ha sido utilizada se destruirá. Los resultados que ya hayan sido obtenidos serán guardados pero cualquier identificador que lo pudiera reconocer a usted será destruido.

Usted puede decidir continuar participando en el estudio o retirarse del estudio. Si usted decide retirarse del estudio, la información que ha sido recolectada hasta ese momento será guardada como parte del estudio pero ninguna otra información adicional será recolectada.

___ Si me gustaría seguir participando en el estudio.
___ No me gustaría seguir participando en el estudio.

Usted puede ver y obtener una copia de su información de salud ligada al estudio de investigación. Su médico investigador puede proveerle con parte de información mientras el estudio este en progreso y el resto de su información al finalizar el estudio.

Riesgos y Molestias
Epo es el único medicamento que no es parte del manejo normal en pacientes con trauma cerebral severo. En estudios clínicos, diarrea, edema, fiebre, vómito, falta de aire, hipo e infecciones respiratorias han ocurrido más comúnmente con Epo que con placebo. Sin embargo, presión arterial alta es un efecto potencial, aunque es raro excepto en pacientes con insuficiencia renal.

En las dosis administradas en este estudio de lesión traumática cerebral, la mayor complicación que ha sido reportada en el tratamiento con Epo es un riesgo incrementado de coágulos sanguíneos en las piernas. Esta complicación ha sido reportada en un estudio de cirugía ortopédica en un estudio grande de pacientes críticamente enfermos que se les administró Epo para mejorar sus niveles de glóbulos rojos en la sangre para reducir el número de transfusiones requeridas. A pesar del riesgo incrementado de formación de coágulos, la mortalidad fue significativamente reducida con Epo en pacientes.
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traumatizados críticamente enfermos del 6.7% al 3.5%.
Complicaciones más serias han sido reportadas donde se han administrado dosis más altas de Epo. En pacientes con insuficiencia renal donde la Epo fue administrada crónicamente los niveles sanguíneos de glóbulos rojos a más de 12 g/dL ocurrió un incremento en el riesgo de complicaciones cardiovasculares y muerte. En otro estudio donde Epo fue administrado en pacientes con embolia cerebral para tratar de mejorar el resultado neurológico ocurrió una mayor tasa de mortalidad y tasa de sangrado dentro del cerebro en los pacientes que recibieron Epo. Para minimizar estos riesgos, este estudio no incluye pacientes con insuficiencia renal crónica o con enfermedad cardíaca significativa, y no trata de incrementar los glóbulos rojos a una cuenta sanguínea mayor de 10gm/dl, y usa la dosis más baja posible de Epo.

Los dos diferentes niveles de transfusión (menos de 7 g/dl y menos de 10 g/dl) son entre los rangos de niveles que son comúnmente usados en pacientes enfermos críticamente. El riesgo de transfusión para mantener la hemoglobina en niveles de 10 g/dl que es nuestra práctica actual, es que sea necesario más sangre y por lo tanto esta el riesgo de complicaciones relacionadas con la transfusión. Estas complicaciones pueden ser infecciosas (hepatitis B 1:100,000, riesgo de VIH 1:1, 000,000), reacciones inmunes incluyendo el riesgo de infecciones adquiridas en el hospital (5.2 a 6 veces es el riesgo incrementado) y líquido en los pulmones. El riesgo de transfundir para mantener la hemoglobina en concentraciones mayores al valor de 7 g/dl es que el cerebro lesionado no puede ser capaz de aumentar el flujo sanguíneo adecuadamente para compensar el contenido de oxígeno y esto podría resultar en menos oxígeno llevado hacia el cerebro. No existe información específica disponible concerniente a este riesgo. Ambas prácticas son clínicamente aceptables y tienen algo de riesgo y beneficio, pero no se conoce la mejor tasa riesgo-beneficio en este subgrupo de pacientes críticamente enfermos.

Sangre, LCR, y muestras de Microdiálisis serán recolectadas específicamente con el propósito del estudio, pero los catéteres requeridos para obtener estas muestras (catéter arterial, ventriculostomía y catéter de Microdiálisis) será colocados como parte del monitoreo estándar en dichos pacientes críticos. Entonces el incremento de riesgo para obtener estas muestras es mínimo. Las pruebas con Doppler transcerebral son realizadas usando métodos no invasivos y sin riesgos significativos.

Además de los estudios fisiológicos, la información acerca de las características demográficas, detalles acerca de la naturaleza y severidad del curso hospitalario serán recolectados. El riesgo de colectar estos datos y perder la confidencialidad del paciente es mínimo.
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El personal del estudio le estará informando de manera oportuna cualquier información nueva que pueda afectar su decisión de permanecer en el estudio.

Beneficios Potenciales
Los beneficios al participar en este estudio pueden ser: El tratamiento con Epo puede resultar en protección cerebral y así un mejor resultado neurológico. El tratamiento con Epo puede reducir la necesidad de transfusiones sanguíneas y puede aumentar la concentración de la hemoglobina. Manteniendo la hemoglobina por lo menos 10 g/dl puede incrementar el aporte de oxígeno al cerebro. Mantener la hemoglobina por lo menos a 7gm/dl reduce el número de complicaciones relacionadas con la transfusión.

Además, los beneficios para la sociedad y para futuros pacientes con lesiones cerebrales pueden ser conocimientos acerca de si Epo es protector en la lesión traumática cerebral y acerca de la concentración óptima de hemoglobina que se necesita mantener en pacientes con trauma cerebral. Sin embargo, usted pudiera no recibir beneficio al participar.

Alternativas
Las siguientes alternativas o tratamientos están disponibles si elige no participar en este estudio: usted recibirá el manejo estándar para paciente con lesión cerebral traumática.

Costos y Pagos del Paciente
No hay costos por participar. A Usted no se le pagará por tomar parte en este estudio.

