**APPENDIX A: PROTOCOL**

**Title:** Hyperbaric Oxygen Brain Injury Treatment (HOBIT) Trial: A Multicenter, Randomized, Prospective Phase II Adaptive Clinical Trial Evaluating the Most Effective *Hyperoxia* Treatment Paradigm for Severe Traumatic Brain Injury

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**Supported by:** The Neurological Treatment Trial Network and National Institute of Neurological Disorders and Stroke.

**Study Intervention Provided by:** N/A

**Sponsor of IND/IDE:** Gaylan L. Rockswold, M.D., Ph.D.
*Study May Proceed Notification - August 2015 (See Appendix B)*

## 1.0 TABLE of ABBREVIATIONS

| | |
|---|---|
| AC: | analytic center |
| AE: | adverse event |
| AIS: | abbreviated injury scale |
| ATA: | atmospheres absolute |
| ATP: | adenosine triphosphate |
| AUC: | area under the curve |
| CCC: | clinical coordinating center |
| CPC: | clinical project coordinator |
| CPP: | cerebral perfusion pressure |
| CRA: | clinical research associates |
| CRF: | case report form |
| CSF: | cerebrospinal fluid |
| CT: | computerized tomography |
| DCR: | data clarification request |
| *DCU:* | *data coordination unit* |
| DM: | data manager |
| DRS: | disability rating scale |
| DSMB: | data and safety management board |
| EC: | executive committee |
| ESC: | external steering committee |
| EtCO2: | end tidal carbon dioxide |
| FiO2: | fraction of inspired oxygen |
| FACTS: | fixed and adaptive clinical trial simulator |
| FM: | financial manager |
| GCP: | good clinical practice |
| GCS: | Glasgow coma scale |
| GOS: | Glasgow outcome scale |
| GOS-E: | Glasgow outcome scale - extended |
| HBO2: | hyperbaric oxygen |
| HCMC: | Hennepin County Medical Center |

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|---|---|
| HOBIT: | hyperbaric oxygen brain injury treatment |
| ICP: | intracranial pressure |
| ICU: | intensive care unit |
| IMM: | internal medical monitor |
| IRB: | institutional review board |
| ITT: | intent to treat |
| IV: | intravenous |
| ISS: | injury severity score |
| LAR: | legally authorized representative |
| MAP: | mean arterial pressure |
| MSM: | medical safety monitor |
| NBH: | normobaric hyperoxia |
| NETT: | Neurological Emergency Treatment Trials |
| NFPA: | National Fire Protection Association |
| NINDS: | National Institutes of Neurological Disorders and Stroke |
| O2: | oxygen |
| OHRP: | Office of Human Research Protection |
| PaO2: | partial pressure of arterial oxygen |
| PEEP: | positive end expiration pressure |
| PI: | principal investigator |
| PM: | project manager |
| PO2: | partial pressure of oxygen |
| ProTECT: | Progesterone for the Treatment of Traumatic Brain Injury |
| RAR: | response-adaptive randomization |
| SAE: | serious adverse event |
| *SC:* | *site coordinator* |
| SCC: | scientific coordinating center |
| SDMC: | statistical and data management center |
| SID: | study identification number |
| SOP: | standard operating procedure |
| TBI: | traumatic brain injury |
| TIL: | therapeutic intensity level |
| TSM: | tivoli storage manager |
| UHMS: | Undersea and Hyperbaric Medical Society |

**Table of Contents**

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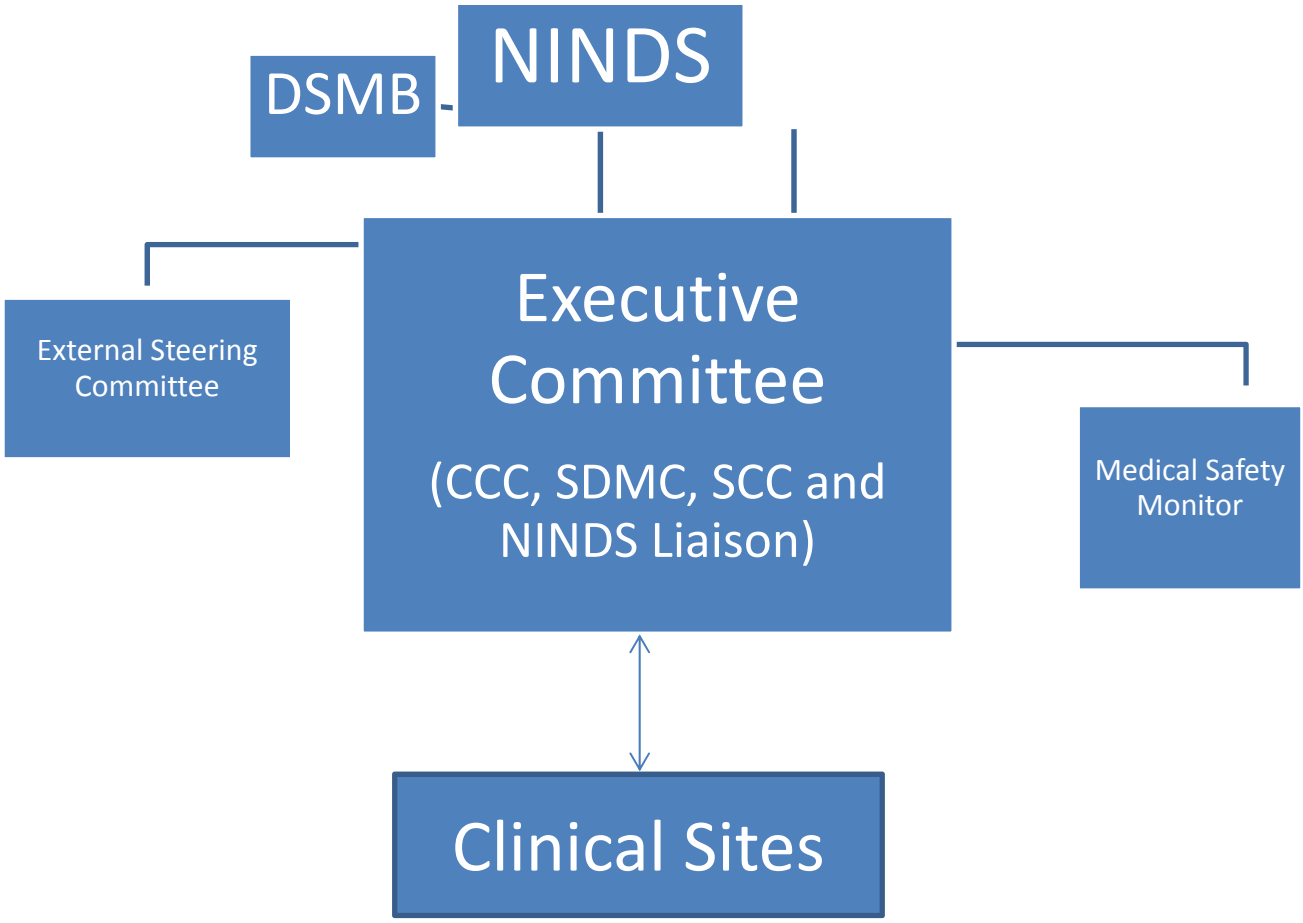
## 4.0 TRIAL ADMINISTRATIVE ORGANIZATION