Lesión relacionada a la investigación
El personal de la investigación tratará de reducir, controlar y tratar cualquier complicación que resulte de esta investigación. Si usted es lesionado por este estudio, usted recibirá los cuidados médicos que usted o su seguro tendrá que pagar como si se tratara de cualquier otro cuidado médico.

Derechos del Paciente
Su firma en este consentimiento significa que usted ha recibido la información acerca del estudio y está de acuerdo en participar.
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Se le entregará una copia de esta forma firmada. Usted no deja de tener sus derechos al firmar esta forma. Aún después de firmar usted puede cambiar de opinión. Por favor contacte el personal del estudio si decide ya no pertenecer al estudio.

El investigador o el patrocinador pueden decidir retirarlo de ser parte de este estudio en cualquier momento. Usted puede ser removido del estudio por razones relacionadas solo con usted (ejemplo, si usted se muda de ciudad, si no toma su medicamento de investigación, o si tiene una reacción seria al medicamento) o porque el estudio por completo se detuvo. El patrocinador puede detener el estudio en cualquier momento.

Puede haber riesgos y malestares desconocidos. El personal del estudio le informará en cualquier momento cualquier nueva información que afecte su salud, bienestar o decisión.

Si usted se lesionó por causas del estudio, usted recibirá cuidados médicos que usted y su compañía de seguro tendrá que pagar como si fuera otro cuido médico. A usted no se le pagará por la lesión.

Información sobre su Salud

Podríamos recolectar información de salud que pudiera tener relación con usted. Esta información de salud pudiera tener su nombre, dirección, número de seguro social o algo más que lo identifique. La ley federal quiere que nosotros pidamos permiso para usar su protegida información de salud para el estudio. Si firma en esta forma significa que nos da permiso para usar información de salud protegida en el estudio de investigación.

Si usted decide ser parte del estudio, su información sobre su salud estará protegida y no será expuesta excepto que sea permitido por la ley o como se ha descrito en esta forma. Todos los que trabajen con su información protegida trabajarán para mantener esta información privada. Los resultados de los datos de este estudio pueden ser publicados. Sin embargo, usted no podrá ser identificado con su nombre.

La gente que otorga atención médica y se asegura de calidad de las instituciones donde se realiza la investigación, los patrocinadores, representantes de los patrocinadores, agentes de la Food and Drug Administration (FDA, por sus siglas en inglés) y agencias reguladoras del Departamento de Salud y Servicios Humanos de U.S., les será permitido revisar secciones de su historial médico y de investigación relacionados con el estudio. Debido a la necesidad del investigador y del personal de dar información a estas personas, privacidad completa no se puede garantizar.
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La gente enlistada en el párrafo anterior tendrá disponible su información tanto como la necesiten, aún después de que el estudio sea completado.

Si usted decide no ser parte del estudio o si usted es retirado del estudio, usted puede decidir ya no permitir que la información protegida de su salud que lo identifique sea usada en esta investigación. Contacte el personal del estudio para decirles esta decisión, ellos le darán una dirección para que informe por escrito al investigador. El investigador respetará su decisión, a menos de que al no estar permitido usar su información afecte la seguridad y calidad del estudio de investigación.

La investigadora CLAUDIA SUE ROBERTSON y/o alguien que ella designe en su lugar podrán responder sus preguntas. Si tiene preguntas o dudas en cualquier momento, o si necesita reportar cualquier incidente relacionado con la investigación, usted puede hablar con un miembro del personal: CLAUDIA ROBERTSON, SHANKAR GOPINATH al número 713 798 4696 durante el día y fuera de horario de oficina. Miembros del comité de revisión para Baylor College of Medicine y hospitales afiliados también pueden contestar sus preguntas y dudas acerca de los derechos del paciente. El número es 713 798 6970.

En caso de lesión por el estudio, Baylor College of Medicine y/o Harris County Hospital District Ben Taub General Hospital no podrán financiar ni absorber costos del tratamiento. Sin embargo, facilidades, tratamientos de urgencia, y servicios profesionales estarán disponibles, como lo están para la población en general.

Si su hijo es uno de los pacientes que se le solicita entrar al protocolo. Cada niño puede estar de acuerdo en tomar parte del estudio por su propio nivel de entendimiento. Cuando usted firma esto, usted también tomo nota que su hijo entendió y está de acuerdo en participar en el estudio.

Por favor, escriba el nombre del niño aquí: ________________________
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Al firmar este consentimiento usted indica que ha leído la forma (o se la han leído), que sus preguntas han sido contestadas satisfactoriamente y que usted voluntariamente está de acuerdo en participar en este estudio. Usted recibirá una copia firmada de este consentimiento.

Sujeto

Fecha

Representante Legal Autorizado
Padre o Tutor

Fecha

Representante Legal Autorizado - Adulto

Fecha

Investigador o quien obtiene el consentimiento

Fecha

Testigo (si aplica)

Fecha

Traductor (si aplica)

Fecha

THE INSTITUTIONAL REVIEW BOARD FOR HUMAN SUBJECT RESEARCH FOR BAYLOR COLLEGE OF MEDICINE & AFFILIATED HOSPITALS
APPROVED FROM 12/22/2010 TO 12/21/2011
AMENDMENT DATE 01/08/2010

Harris County Hospital District
Protocol number: H-20405
Approval Date: 1-20-11
Expiration Date: 12-21-11

BCM

10
Narrative for family members contacted by phone

I am asking for your consent for your relative, [name of patient], to be in a study of a new treatment for traumatic brain injury. Your relative has suffered a brain injury from [give cause, e.g., car accident, fall, gunshot wound, etc.]. My name is [researcher’s name] and I am on the team of people who are caring for your relative at Ben Taub General Hospital.

The overall purpose of this study is to try to improve the outcome of brain injury. I will describe the study to you. I will then answer your questions. When you get here to Ben Taub we will go over the study in more detail. At that time, we will ask you to sign a written consent form. We need to get your decision now, so that we can start the study. By starting right away, we have the best chance of benefiting your relative.