**Trial Administrative Organization**

***Overall.*** The HOBIT trial will be conducted in the Neurological Emergency Treatment Trial (NETT) Network funded by the National Institutes of Neurological Disorders and Stroke (NINDS). The Clinical Coordinating Center (CCC) for the HOBIT trial will be the NETT CCC at the University of Michigan and the Statistical and Data Management Center (SDMC) will be the NETT SDMC at the Medical University of South Carolina working with the Analytical Center (AC) at the University of Kansas for the adaptive design component. The Scientific Coordinating Center (SCC) will be at the University of Minnesota/Hennepin County Medical Center (HCMC).

***Clinical Coordinating Center*.** The CCC is responsible for coordinating the Network and HOBIT enrolling site leadership and for overall organization, administration, and communication. These responsibilities include site management (regulatory management, enrollment performance, data monitoring, etc.), trial management (coordination of trial recruitment, publications, clinical translation), and management of study operations (protection of human subjects, outcomes assessment, training and education, etc.). The CCC personnel include William Barsan, principal investigator (PI) of the CCC; physician investigators, administrative leadership, project managers, site monitors, and coordinators for human subjects protection and for education.

***Statistical and Data Management Center***. The main responsibilities of the SDMC are to provide database, data management, and statistical support for the HOBIT trial. The SDMC will also be responsible for data processing and management of data obtained at all study sites and generation and distribution of progress reports as well as reports to the Data and Safety Management Board (DSMB).

***Analytic Center.*** The personnel of the AC are Byron Gajewski, who is the PI of the AC, as well as Scott Berry and a statistical technician (to be named). The AC is responsible for the Bayesian adaptive portion of the project. Dr. Gajewski will write and conduct the computer code of the adaptive design procedure and perform final statistical analysis. He will be responsible for providing initial adaptive design study interpretations and reviewing and verifying all conclusions drawn from these analyses.

***Scientific Coordinating Center.*** The SCC consists of the contact PI, the clinical project coordinator (CPC), the internal medical monitor (IMM), and the HOBIT trial financial manager (FM). The PI provides overall leadership to the entire HOBIT trial to ensure a successful implementation. He is specifically responsible for monitoring the conduct and progress of the clinical investigations as well as reviewing and evaluating the information relevant to the safety of hyperbaric oxygen (HBO2) administration. The CPC assists the PI in day-to-day implementation in various trial activities. The IMM will be responsible for reviewing and coding adverse events (AE) prior to being forwarded to the medical safety monitor (MSM). The IMM will also assist the PI, the CPC, CCC and SDMC in monitoring protocol compliance. The FM, together with the PI, is responsible for the budgetary management of the grant which funds the CCC, the SDMC, the AC, and all United States and Canadian clinical sites.

***Multiple Principle Investigators*.** Dr. Rockswold is a neurosurgeon and will serve as the contact PI. He will supervise the overall conduct of the study, experimental design, data analysis and manuscript preparation. He has extensive experience in investigating HBO2 in the treatment of severe TBI and also in the management of TBI itself. Dr. Barsan is an emergency medicine physician and the PI for the NETT CCC and will be the PI responsible for the clinical coordination of the trial at the NETT CCC. Dr. Gajewski is a biostatistician. He will be the PI responsible for the Bayesian adaptive portion of the project and will conduct the adaptive design modeling and the creation of the randomization probabilities that will be provided to the SDMC. Dr. Martin is the PI for the SDMC at the Medical University of South Carolina. She will provide statistical support as well as management and monitoring of data obtained at all study sites. This arrangement allows for a balanced split of the overall research project management, the site management, and the statistical analysis.

***Executive Committee (EC).*** The EC consists of the leadership of the SCC, the CCC, the SDMC and the AC and an NINDS-appointed liaison. The EC is a working group responsible for the development and amendment of the study documents (e.g., protocol, case report forms and manual of procedures), collection, review, and oversight of dissemination of severe adverse events (SAE) (occurrences and other important events pertinent to the study), and communication among all components of the study participants (e.g., CCC, SDMC, clinical sites, and the NINDS).

***External Steering Committee (ESC).*** The ESC membership is composed of nationally recognized leaders in the fields of traumatic brain injury (TBI), critical care hyperbaric medicine, and clinical trials. The members are *Ross Bullock, neurosurgeon*, Lori Shutter, MD, neurointensivist; Lindell Weaver, MD, critical care and hyperbaric medicine; and David Wright, MD, clinical trial expert. The ESC has already played an important role in study design and project development. Individuals have reviewed the grant and protocol and provided advice and insight. The ESC will continue this role during the planning and implementation phase of the trial.

***Medical Safety Monitor*.** The MSM is a neurointensivist experienced in severe TBI management as well as serving as a MSM. She is not affiliated with any of the institutions

participating in the HOBIT trial. The MSM responsibilities are to review all SAEs and determine whether they are possibly related to HBO2 administration and to adjudicate adverse outcome events. The MSM will have a backup neurointensivist in the unlikely event she is unable to review the SAEs in a timely manner.

***Data and Safety Monitoring Board.*** The DSMB is appointed by the NINDS director and managed by the NINDS clinical trials group. Its overarching responsibility is the oversight of safety of the trial participants. They review reports on SAEs, request additional data/information if necessary, and must be cognizant of external new information regarding the safety of HBO2 treatment. Upon review of the periodic data, they advise the NINDS regarding continuation of the trial.

## 5.0 Protocol Summary

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|---|---|
| **Protocol Title** | Hyperbaric Oxygen Brain Injury Treatment (HOBIT) Trial: A Multicenter, Randomized, Prospective Phase II Adaptive Clinical Trial Evaluating the Most Effective *Hyperoxia* Treatment Paradigm for Severe Traumatic Brain Injury |
| **Study Objective** | 1. (Dose selection) To select, in patients with severe TBI, the combination of treatment parameters (pressure and intervening normobaric hyperoxia [NBH]) that is most likely to demonstrate improvement in the rate of good neurological outcome versus control in a subsequent confirmatory trial.<br>2. (Signal of efficacy) To determine, in patients with severe TBI, whether there is a >50% probability of hyperoxia treatment demonstrating improvement in the rate of good neurological outcome versus control in a subsequent confirmatory trial. |
| **Clinical Trial Phase** | Phase II |
| **Study Design** | This trial is designed as a multicenter, prospective, randomized, adaptive Phase II trial. |
| **Primary Outcome Measure** | To assess efficacy, the treatment groups will be compared with respect to the proportion of subjects with favorable outcome at 6 months post-randomization. Favorable outcome is defined based on the sliding dichotomy methodology whereby subjects with the most severe injury and whose initial Glasgow Coma Scale (GCS) scores are 3-5 are considered to have a favorable outcome if their 6-month Glasgow Outcome Scale – Extended (GOS-E) score is good recovery to severe disability; subjects with less severe injury and whose initial GCS scores are 6-8 are considered to have a favorable outcome if their 6-month GOS-E score is good recovery to moderate disability. |
| **Secondary and Exploratory Outcome Measures** | 1. To analyze the level and duration of intracranial hypertension (> 20 mmHg) using area under the curve (AUC) methodology in hyperoxia-treated versus control groups (Vik 2008).<br>2. To analyze the therapeutic intensity level (TIL) scores for controlling intracranial pressure (ICP) in hyperoxia-treated patients compared to controls.<br>3. At sites utilizing Licox brain tissue partial pressure of oxygen (PO2) monitoring, analyze the level and duration of brain tissue hypoxia (brain tissue PO2 < *20* mmHg) in HBO2-treated groups versus control (van den Brink 2000).<br>4. To compare the type and rate of serious adverse events (SAEs) |

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|---|---|
| | between *hyperoxia* treatment arms and control. |
| **Eligibility and Randomization** | All individuals presenting to a collaborating institution with a severe TBI defined as a GCS score of 3 to 8 (age 16 to 65 years) are potential candidates for inclusion. Patients with GCS score 7 or 8 will be required to have a clearly abnormal computerized tomography (CT) scan (≥ Marshall score 3) (Table 1). A central randomization module will be developed within the web-based trial management system. |
| **Intervention Administration and Duration** | Patients not requiring a craniotomy/craniectomy or any other major surgical procedure will be enrolled and the first *hyperoxia* treatment initiated within 6 hours of admission. If the patient does require a craniotomy/craniectomy or major surgical procedure, the enrollment and initial *hyperoxia* treatment shall be initiated within 12 hours *of admission*. No participant will be enrolled more than 24 hours after injury. |
| **Sites** | Fourteen clinical centers in the United States and Canada. |
| **Study Period** | Planned enrollment period - 3 years<br>Planned duration of the study - 5 years |
| **Sample Size** | Maximum of 200 |
| **Statistical Analysis** | The trial design is adaptive. The primary outcome is the severity adjusted GOS-E at 6 months. However, clinical data from *admission*, 30 days, and 3 months will be used to predict 6 month data. The trial will explore seven different active treatment arms for relative efficacy and comparison to the control arm. *Four* pressures (1.0, 1.5, 2.0 and 2.5 atmospheres absolute [ATA]) and with or without NBH will be studied. If there is at least one experimental treatment arm promising enough, it will be a candidate and will be compared for superiority to the control in the future phase III trial. The maximum number of subjects to be enrolled is 200 at approximately 14 clinical centers. The trial will utilize response adaptive rate randomization to favor the better performing experimental arms. Also, using adaptive randomization (being able to change how we assign subjects to the groups during the study based on information gained during the study) allows for substantially smaller sample sizes and provides better conclusions about the most effective treatment because it lets us stop the study early if we find strong results or identify futility before the scheduled end of the study (Gajewski 2015). |

## 6 STUDY OBJECTIVES

### 6.1 Primary Objective

The primary goals of the HOBIT trial is to definitively determine the most effective *hyperoxia* therapy paradigm in terms of pressure and to predict the probability that this treatment will result in a successful Phase III trial. Based on past preclinical and clinical investigations, the use of NBH, that is 100% fraction of inspired oxygen (FiO2) at 1.0 ATA following HBO2 will be evaluated for improved efficacy and clinical outcome.

### 6.2 Secondary Objectives

1. To analyze the level and duration of intracranial hypertension (> 20 mmHg) using area under the curve (AUC) methodology in HBO2-treated versus control groups (Vik 2008).
2. To analyze the TIL scores for controlling intracranial pressure (ICP) in HBO2-treated patients compared to controls *(Table 3)*.

3. Utilizing Licox brain tissue partial pressure of oxygen (PO2) monitoring, analyze the level and duration of brain tissue hypoxia (PO2 < *20* mmHg) using AUC methodology in HBO2-treated groups versus control (van den Brink 2000).
4. To compare the type and incidence of SAEs between hyperoxia treatment arms and control.

# 7 BACKGROUND

## 7.1 Rationale for Study Population

One of the significant factors in the failure of previous clinical trials to show efficacy in severe TBI may be the fact that the patient population was "frontloaded" with patients who have a relatively good prognosis (Narayan 2002). If one pools the patients from three large multisite trials, approximately 50% of the patients enrolled had either a GCS of 7 or 8 or a GCS motor score of 4 or 5 (Maas 2006, Marshall 1998, Morris 1999). Forty-four percent of the patients had a "diffuse injury" or a Marshall CT score of 2 (Marshall 1991). These patients had a favorable outcome on the dichotomized Glasgow Outcome Scale (GOS) score in the 70-80% range.