The drug that we are studying, Epo, is an FDA-approved drug that is given to patients to treat a low blood count. We are trying to see if Epo may also improve recovery of brain function after a severe injury. Patients who are enrolled in this study will all receive standard treatment for their head injury. In addition to standard treatment, half of the patients will receive Epo and half will receive placebo. All of the patients will be followed for 6 months after their injury to see how well they recover. The potential benefits of participating in the study are: Epo may improve the blood count and reduce the number of blood transfusions that are needed. Epo may reduce damage to the brain. The potential risks of Epo are that it may cause or worsen high blood pressure, and that it may cause blood clots.

There will be no financial cost to your relative or to you from his/her being in the study.

If you do not consent to having your relative in the study, he/she will receive all of the usual medical and surgical care for brain trauma. If you initially consent to having your relative in the study, but later change your mind, you can withdraw your relative from the study without jeopardizing any medical care to which (s)he is entitled.

Do you have any questions?

Is it OK with you for your relative to be in the study of traumatic brain injury?
Appendix X. Pharmacy Order Sheet for Erythropoietin

RESEARCH RELATED PHYSICIAN ORDER
FOR INPATIENT INVESTIGATIONAL DRUG USE ONLY

Principal Investigator: Claudia Robertson, M.D. IRB Protocol # H-20405
Authorized Prescribers: Claudia Robertson, M.D, Shankar Gopinath, MD, Daniel Fahim, MD, Baraa Al-Hafez, MD, Vikas Rao, MD, Duemani Reddy, MD.

PRIMARY DIAGNOSIS: TRAUMATIC BRAIN INJURY DOB: ___________ NICU Bed # ______
ALLERGIES: __________________________

CONSENT FORM SIGNED: ☐Yes (check & initial) DATE SIGNED: ____________________

STUDY MEDICATION: Epoetin Alfa (EpoGen®) / placebo

Administer EpoGen® 500 units/kg or placebo IV push in the first day (Dose 1), then every week for 2 additional doses (Dose 2 & Dose 3).

☐ Dose 1: Dosing Weight: _______ (kg) EpoGen/placebo Dose: _______ (units)
☐ Dose 2 or ☐ Dose 3 Dosing Weight: _______ (kg) EpoGen/placebo Dose: _______ (units)

Dose Delivery DATE: __/___/______ Dose Delivery TIME: ___:___
Dose Administration DATE: __/___/______ Dose Administration TIME: ___:___

☐ For Dose 2 or 3, if the hemoglobin concentration is greater than 12g/dl or the rate of rise of hemoglobin is greater than 1.0g/dl over 2 weeks, hold EpoGen/placebo dose.

For questions contact Dr. Claudia Robertson at (713) 683-4894

Please FAX completed order to the Inpatient Pharmacy at (713) 873-8711, Phone: (713) 873-2979

☐ PLEASE PRINT EXTRA DRUG LABEL FOR DELIVERY TO STUDY TEAM

PATIENT ID

Physician’s Signature: ____________________________
HCHD ID#: __________________ Date/Time: ______________
Faxed: ______________ Confirmed: ______________
Researcher Pager #: ______________

Harris County Hospital District 282261 (07/03)
RX-IDS Protocol # H-20405 (03/2011)
Epogen Study H-20405
Pharmacist Double Check
(To be filled out by Pharmacist NOT entering order)

Patient Initials: _______ Dose#: _______

Stratification Factor: ________________________________
(≤3 hours from injury or > 3 hours from injury)

Randomization: ______________________________________
(Epogen or Placebo)

Transfusion Trigger: _________________________________
(7gm/dL or 10gm/dL)

Accountability Log: ____________________________
(please initial)
(Epogen or Placebo Accountability Log filled completely)

Extra Label Printed: _______ Subject#: ____________
(yes or no) (found on Randomization Log and printed on Label)

Pharmacist Signature: _____________________________ Date: ____________

Time Received Order: ______________ Time Medication Left Pharmacy: ______________

**The FIRST DOSE MUST be delivered within 60 MINUTES of RECEIPT of the order!!**

NOTE: ALL BLANKS MUST BE FILLED OUT BY HAND

IF YOU HAVE ANY QUESTIONS PLEASE DO NOT HESITATE TO PAGE IDS
Jennifer Chistensen 281-952-0123  Sara Ruppelt 281-963-0802
Appendix XI. Justification of the Emergency Consent Exception

The study meets the criteria for exemption from informed consent requirements for emergency research under 21 CFR 50.24:

1. **TBI is life-threatening disorder with no effective treatment:** Patients with severe TBI who will be eligible for this study have a life-threatening condition with no satisfactory alternative treatment, and the proposed randomized trial is necessary to determine the effectiveness of the treatment with erythropoietin and also to determine the optimal transfusion trigger for this patient group.

   **Details:**
   1.a. The mortality rate for patients who are admitted to the hospital in coma due to a traumatic brain injury ranges from 25-35%. In a previous clinical trial performed at Ben Taub General Hospital, with similar entry criteria to the currently on-going Epo study, 46/189 (24%) of patients enrolled in the study died (1).
   
   1.b. The most recent version of the head injury guidelines published by the Brain Trauma Foundation (2) reviews the current literature and reports no specific treatment that has improved neurological outcome from severe traumatic brain injury. The current recommended treatment is simply good critical care management with control of intracranial hypertension and prevention of secondary injury to the brain.
   
   1.c. There is abundant experimental data demonstrating neuroprotection with erythropoietin in models of CNS injury, including models of TBI (see review in Appendix 1). Erythropoietin is FDA approved for the treatment of chronic anemia. While erythropoietin is sometimes used in the critical care setting to treat anemia associated with critical illness, its routine use is not currently recommended in this setting. Erythropoietin has been shown to reduce the need for blood transfusions, but this has not been shown to improve outcome in the critically ill patient. A well-designed randomized clinical trial is needed to determine effects of erythropoietin on neurological outcome and on anemia and blood transfusion requirements in patients with severe TBI.
   