In our phase II clinical trial evaluating HBO2 in the treatment of severe TBI patients, there was no improvement in favorable outcome using the dichotomized GOS at 6 or 12 months (Rockswold 1992). After a careful reanalysis of the raw data and outcomes from that study by the SDMC at the Medical University of South Carolina, it was determined that if all patients with an enrollment GCS score of *7, 8, or* 9 with diffuse injury, are eliminated from the analysis, 19 of 57 (33.3%) have a favorable outcome in the control group and 27 of 60 (45%) of the HBO2-treated group have a favorable outcome using the dichotomized GOS. When a sliding dichotomized GOS was used, 26 of 57 (45.6%) in the control group compared to 35 of 60 (58.3%) in the treatment group achieved a favorable outcome. This represents an absolute 11.7% or a 12.7% improvement in favorable outcome using the dichotomized versus the sliding dichotomized GOS respectively. The subgroup eliminated (patients with an enrollment GCS score of 9, 8 and 7 with diffuse injury) had a favorable outcome rate of 78% on either the dichotomized or stratified dichotomized GOS. Although the *n* is too small to produce statistical significance, the approach strongly suggests that eliminating these less severely injured patients with a relatively good prognosis in the proposed study will significantly increase the chances of a positive study and one that will advance the prospects for patients suffering a severe TBI.

Based on the above considerations, all individuals, aged 16 to 65, presenting to a collaborating institution with a severe TBI defined as a GCS score 3 to 8 are potential candidates for inclusion. Patients with a GCS score of 7 or 8 with a Marshall CT score of 1 or 2 are excluded. Patients with a GCS score of 3 **AND** bilateral midposition, nonreactive pupils are excluded because of their grim prognosis and the fact that it is doubtful any treatment could have a neuroprotective effect. Previous preliminary studies have not included children < 16 years old because safety data is not available for them. Also, children under the age of 16 require a different team of providers and ICU compared to adults. Patients over 65 years old are excluded because they have increased co-morbidity and a higher mortality from severe TBI that would tend to obscure the positive effect from treatment.

## 7.2 *Rationale for the Potential Economic Impact if HBO2 is a Successful Treatment*

The Center for Disease Control estimates that there were 300,000 individuals hospitalized for a TBI in the USA in 2012. Approximately 10% of patients admitted to hospitals have sustained a severe TBI as defined by the GCS (Kraus 1993, Thurman 2001). Approximately 30% of these individuals die and 40% achieve a favorable outcome as defined by the dichotomized GOS. Therefore, approximately 30% of severe TBI patients are permanently severely disabled or

vegetative. The average age of an individual sustaining a TBI is about 40 years, and the average life expectancy after TBI is an additional 20 years. The annual average cost of a TBI victim requiring custodial care in the state of Minnesota is $80,000 ($1.6 million on average per disabled severe TBI patient over their lifetime). Using the above suppositions, we can therefore calculate that of the approximately 30,000 severe TBI patients there would be 9,000 left severely disabled or vegetative. Supposing there is a 10% improvement to favorable or functional abilities in 900 patients, this would translate into a savings of 1.44 billion over the lifetime of the increased number of functional survivors *occurring* each year. The cost of an HBO2 monoplace chamber and installation is approximately $250,000. To modify an existing monoplace chamber to accommodate and monitor severe TBI patients costs approximately $25,000. If 100 monoplace chambers are installed across the country at a cost of approximately $300,000 per unit, this would total $30 million. Just from these rough calculations, it is obvious that the cost of this trial and the cost of a subsequent Phase III trial, as well as the cost of multiple monoplace chambers in TBI centers would be a relatively small fraction of the savings produced in one year. In addition, this estimate does not include the productivity gains that would be substantial. *Also, HBO2 chambers are not limited to treating only severe TBI patients. There are significant numbers of legitimate indications for HBO2 treatments reimbursed by Medicare and insurance companies which makes the typical HBO2 unit profitable for the hospital (Table 4).*

Two types of HBO2 delivery systems exist. One is the traditional multiple-occupancy large compartment chamber. It is designed to accommodate several patients and attendant medical personnel and has long represented the technology standard. Advantages include the fact that multiple patients can be treated at one time and there is direct patient attendance during each HBO2 treatment. There are no modifications needed to a multiplace chamber to treat TBI patients. There are significant disadvantages, including the greater degree of technology and related support requirements, a larger physical plant footprint, and higher capitalization and operating costs.

An alternate delivery system is the monoplace chamber. It supports a single patient with attendance and support provided from the chamber exterior. The monoplace chamber has been employed across a broad range of patient conditions to an increasing degree over the past two decades. Our institution has found it entirely adequate for the safe care and management of critically ill and ventilator-dependent patients sustaining severe TBI and multiple injuries (Gossett 2010). The major advantages of the monoplace chamber are 1) minimal physical space footprint, 2) easily incorporate in and adjacent to a critical care support area, 3) minimal technology demands, 4) the delivery system can be effectively and safely operated by existing nursing, respiratory, and standard medical support staff upon appropriate training and preceptorship, 5) lower capitalization and operating costs, and 6) no risk of iatrogenic decompression sickness in support staff. It should be emphasized that the monoplace chamber becomes an extension of the critical care environment.

*7.3* ***The problem of "generalizability" of HBO2 treatment of severe TBI patients from one center to a multicenter trial and potentially to a national/international treatment***

*In terms of a multicenter trial, enrolling sites have been chosen because of their expertise in critical care hyperbaric medicine and in the care of severe TBI patients (Table 5). A 2-day focus course in the management of severe TBI patients in both monoplace and multiplace chambers will be conducted at HCMC for appropriate enrolling site personnel during the first six months of funding prior to enrolling patients. Following that will be a required run-in period for each enrolling site during which close monitoring will be conducted to ensure that the procedures are carried out without jeopardizing patient safety or data quality. Frequent interaction with*

*appropriate consultants via telephone or video conferences to discuss problems and solutions will be particularly important during this run-in period. Close monitoring by the PIs, CPC, and SCs of all aspects of the process will be critical. If HBO2 ultimately proves to be an effective treatment for severe TBI patients, the above described process will have to be carried out at multiple centers. A strong case could be made for the centralization of the management of severe TBI patients. There are a number of hospital-based emergent/critical care 24/7 HBO2 facilities being installed in the country at the present time. Undersea and Hyperbaric Medicine is a recognized sub-specialty by the American Board of Medical Specialties (ABMS) and there are increasing numbers of physicians completing fellowships and becoming certified in this area. Experience at HCMC has demonstrated that HBO2 therapy can be delivered to severe TBI patients safely. As with any new medical procedure, the process has to be taught to other centers. A strong economic case can be made for doing this (see above page 11). Novel clinical trials can drive practice if new treatments show beneficial effects in randomized trials. The NINDS tPA trial in the early 90's changed treatment of ischemic stroke by proving that rapid treatment led to improved outcomes. This trial led to the development of primary and comprehensive stroke centers to address the need to treat quickly and dramatically changed practice.*

## 7.4 **Supporting Data**

7.4.1 ***Potential Mechanisms of Action of Hyperoxia in Severe TBI.*** It can be postulated that one of the factors that has contributed to the failure of previous clinical TBI trials is their narrow focus on a single potential mechanism of injury. Most previously studied interventions had a selective neuroprotective effect with respect to the complexity of the process leading to brain cell death. On the other hand hyperoxia appears to have several protective mechanisms of action in severe TBI, likely increasing its potential effectiveness. These mechanisms have been demonstrated in both experimental and clinical investigations, and include improved oxidative metabolism and mitochondrial function, and reductions in intracranial hypertension, apoptosis, neuroinflammation, and free radical mediated damage (Daugherty 2004, *Menzel 1999*, Miller 1970, Palzur 2004, Palzur 2008, Rockswold 1992, Rockswold *2001, Rockswold 2010, Rockswold 2013, Rogatsky 2005, Soustiel 2008, Tisdall 2008, Tolias 2004*, Vlodavsky 2005, Vlodavsky 2006, Wada 1996, Wada 2001, Zhou 2007).

Cellular energy failure appears to be the initiating event in the complex processes leading to brain cell death (Saatman 2008, Signoretti 2008, Tisdall 2008, Zauner 1997). In the first 24 hours after brain injury, ischemia is present, leading to decreased oxygen (O2) delivery that is inadequate to maintain efficient oxidative cerebral metabolism (Bouma 1991, Bouma 1992, Vigue 1999). This abnormal metabolic state appears to trigger a marked increase in the glycolytic metabolism of glucose (Bergsneider 1997, Bergsneider 2001, Hovda 1991); this relatively inefficient anaerobic metabolism results in the depletion of cellular energy. A cascade of biochemical events leads to mitochondrial dysfunction and a prolonged period of hypometabolism (Bergsneider 1997, Lifshitz 2004, Signoretti 2001, Signoretti 2008, Verweij 2000). Diffusion barriers to the cellular delivery of O2 develop and persist; this appears to reduce the ability of the brain to increase O2 extraction in response to hypoperfusion (Menon 2004). The degree to which cerebral oxidative metabolism is restored in the acute phase after injury correlates with eventual clinical outcome (Glenn 2003, *Jaggi 1990)*. In addition, traumatic insult to the brain results in hematomas, contusion, and cerebral edema, all of which lead to intracranial hypertension. Intracranial hypertension is the major treatable cause of deterioration and death from severe TBI (Juul 2000).

In both animal and human investigations, hyperoxia increases O2 delivery to traumatized brain (Daugherty 2004, *Menzel 1999,* Rockswold 2010, Rockswold 2013, *Tolias 2004*). Thus, hyperoxia can potentially reverse the ischemia that precipitates cellular energy failure and the subsequent destructive biochemical cascade. Elevated brain tissue PO2 favorably influence the binding of O2 in mitochondrial redox enzyme systems, leading to improved mitochondrial function and adenosine triphosphate (ATP) production (Zhou 2007). Further experimental studies have found that hyperoxia restores the loss of mitochondrial transmembrane potential, and that the reduction of apoptotic cell death mediated by hyperoxia is achieved by a mitochondrial protective effect (Palzur 2008, Soustiel 2008). These investigators theorize that the increased intracellular O2 bioavailability resulting from HBO2 may contribute to the preservation of mitochondrial integrity and reduce the activation of the mitochondrial pathway of apoptosis. Clinical trials have shown increased global O2 consumption lasting for at least 6 hours post HBO2 treatment which would be secondary to improved mitochondrial function. In addition, this effect is seen for at least 5 days post injury in TBI patients treated with HBO2 (Rockswold 2001, Rockswold 2010). Thus, HBO2 improves oxidative metabolism during the period of prolonged post trauma hypometabolism. In addition, HBO2 has been shown in both experimental and clinical studies to reduce ICP (Brown 1988, Hayakawa 1971, Miller 1971, Rockswold 1992, Rockswold 2001, Rockswold 2010, Rockswold 2013, Sukoff 1982) and cerebral edema after severe brain injury (Mink 1995, Nida 1995, Palzur 2004, Sukoff 1968). These latter studies suggest that HBO2 may promote blood-brain barrier integrity, thus reducing cerebral edema and hyperemia, and therefore reducing the elevated ICP.

7.4.2 ***Safety Record for Hyperoxia Treatment.*** An exemplary safety record for HBO2 treatment has been demonstrated over the course of four clinical trials at the Hennepin County Medical Center (Gossett 2010, Rockswold 1992, Rockswold 2001, Rockswold 2010, Rockswold 2013). There were 1,984 HBO2 treatments delivered to 167 patients with no permanent complications related to the HBO2 treatment and no patient emergently evacuated from the chamber. *In August 2015, the FDA gave the HOBIT Trial a "Study May Proceed" notification (see Appendix B). All SAEs for our four clinical trials were presented for the FDA review. All of the HBO2 chambers at our 14 enrolling sites have been granted an investigational device exemption (IDE) and certified for safety by the FDA. Overall, there are four essential factors in maintaining the safety of the severe TBI patient during HBO2 treatment. First is that the inclusion/exclusion criteria for the patient entering the study be strictly enforced. The patient must be hemodynamically stable and the patient's respiratory status must meet the criteria outlined in the protocol. Second, it is essential that the same level of care provided in the ICU be continued throughout the patient's transport to and from the HBO2 chamber (Weaver 1999). Third, the HBO2 chamber and its environment must become an extension of the ICU. Expertise of appropriate personnel must be as readily available in the HBO2 environment as it is in the ICU. Unlike the ICUs where the patients may be left unattended for brief periods of time, the patient is under the constant observation and supervision by several staff members during the HBO2 treatment. Fourth, the safe application of HBO2 requires an additional set of skills, knowledge base, and experience that are unique to hyperbaric medicine and essential to the patient and staff safety. A well trained staff of hyperbaric nurses and technicians working under the supervision of a qualified HBO2 physician, each of whom have a thorough knowledge of the procedures and physiology of HBO2 therapy, is required. All clinical sites participating in the HOBIT Trial have a team of trained personnel who are aware and fully capable of carrying out these critical procedures (see pages 10-22; Facilities and Other Resources).*