   1.d. There is clinical equipoise for studying the optimal transfusion trigger in patients with traumatic brain injury (see review in Appendix 1). A transfusion trigger of 10gm/dl provides the optimal oxygen carrying capacity and optimal blood viscosity for cerebral blood flow and therefore provides the best oxygen delivery to the brain, but requires greater number of blood transfusions and therefore a greater risk of transfusion-related complications. A transfusion trigger of 7gm/dl, which reduces the risk of transfusion-related complications, is well-tolerated in most critically ill patients, but has not been systematically studied in brain-injured patients. The potential risk of anemia in a patient with traumatic brain injury is exacerbation of brain ischemia and of intracranial hypertension. Both transfusion triggers are commonly practiced in TBI patients, but no data clearly indicates which is best practice. A well-designed randomized clinical trial is needed to determine the optimal hemoglobin concentration for patients with severe TBI (3,4,5,6).

2. **Obtaining written informed consent is not feasible:** Obtaining informed consent for this study is not feasible because the patients eligible for the study will not be able to give informed consent, the treatment with erythropoietin must be given within 6 hr of injury in order to be effective and surrogates for informed consent are not likely to be available at the hospital within this time frame for a large percentage of the eligible patients, and there is no way to identify prospectively the patients that will be eligible for the study.

   **Details:**
   2.a. Patients who are eligible for this study are in coma and will not be able to give informed consent.
   
   2.b. In experimental models of TBI, treatment with erythropoietin more than 6 hours after injury has no significant neuroprotective effects (see section 4 below).
2.c. The percentage of patients with relatives available to give informed consent increases with time after injury. Few patients with traumatic injury have relatives immediately available at the time of arrival at the hospital.

In a past TBI study where we prospectively tracked the availability of relatives for consent, we found that the percentage of patients with relatives increased from 3% at 1 hr to 25% at 3 hr, 43% at 6 hr, and 58% at 12 hr after injury (solid line in graph below). Some time after the family arrives is required to explain the patient’s condition and then to discuss the research protocol and for the family to make a decision about participating (dotted line in graph below). In addition, time is required after the consent is signed for the pharmacy to make up the drug that is to be given.

This data from a past TBI study is very similar to the experience in our ongoing study which is presented in section 5. Of the 59 patients who were potentially eligible for the study during the first 10 months of enrollment, families were available for 10% at 1 hr post-injury, 22% at 3 hr post-injury, and for 42% at 6 hr post-injury.

As will be shown with our experience in the current trial of Epo (see section 6), these time constraints make it very difficult to enroll patients early enough that they will receive a study drug within 6 hr of injury. It is nearly impossible to administer a study drug using prospective written consent within 3 hr of injury when neuroprotective agents like Epo would be expected to have the most benefit.

2.d. Anyone in the city of Houston can be a victim of trauma, and therefore it is not possible to identify patients that might be eligible for the study prospectively.

3. **Epo study has potential direct benefit to patients**: Participation in the study has potential direct benefit for the patients. All patients enrolled in the trial will receive standard management of their head injury. Experimental studies in models of traumatic brain injury have shown significant improvements in outcome with erythropoietin treatment (see review in Appendix 1).

4. **Epo study has reasonable risk relative to medical condition of patients**: The risk/benefit ratio of the study is favorable, especially considering the high mortality/morbidity of severe TBI.

The risk of erythropoietin (with the target hemoglobin levels planned in this study) for trauma patients who are critically ill has been quite low, consisting primarily of an increased risk of thrombophlebitis. Anemia is very common in this patient population, and most patients receive blood products as a part of their acute care treatment. In our center 60% of severe TBI patients require transfusion of at least one unit of packed RBCs during their acute hospitalization. Two large multi-center studies have been completed, showing higher hemoglobin concentrations, reduced need for transfusions, and in the most recent trial (EPO-3, reported at the SCCM meeting in February 2007) a 50% reduction in mortality rate
with Epo administration (7,8). In our trial, we may see these benefits, plus the possibility of an improved neurological recovery.

The potential adverse effects with administration of Epo have recently been emphasized in an FDA bulletin. These adverse effects have included hypertension, increased mortality and cardiovascular adverse events, and tumor progression in patients with cancer. These increased risks have primarily occurred in studies where a hemoglobin concentration greater than 12g/dl has been targeted, and in patients with chronic renal failure or cancer, respectively. In addition, an increased incidence of thrombophlebitis was observed post-op in orthopedic patients. To minimize these risks, our study excludes patients with uncontrolled hypertension, with significant preexisting cardiovascular disease, chronic renal disease, and with active cancer. In addition, the maximum hemoglobin concentration targeted in the study is 10g/dl, and the study uses the recommended practice of holding the weekly doses of study drug if the hemoglobin concentration is greater than 12g/dl or has increased more than 1g/dl over 2 weeks.

Patients with severe TBI have a high risk for developing thrombophlebitis, but they also have a contraindication to heparin for prophylaxis because of the potential for intracranial hemorrhage after brain trauma. To minimize the risk of thrombophlebitis, venous compression devices are therefore used as DVT prophylaxis during the first few days post-injury, and then heparin is added whenever the risk of intracranial hemorrhage resolves.

In summary, the potential benefits of the study may include maintenance of a higher hemoglobin concentration with a reduced blood transfusion requirement, and improved neurological outcome. The major potential risks for this patient population include hypertension, and an increased risk of thrombophlebitis. These risks will be minimized by excluding patients who are at greatest risk for these complications, by close monitoring of hemoglobin concentration and holding the weekly doses of Epo if hemoglobin concentration increases too much, and by use of DVT prophylaxis as part of our standard management.

5. **Time window for Epo neuroprotection**: The therapeutic window for neuroprotection with erythropoietin has been studied in experimental models. Like most neuroprotective agents, the effectiveness of Epo is best when given very early after injury (2-3 hours after injury), but still has some significant neuroprotective effects as late as 6 hours after injury. By 9 hours post-injury, there is no significant effect with Epo administration. A summary of the available information is given in the table below.

<table>
<thead>
<tr>
<th>Species</th>
<th>Injury Model</th>
<th>Time Points</th>
<th>Time Window Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In Vivo Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouse</td>
<td>Controlled cortical impact injury</td>
<td>pre-injury, 0, 3, 6hr post-injury</td>
<td>data not shown but text states “the animals receiving r-Hu-EPO at 0, 3, or 6 h in relationship to trauma revealed a similar protection as pretreatment with r-Hu-EPO”</td>
<td>(9,10)</td>
</tr>
<tr>
<td>Mouse</td>
<td>mca infarct pre-ischemia, 0, 3, 6, 9 hrs post-ischemia</td>
<td></td>
<td>The infarct volume was significantly reduced when Epo was given pre-ischemia, and at 0, 3, and 6 hrs after ischemia. The reduction in infarct volume was less at 6 hrs compared to 3 hrs.</td>
<td>(9)</td>
</tr>
<tr>
<td>Rat</td>
<td>Controlled cortical impact injury</td>
<td>5min, 1, 3, 6, 9, 12 hr post-injury</td>
<td>Contusion volume and neuron loss in hippocampus reduced when given 5min, 1, 3, and 6 hrs post-injury. Contusion volume less when given at 3 hr compared to 6 hr</td>
<td>(11)</td>
</tr>
<tr>
<td><strong>In vitro Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cultured hippocampal</td>
<td>Anoxia</td>
<td>2, 4, 6, and 12 hr</td>
<td>Best preservation of neurons occurred with Epo at 2 hr post-anoxia, and</td>
<td>(12)</td>
</tr>
</tbody>
</table>
neurons post-anoxia protective effect was reduced with Epo at 6hr post-anoxia and absent with Epo at 12 hr post-anoxia

| Endothelial cells and hippocampal neurons in culture | NO exposure | 2, 4, 6, and 12 hr post-NO exposure | Best preservation of endothelial cells and neurons occurred following administration of Epo at 2 hr, no effect with administration at 12 hr, and an intermediate effect with administration of Epo at 4 and 6hrs | (13) and (14) |

| Neuron cultures | Glutamate toxicity, kainite | pre-treatment is necessary, post-treatment is not effective | (15) and (9) |

| hippocampal slices | Trauma | administration of Epo at times up to 30 minutes after the traumatic injury improved outcome. At 60 minutes after the traumatic injury, no effect on outcome was seen | (16) |

In addition to these acute neuroprotective effects, there are a few studies that suggest that other beneficial effects of Epo (including neurogenesis and angiogenesis) may occur and improve neurobehavioral outcome after stroke and trauma even when given 24 hr after the neurological injury (17,18).

6. **Epo study is impracticable without exception**: The proposed study is impracticable without waived consent for two reasons. First, we may not be able to enroll a sufficient number of patients to complete the study in a reasonable amount of time using prospective written consent, and secondly we are not able to enroll any patients within the time frame that is probably needed to have optimal neuroprotection with erythropoietin using prospective written consent. The enrollment in our ongoing trial is detailed in the tables below.

**Details:**

6a. We began enrolling patients in the study in May 2006, using prospective written consent from family members of patients. We need to enroll 4-5 patients per month in order to complete the study within the approved 5 year funding period. A summary of enrollment from May 2006 through April 2007 is shown in the table below.
A total of 69 patients who were eligible for the study were admitted to the hospital during the first 12 months of the study. Of these 69 patients, only 29 (42%) had a relative available to give informed consent within the time window of the study. Twenty-three (33%) of the 69 patients were able to be enrolled in the study, and 6 (9%) of the families either decided not to participate in the study. We have been able to enroll less than half of the number of patients that we need to complete the study.

6b. In addition to the 23 patients that were enrolled in the study within the first 12 months of the study, there was one patient where family arrived near the end of the 6hr time window, but they were unable to make a decision in time to enroll him. There were another 42 patients who were otherwise eligible for the study but relatives were not available within the 6 hour time window. In 13 of these 42 cases, we were able to contact a family member by phone but they were unable to get into the hospital to sign the written consent form within the 6 hour time window. In 5 cases, we had early contact with a friend or distant relative, but no close relative that could give consent for research was contacted within the 6 hour time window. In the remaining 24 cases, we had no contact with any family members within the 6 hour time window. The table below details this information.