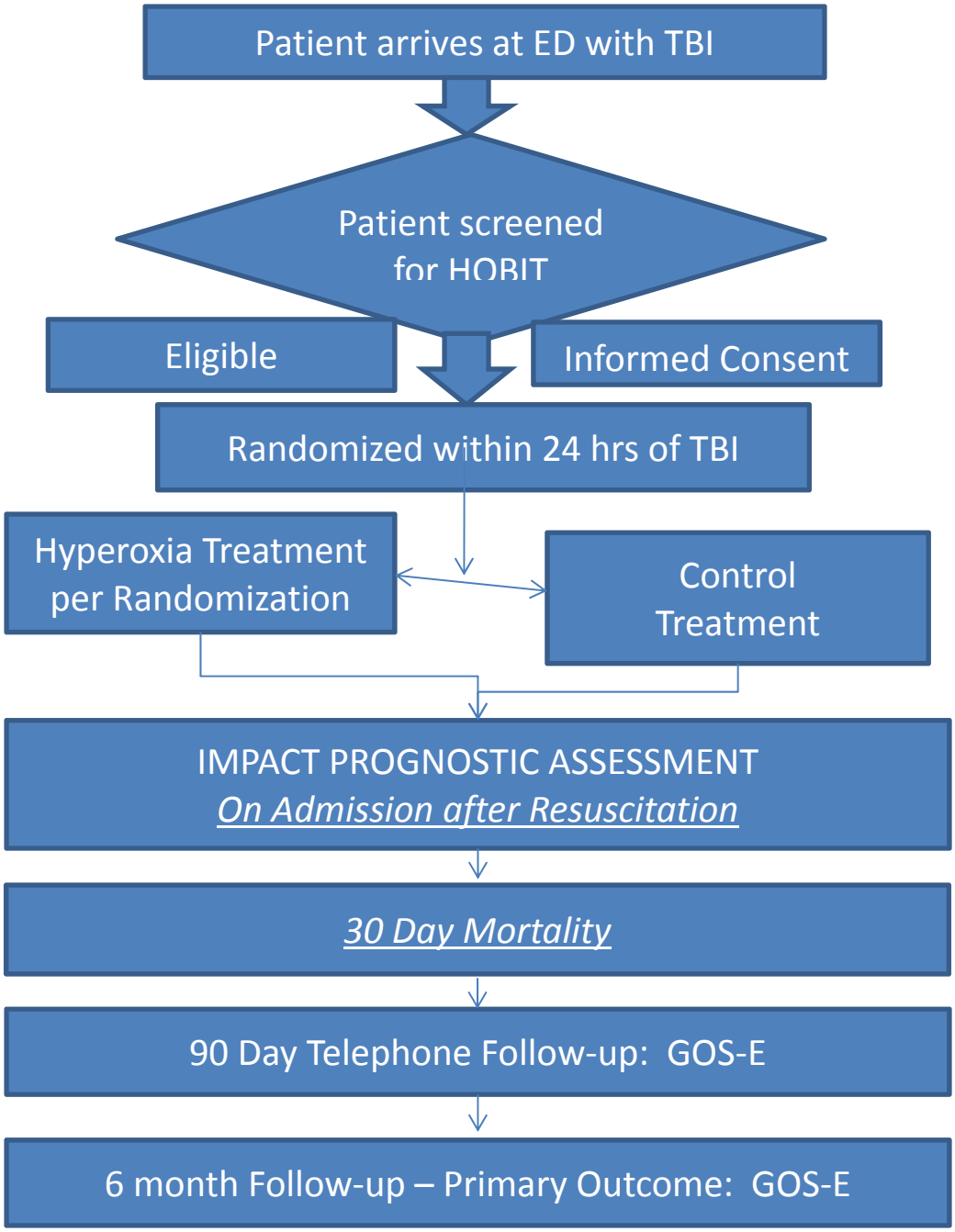
Fire hazard is a potential risk in HBO2 chambers. The National Fire Protection Association (NFPA) has produced a hyperbaric safety standard which has been in place since 1967 (NFPA

99, Standard for Health Care Facilities 2005). In facilities that rigidly follow these standards, there have been no fatalities due to hyperbaric chamber fire in North America.

The patients receiving NBH (100% FiO2 at 1 ATA) will remain in the ICU to receive their treatments. There would be no increased risk of AEs compared to controls (standard treatment) other than the potential of O2 toxicity.

## 8 STUDY DESIGN

This trial is designed as multicenter, prospective, randomized, adaptive phase II clinical trial. All individuals presenting at an enrolling site with a severe TBI defined as a GCS score of 3-8 (age 16 to 65 years) are initially eligible for inclusion. Patients with a GCS score of 7 or 8 and a Marshall CT score of 1 or 2, as well as patients with a GCS score of 3 and bilaterally mid position, non-reactive pupils will be excluded. No exclusion criteria will be based on race, ethnicity, or gender. The trial design is adaptive. The primary outcome is a sliding dichotomized adjusted GOS-E at 6 months. However, clinical data from *admission,* 30 days, and 3 months will be used to predict 6-month data. The trial will explore *seven* different active treatment arms for relative efficacy in comparison of the control arm. *Four* pressures (*1.0,* 1.5, 2.0 and 2.5 ATA) and HBO2 with or without NBH will be studied. *NBH will also be evaluated without HBO2, serving both as a treatment arm and a control for the effect of pressure.* Utilizing *the most promising* treatment arm, the posterior predictive probability of whether there is a > 50% probability of this treatment arm demonstrating improvement in outcome in a subsequent phase III trial will be calculated. *If the probability is > 50%, this treatment arm will be compared for superiority to the control in a future phase III trial.* The maximum number of subjects to be enrolled is 200 at approximately *14* clinical centers. The trial will utilize response adaptive rate randomization to favor the better performing experimental arms. Also, using adaptive randomization (being able to change how we assign subjects to the groups during the study based on information gained during the study) allows for substantially smaller sample size and provides better conclusions about the most effective treatment because it *allows* the study to *stop* early if strong results or futility *are identified* before the scheduled end of the study. Safety of the trial will be carefully assessed including a statistical analysis of the SAEs. This study, in addition to identifying the optimal dose, offers the opportunity to explore the treatment effect and other important outcome domains using ICP, TIL scores and brain tissue PO2. These analyses will allow us to further support a go/no-go decision regarding a subsequent definitive efficacy trial.




## 9 SELECTION AND ENROLLMENT OF SUBJECTS

| Inclusion Criteria | Rationale |
|---|---|
| GCS score ≤ 6 or GCS score 7 or 8 and Marshall CT score ≥ 3 | Patients most likely to benefit from treatment |
| Age ≥ 16 and ≤ 65 | Safety not established in children. Elderly have relatively poor outcome. |
| If no craniotomy/major operative procedure = 6 | Pre-clinical/clinical data support this treatment window |

| Exclusion Criteria | Rationale |
|---|---|
| GCS 3 **AND** bilaterally unreactive pupils ≥ 4 mm | Death highly likely |
| Severe pre-existing neurological deficits, e.g., previous TBI, stroke | Prevent good recovery |
| Acute spinal cord injury | Alters neurologic recovery |

| | |
|---|---|
| hr treatment window. If major procedure required = 12 hr. No patient enrolled > 24 hrs after injury | |
| Informed consent obtained | Required |
| Blunt mechanism only | Pathophysiologic and anatomic differences with penetrating injury |

| | |
|---|---|
| | |
| Fixed coagulopathy. INR > 1.4 despite correction attempts. | Poor prognosis; appropriate procedures can't be done |
| Pregnancy | Effects of HBO2 on fetus uncertain |

**Decompressive craniectomy is not a contraindication to HBO2 treatment.**

## 9.2 Study Enrollment Procedures

9.2.1. ***Identifying and Recruiting Candidates*.** Potential subjects for this trial will be recruited from all patients with a severe TBI presenting within 24 hours of injury to the 14 clinical sites participating in this trial. All participating clinical sites are staffed by trained research personnel capable of performing careful screening of each potential subject according to the inclusion/exclusion criteria described above.

9.2.2 ***Screen Failure Logs.*** A log of all screen failures will be maintained at each site. The information collected on the screen failure log will include basic demographic information as well as the reason for excluding the patient from randomization. The Screen Failure Log allows for the assessment of any selection bias in the enrollment of patients (Slieker 2008).

9.2.3 ***Informed Consent Procedures.*** Upon confirmation of a patient's eligibility for the trial, consent is obtained by either the clinical site PI or by individuals to whom the clinical site PI has delegated authority to obtain informed consent. The delegation of authority must be documented and a current copy of this document must be maintained at the clinical site. As with most clinical trial responsibilities delegated by the clinical site PI, it is his/her responsibility to ensure that the delegation is made only to those individuals who are qualified to undertake the delegated tasks, and that there is adherence to all applicable regulatory requirements and Good Clinical Practices (GCP) Guidelines. Additionally, it is the investigator's responsibility to ensure that the patient's legally authorized representative (LAR) has been given an adequate explanation of the purpose, methods, risks, potential benefits and patient responsibilities of the study. The consent form must be an up-to-date document that has been approved by the clinical site's institutional review board (IRB). A written signed and dated informed consent is required prior to randomization. A sample informed consent form is provided as ***Appendix F***.

In the HOBIT Trial, all subjects will be comatose, therefore, informed consent will be obtained from a LAR or person with power of attorney for the patient. Every attempt will be made to contact the patient's family as soon as possible after the patient's admission, and in accordance with the individual hospital's protocol. To the extent possible, these discussions should be carried out in a private setting without distraction. No coercion will be applied, and the LAR and other family members will be given an opportunity to read the informed consent document, ask and have answered any questions they may have about the study.

9.2.4 ***Randomization Procedures.*** A web-based central randomization system will be developed by the SDMC and installed on the WebDCU™ HOBIT study website. The objective of randomization is to prevent possible selection bias by providing random treatment assignment to each subject, and to prevent accidental treatment imbalances for the known prognostic variables. Balancing of prognostic variables will be conducted using the Minimal

Sufficient Balance randomization algorithm which aims to maximize the treatment allocation randomness while containing the baseline covariate imbalances within a pre-specified limit. The randomization scheme will be equal allocation balanced across pre-specified covariates during a burn-in period (first 50 randomizations; 5 per arm). Imbalances in the following baseline covariates between the treatment groups will be controlled: *age, GCS score, and enrolling site*. Once 50 subjects are randomized (in order to accrue outcome information in each arm), response-adaptive randomization (RAR) will be utilized for a maximum of 200 subjects with the goal of maximizing the likelihood of identifying the most effective treatment arm with regards to the GOS-E response. The allocation probabilities will be proportional to the probability that the arm is the best. The target allocation ratio will be updated every 13 weeks. To ensure proper randomization, the unblinded statistical programmer will have access to the randomization information in order to oversee the quality control of the computer program. Randomization will occur via the study-specific password-protected website accessed by an authorized research coordinator or investigator at the clinical site. If, in rare circumstances, the web system is not available, the coordinator or investigator will have access to emergency randomization procedures that will allow the site to randomize the patient. Upon randomization by the authorized person at each center, an e-mail notification will be sent to the Study EC, Site PI, Site Primary Study Coordinator and relevant NETT CCC and SDMC personnel. Subjects will be considered enrolled in this trial at the time of randomization, regardless of whether or not they start or complete study treatment. The entire randomization process will be blind to all study team members.

*9.2.5. **Blinding.** Following serious consideration of sham HBO2 treatments for the control group, the decision was made not to proceed with blinding for the following reasons. 1) It is impossible to perfectly blind a sham HBO2 treatment (Weaver 2002, Clarke 2009). The HBO2 technician administering the HBO2 and managing the chamber will be obviously aware of the treatment administered. In the case of a multiplace chamber, it will be completely obvious to the critical care hyperbaric nurse and any other personnel in attendance in the chamber whether there is a pressure being applied. In addition, even in the case of a monoplace chamber where brain tissue O2 monitoring is carried out, the treatment applied will be obvious. If for any reason blood gases have to be performed, treatment will be obvious. There are other management situations where it will be required by the treatment team to know whether or not the patient is under pressure. 2) Evaluation of any potential harm from HBO2 treatment should include the potential increased morbidity associated with transporting patients to an HBO2 chamber. Any outcome difference resulting from transportation of critically ill patients should be accounted for in the HBO2 group only. 3) Outcome assessment will be blinded and will be done by independent evaluators who are not involved in the treatment portion of the patient's course.*

## 10 STUDY INTERVENTIONS

### 10.1 Interventions, Administration, and Duration

10.1.2 ***Treatment Window.*** It is considerably more difficult to initiate a complex treatment like HBO2 as compared to initiating a drug therapy intravenously. HBO2 treatment cannot occur until acute resuscitation, including intubation, hemodynamic stabilization, emergency surgery as needed and management of other traumatic injuries has occurred. Informed consent must be obtained from the LAR. Based on our past experience, patients not requiring a craniotomy/craniectomy or any other major surgical procedure will be enrolled and the first HBO2 treatment initiated within 6 hours of admission. If the patient does require craniotomy/craniectomy or a major surgical procedure, the enrollment and initial HBO2

treatment shall be initiated within 12 hours. No patient will be enrolled more than 24 hours after the injury.