<table>
<thead>
<tr>
<th>Time After Injury (hours)</th>
<th>Arrive at BTGH</th>
<th>Arrive of Relative</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>8451</td>
<td>.37</td>
<td>&gt;12hr</td>
<td>no identifying information for patient</td>
</tr>
<tr>
<td>8475</td>
<td>1.68</td>
<td>8.0</td>
<td>family was contacted and agreed to study but could not get to hospital until 8hr</td>
</tr>
<tr>
<td>8516</td>
<td>3.05</td>
<td>7.0</td>
<td>contacted wife by phone within 6hr, but she could not get to the hospital until later</td>
</tr>
<tr>
<td>8539</td>
<td>3.68</td>
<td>&gt;12hr</td>
<td>uncle arrived within 2hr of injury, but no other relatives present in the country</td>
</tr>
<tr>
<td>8561</td>
<td>.75</td>
<td>&gt;12hr</td>
<td>family all in PA, contacted by phone but no one</td>
</tr>
<tr>
<td>ID</td>
<td>Time</td>
<td>Cause</td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>-------</td>
<td>----------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>8599</td>
<td>.72</td>
<td>&gt;12hr no identifying information for patient</td>
<td></td>
</tr>
<tr>
<td>8722</td>
<td>.38</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>8723</td>
<td>.28</td>
<td>5.33 family arrived, but could not make decision by 6hr post-injury, they finally decided to participate but it was too late to enroll him</td>
<td></td>
</tr>
<tr>
<td>8738</td>
<td>.65</td>
<td>.65 daughter was at the hospital very briefly, but left and did not return to the hospital until after 6 hr, could be reached by cell phone.</td>
<td></td>
</tr>
<tr>
<td>8772</td>
<td>1.0</td>
<td>8.0 wife contacted by phone within 6 hr but could not get to hospital in time</td>
<td></td>
</tr>
<tr>
<td>8775</td>
<td>.77</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>8787</td>
<td>.95</td>
<td>&gt;12hr no identifying information for patient</td>
<td></td>
</tr>
<tr>
<td>8799</td>
<td>.5</td>
<td>&gt;12hr called phone number, but no answer</td>
<td></td>
</tr>
<tr>
<td>8851</td>
<td>.9</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>8874</td>
<td>.70</td>
<td>6.33 called phone number, but no one answered</td>
<td></td>
</tr>
<tr>
<td>8888</td>
<td>.73</td>
<td>&gt;12</td>
<td></td>
</tr>
<tr>
<td>8938</td>
<td>.08</td>
<td>6.5 family contacted, but unable to get to hospital until 6.5 hr post-injury</td>
<td></td>
</tr>
<tr>
<td>8952</td>
<td>1.43</td>
<td>&gt;12 contacted mother in Austin, unable to get to hospital until next day</td>
<td></td>
</tr>
<tr>
<td>8959</td>
<td>.83</td>
<td>&gt;12 no identifying information for patient</td>
<td></td>
</tr>
<tr>
<td>8961</td>
<td>.80</td>
<td>5.95 mother contacted, but did not arrive in time to enroll</td>
<td></td>
</tr>
<tr>
<td>8983</td>
<td>.83</td>
<td>&gt;12 family contacted, but did not arrive in time</td>
<td></td>
</tr>
<tr>
<td>9003</td>
<td>.62</td>
<td>&gt;12 family out of town, contacted, but could not arrive until next day</td>
<td></td>
</tr>
<tr>
<td>9023</td>
<td>.58</td>
<td>&gt;12 no identifying information for patient</td>
<td></td>
</tr>
<tr>
<td>9077</td>
<td>.50</td>
<td>7.08 family contacted, but did not arrive until 7hr</td>
<td></td>
</tr>
<tr>
<td>9088</td>
<td>3.95</td>
<td>11.5 wife not located until 11.5 hr</td>
<td></td>
</tr>
<tr>
<td>9119</td>
<td>.75</td>
<td>&gt;12 sister-in-law was the closest relative in US</td>
<td></td>
</tr>
<tr>
<td>9132</td>
<td>.50</td>
<td>&gt;12 unknown</td>
<td></td>
</tr>
<tr>
<td>9195</td>
<td>.97</td>
<td>6.25 police located family, but they did not arrive until after 6 hr</td>
<td></td>
</tr>
<tr>
<td>9199</td>
<td>.67</td>
<td>&gt;12 no identifying information about patient</td>
<td></td>
</tr>
<tr>
<td>9206</td>
<td>.57</td>
<td>&gt;12 no identifying information about patient</td>
<td></td>
</tr>
<tr>
<td>9211</td>
<td>.37</td>
<td>&gt;12 phone number called, but no answer</td>
<td></td>
</tr>
<tr>
<td>9217</td>
<td>.85</td>
<td>&gt;12 no identifying information about patient</td>
<td></td>
</tr>
<tr>
<td>9237</td>
<td>.42</td>
<td>&gt;12 friends found, but no family in US</td>
<td></td>
</tr>
<tr>
<td>9245</td>
<td>.42</td>
<td>&gt;12 called phone number, but no answer</td>
<td></td>
</tr>
<tr>
<td>9263</td>
<td>.55</td>
<td>21 family in Mexico, contacted but could not get here until next day</td>
<td></td>
</tr>
<tr>
<td>9296</td>
<td>.5</td>
<td>&gt;12 unknown, the only person who knew about his family was killed in the same accident</td>
<td></td>
</tr>
<tr>
<td>9344</td>
<td>.63</td>
<td>&gt;12 no direct family in US, all living in Honduras</td>
<td></td>
</tr>
<tr>
<td>9355</td>
<td>.50</td>
<td>&gt;12 No direct family in the USA. Family members currently living in Guatemala per pt's friend</td>
<td></td>
</tr>
<tr>
<td>9417</td>
<td>.53</td>
<td>&gt;12 patient had cell phone with a name and phone number on the screen, but the phone was locked. Internet search indicated the phone number was from NY, name search produced multiple matches, social worker also contacted to assist</td>
<td></td>
</tr>
<tr>
<td>9434</td>
<td>.72</td>
<td>&gt;12 patient's name was known, but unable to locate any relatives</td>
<td></td>
</tr>
</tbody>
</table>
Mean 1.09

6c. With neuroprotective agents, usually the earlier that a drug can be given the greater the benefit. In experimental models of CNS injury (see section 5 above), the best outcome with Epo occurs when the dose is given within 2-3 hours after injury. There is still a significant reduction in injury when the dose is given at 6 hours after injury, but the neuroprotective effect is less than when the dose is given at 3 hours after injury. Beyond 6 hours post-injury, there is no significant neuroprotective effect with Epo administration.

The time of the first dose of the Epo study drug in the 23 patients who have been enrolled in the study so far is shown below. Although most of the patients arrived at the hospital less than 1 hour post-injury, the average time for obtaining written informed consent was 4.23 hours after injury, and the first dose of the drug was given at 5.58 hours after injury. Only 2 patients were enrolled in the study within 3 hours of injury, and none of the patients received the first dose of the study drug within 3 hours of injury.

<table>
<thead>
<tr>
<th>Time After Injury (hours)</th>
<th>Arrival at BTGH</th>
<th>Arrival of Relative</th>
<th>Enrollment</th>
<th>First Dose (where dose was given)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8461-Epo 1</td>
<td>.55</td>
<td>1.72</td>
<td>3.72</td>
<td>6.0 (ICU)</td>
</tr>
<tr>
<td>8532-Epo 2</td>
<td>.57</td>
<td>1.17</td>
<td>3.25</td>
<td>5.0 (OR)</td>
</tr>
<tr>
<td>8544-Epo 3</td>
<td>.52</td>
<td>0.58</td>
<td>3.58</td>
<td>7.0 (ICU)</td>
</tr>
<tr>
<td>8562-Epo 4</td>
<td>.60</td>
<td>3.83</td>
<td>4.23</td>
<td>5.8 (ICU)</td>
</tr>
<tr>
<td>8600-Epo 5</td>
<td>1.75</td>
<td>1.75</td>
<td>3.32</td>
<td>5.3 (OR)</td>
</tr>
<tr>
<td>8626-Epo 6</td>
<td>.58</td>
<td>4.12</td>
<td>4.62</td>
<td>6.0 (OR)</td>
</tr>
<tr>
<td>8644-Epo 7</td>
<td>.67</td>
<td>2.67</td>
<td>2.80</td>
<td>4.3 (ICU)</td>
</tr>
<tr>
<td>8659-Epo 8</td>
<td>.63</td>
<td>5.00</td>
<td>5.55</td>
<td>6.0 (ICU)</td>
</tr>
<tr>
<td>8694-Epo 9</td>
<td>.63</td>
<td>0.63</td>
<td>3.15</td>
<td>4.8 (ICU)</td>
</tr>
<tr>
<td>8807-Epo 10</td>
<td>.60</td>
<td>4.50</td>
<td>5.33</td>
<td>6.0 (ICU)</td>
</tr>
<tr>
<td>8820-Epo 11</td>
<td>.32</td>
<td>3.75</td>
<td>4.58</td>
<td>5.8 (ICU)</td>
</tr>
<tr>
<td>8897 Epo 12</td>
<td>1.30</td>
<td>1.30</td>
<td>3.92</td>
<td>6.00 (ICU)</td>
</tr>
<tr>
<td>8982 Epo 13</td>
<td>.63</td>
<td>3.45</td>
<td>4.78</td>
<td>5.87 (ICU)</td>
</tr>
<tr>
<td>9040 Epo 14</td>
<td>.58</td>
<td>3.53</td>
<td>5.28</td>
<td>6.00 (ICU)</td>
</tr>
<tr>
<td>9044 Epo 15</td>
<td>.67</td>
<td>.92</td>
<td>5.12</td>
<td>5.92 (ICU)</td>
</tr>
<tr>
<td>9057 Epo 16</td>
<td>.60</td>
<td>3.87</td>
<td>4.28</td>
<td>5.37 (ICU)</td>
</tr>
<tr>
<td>9065 Epo 17</td>
<td>.23</td>
<td>.50</td>
<td>2.83</td>
<td>3.50 (ICU)</td>
</tr>
<tr>
<td>9072 Epo 18</td>
<td>.65</td>
<td>3.37</td>
<td>3.70</td>
<td>4.83 (ICU)</td>
</tr>
<tr>
<td>9097 Epo 19</td>
<td>.38</td>
<td>.62</td>
<td>3.62</td>
<td>5.37 (ICU)</td>
</tr>
<tr>
<td>9169 Epo 20</td>
<td>.62</td>
<td>3.00</td>
<td>4.00</td>
<td>5.75 (OR)</td>
</tr>
<tr>
<td>9283 Epo 21</td>
<td>.57</td>
<td>3.48</td>
<td>5.00</td>
<td>5.97 (ICU)</td>
</tr>
<tr>
<td>9300 Epo 22</td>
<td>.45</td>
<td>3.00</td>
<td>5.17</td>
<td>6.33 (ICU)</td>
</tr>
<tr>
<td>9460-Epo 23</td>
<td>.53</td>
<td>2.70</td>
<td>5.37</td>
<td>5.87 (ICU)</td>
</tr>
</tbody>
</table>

Mean .64±.31 2.58±1.40 4.23±.87 5.58±.73

It is possible that we can shorten the time between enrollment and administration of the drug somewhat, but it is unlikely that we will be able to alter either the time to arrival of the relative or the time required to obtain informed consent. As a result, we will be unable to get early
drug administration at a time when the drug is most effective in experimental studies while prospective written informed consent is required.

6d. We are adding an additional study site in June 2007 and may be able to enroll a sufficient number of patients to complete the study. However, the other site that we are adding will not be able to do the detailed physiological studies that are unique to our center. We will only be able to look at the effects of Epo on long-term neurological outcome in these additional patients. Most importantly, addition of other sites will not alter the time that is required to enroll patients using prospective informed consent, and it is likely that almost all patients will continue to receive the study drug near the end of the 6 hour therapeutic window.

7. **DSMB committee:** We have an independent DSMB committee, appointed by NIH, to monitor the study. The DSMB had two conference calls prior to approving the start of the study, and the first meeting occurred in Houston on November 30, 2006. In this meeting, after reviewing the results so far, they recommended that we pursue the emergency consent exception so that the administration of the study drug can be earlier. The next meeting is scheduled for June 11, 2007. The members are listed at the start of the protocol.

**Proposed plan for obtaining consent**

We will try to contact relatives for the first 3 hours after injury. We will work with the social worker in the Ben Taub EC to find any identifying information available with the patient, and to call all phone numbers identified as possible relatives at least once, leaving messages when possible. If family arrives at the hospital within 3 hours after injury, then we will enroll the patient only if they give permission and sign the informed consent.

If we are able to contact relatives by phone within the first 3 hours, but they are not able to get to the hospital quickly then we will describe the study to the relative by phone following the narrative that is attached. If they are agreeable, we will enroll the patient in the study. When the family arrives at the hospital, we will discuss the study with them again and have them sign the consent form to continue participation in the study.

If no family is located within the first 3 hours then we will enroll the patient using the emergency exception. When family is subsequently found, we will inform them about the study and allow them the opportunity to continue to participate. If they agree, we will have them sign the consent form to continue participation in the study.

It is possible that a patient might be enrolled in the study using the emergency exception from informed consent, and then die prior to locating the family. If this should happen and any relatives are subsequently identified, they will be informed about the patient's participation in the study.

We will summarize these events for the IRB at the time of each annual review.

**Results of Community Consultations**

We have consulted with approximately 300 people in the Houston area in 13 separate activities regarding this study. We have targeted the areas of Houston that are the highest patient areas for Ben Taub General Hospital, and included groups that were predominantly African American and/or Hispanic, which are the two major minority groups cared for at the hospital. A complete documentation of these consultation activities is included in Appendix 1. Briefly, the results are summarized below.

The following is the information that was provided at the meetings about the study:

*The Neurosurgery Department at Baylor College of Medicine and Ben Taub General Hospital is conducting a clinical trial of a drug called Erythropoietin (or Epo) in patients who have suffered a severe brain injury from trauma. We would like to tell you about this study, and ask your opinion about it.*
The drug that we are studying, Epo, is an FDA-approved drug that is given to patients to treat a low blood count. We are trying to see if Epo may also improve recovery of brain function after a severe injury. Patients who are enrolled in this study will all receive standard treatment for their head injury. In addition to standard treatment, half of the patients will receive Epo and half will receive placebo. All of the patients will be followed for 6 months after their injury to see how well they recover. The potential benefits of participating in the study are: Epo may improve the blood count and reduce the number of blood transfusions that are needed. Epo may reduce damage to the brain. The potential risks of Epo are that it may cause or worsen high blood pressure, and that it may cause blood clots.

Normally for a research study like this, we would ask the patient or the patient’s family if they would like to participate in the study and have them sign a consent form explaining all of potential benefits and risks of the study and explaining their rights as a research subject. However, for this study the drug must be given very soon after the brain injury to help. The patients will not be able to give consent because of their brain injury. Many patients do have not family members available at the hospital rapidly enough to give the usual informed consent for the study. When this is the case, federal law allows investigators to apply for an exception to the usual informed consent. In the place of initial written informed consent, the investigators must notify the community that the study will be taking place without consent, and ask the community for feedback about whether they think that the study should take place without the usual informed consent for all patients.

We will try to find relatives of patients for up to 3 hours after injury. If we find a relative, we will only enroll the patient if the relative agrees and signs a consent form. If no relatives are found within 3 hours after injury, we will enroll the patient in the study. Then when relatives are located or if the patient recovers, we will tell them about the study and let them decide if they wish to continue to participate or withdraw from the study. As with any research study, patients can withdraw from the study any time that they wish.

After any questions and/or discussion that ensued, we then asked for the participants to fill out a survey with 6 questions about the study. The results are summarized below.

**Question 1 Results: Do you understand the study?**

- Strongly agree = 124 (42%)
- Agree = 161 (55%)
- Disagree = 5 (2%)
- Strongly disagree = 1 (0.3%)
- No answer = 3 (1%)
- “unsure” = 1 (0.3%)

Total agree = 285 (97%)

**Question 2 Results: Do you understand that most of the patients will be enrolled in the study initially without their consent?**

- Strongly agree = 108 (37%)
- Agree = 166 (56%)
- Disagree = 13 (4%)
- Strongly disagree = 4 (1%)
- No answer = 2 (0.7%)
- “unsure” = 2 (0.7%)

Total agree = 274 (93%)

**Question 3 Results: Do you understand that patients will be randomly assigned to receive erythropoietin or placebo?**

- Strongly agree = 109 (37%)
- Agree = 162 (55%)
- Disagree = 16 (5%)
- Strongly disagree = 6 (2%)
- No answer = 2 (0.7%)

Total agree = 271 (92%)
**Question 4 Results:** Do you understand that all patients will receive standard care for head injury, regardless of whether or not they receive erythropoietin?

- Strongly agree = 149 (51%)
- Agree = 131 (44%)
- Disagree = 10 (3%)
- Strongly disagree = 2 (0.7%)
- No answer = 3 (1%)
- Total agree = 280 (95%)

**Question 5 Results:** Are you willing for this study to be done in your community?

- Strongly agree = 129 (44%)
- Agree = 147 (50%)
- Disagree = 5 (2%)
- Strongly disagree = 8 (3%)
- “not sure” = 2 (0.7%)
- “n/a” = 2 (0.7%)
- No answer = 1 (0.3%)
- “you need to widely publicize the study” = 1 (0.3%)

**Question 6 Results:** Would you be willing to participate in the study if you were to have a head injury?

- Strongly agree = 138 (47%)
- Agree = 126 (43%)
- Disagree = 15 (5%)
- Strongly disagree = 11 (4%)
- No answer = 3 (1%)
- “unsure” = 2 (0.7%)
- Total agree = 264 (89%)

**Public Disclosure of Plans to Use Emergency Consent Exception**

As a part of doing the community consultation activities, we have done some work that has begun to notify the public of these plans. We have set up a website for the study that is linked to the Baylor Neurosurgery department site. Working with Baylor and HCHD public relations we have put out a press release about the study. Details of these notifications are described in Appendix 1. When the emergency consent exception is approved, we will then provide more extensive notification of the public through additional press releases, advertisements, and public service announcements.

**Plan to publicly disclose the results of the study at completion.**

We will work with Baylor College of Medicine and Harris County Hospital District public relations to put together a press release with the major findings of the study. We will also summarize the findings of the study on our study website which is linked to the Baylor Neurosurgery department site.

**Reporting details of obtaining informed consent**

In our yearly renewal, we will provide the IRB with a summary of the number of patients enrolled by the exception, and a summary of how informed consent was subsequently obtained.

**References for Appendix XI**