10.1.3 ***Treatment Frequency.*** If a patient does not receive a treatment on schedule (+/- 2 hours), this treatment is not performed. In previous trials, due to restraints on personnel availability, it has been necessary to allow flexibility in delivering HBO2 to avoid repeated treatments in the middle of the night. Therefore, if the first HBO2 treatment is delivered between 10:00 p.m. and 4:00 a.m., the protocol will allow a window of +/- 4 hours for the subsequent middle of the night treatment. The treatment schedule will then be adjusted to maintain an approximately every 12 hours schedule. There must be at least 8 hours between any two treatments.

*10.1.4* ***HBO2 Treatments.***

*If the patient meets inclusion criteria and informed consent is obtained, they will be randomized to one of six HBO2 treatment paradigms, one NBH treatment paradigm, and a control group. Oxygen toxicity unit (OTU) is a means of quantitating the amount of O2 exposure to the patient based on duration and pressure.*

| *Treatment* | *OTD* |
|---|---|
| *1. 1.5 ATA 60 minutes twice a day* | *130 x 2 = 260* |
| *2. 2.0 ATA 60 minutes twice a day* | *208 x 2 = 416* |
| *3. NBH (100% O2 at 1.0 ATA) 4.5 hours twice a day* | *270 x 2 = 540* |
| *4. 2.5 ATA 60 minutes twice a day* | *296 x 2 = 592* |
| *5. 1.5 ATA 60 minutes with NBH twice a day* | *310 x 2 = 620* |
| *6. 2.0 ATA 60 minutes with NBH twice a day* | *388 x 2 = 776* |
| *7. 2.5 ATA 60 minutes with NBH twice a day* | *476 x 2 = 952* |
| *8. Control (no hyperoxia treatment)* | |

*HBO2 treatments will be delivered in both monoplace and multiplace chambers. Compression and decompression will occur at a standard 2 feet per minute. Total compression/decompression time for 2.5 ATA is 50 minutes, for 2.0 ATA 33 minutes, and for 1.5 ATA 16.5 minutes. Each treatment will be for 60 minutes at the specified pressure. NBH will consist of the patient breathing 100% O2 for 3 hours following HBO2 decompression which will be continued in the ICU. The NBH without HBO2 treatment arm will likewise be ventilated with 100% O2 for 4.5 hours at 1.0 ATA in the ICU. The treatment paradigm will be continued for five days or until the patient is following commands or determined to be brain dead.*

*10.1.5.* ***Total Oxygen Exposure.*** *The FDA reviewers recommended that "investigators should record the duration, mode of administration and concentration for any oxygen administration outside the treatment period" (Appendix B). This is a beneficial suggestion. By recording the total amount of oxygen delivered in terms of OTUs, a quantitative description of the total amount of oxygen delivered will enhance safety of the study. More severely injured patients, particularly those with direct lung injuries or acquired ventilation pneumonia will require an increased FiO2 between treatments. The total amount of oxygen delivered can be correlated with oxygen toxicity to the lungs and SAEs related to hyperoxia.*

10.1.6 ***Transport of the Severe TBI Patient.*** Transport of critically ill patients has been shown to be associated with potential AEs (Beckmann 2004, Shirley 2004). It is essential that the same level of care provided in the ICU is continued throughout patient transport (Weaver 1999). Monitoring the ventilatory status of severe TBI patients during transport is critical. If the patient requires mechanical ventilation with positive end expiration pressure (PEEP) in the ICU, then a

transport ventilator with PEEP or a manually-operated resuscitation bag with a PEEP valve is used. Pulse oximetry to monitor O2 saturations and portable end tidal carbon dioxide (EtCO2) monitor is used routinely. Ideally, the HBO2 unit should be within or in close proximity to the ICU. This arrangement minimizes the time and the potential problems associated with transport and makes advantageous use of the experienced ICU support staff.

## 10.2 **Handling of Study Interventions**

### *10.2.1* ***Preparation of the Severe TBI Patient for HBO2***

*It is critical that any hemodynamic, pulmonary or intracranial instability occurring in a patient prior to HBO2 treatment be thoroughly assessed and stabilized prior to consideration of transport to the HBO2 chamber. This is particularly critical prior to the first treatment occurring within several hours of admission to the hospital. It should be emphasized that these issues are intrinsic to the severity of the injury the patient has sustained both to the brain as well as to other regions of the body. The Clinical Standardization Guidelines presented in the protocol are state-of-the-art and will be adhered to and monitored closely (see Appendix E). All major intracranial procedures such as evacuation of mass lesions and/or decompressive craniectomy, or thoracotomy, or laparotomy for internal bleeding or injury are performed per protocol. Spine fractures must be thoroughly evaluated and appropriate management instituted. All patients will have an external ventricular drain placed for both ICP monitoring as well as treatment of intracranial hypertension by removal of CSF. Routine systemic monitoring of the patient includes continual heart rate, blood pressure, electrocardiogram, and central venous or wedge pressures as needed. Patient transport to the HBO2 chamber and HBO2 treatment will not occur if the patient is judged to be unstable by the team of providers (neurointensivist, neurosurgeon, and hyperbaric staff physician). This would include situations where 1) ICP is labile or persisting over a level of 20 mmHg despite treatment according to the TIL; 2) cerebral perfusion pressure (mean arterial pressure minus ICP) is < 60 mmHg; 3) systolic blood pressure is < 100 mmHg. Appropriate measures per protocol will be taken to correct these critical parameters prior to considering HBO2 treatment.*

As discussed above, the lung is particularly susceptible to damage by hyperoxia because of the large surface area exposed to O2 in the lungs. Patients with severe TBI are prone to the development of atelectasis and ventilator-acquired pneumonia. It is frequently difficult to distinguish the relative impact of an initial lung contusion and/or aspiration from the possible toxicity of HBO2 therapy. Based on our past experience, no patient will undergo HBO2 therapy if the FiO2 requirement is > 50% to maintain a PaO2 > 70 mmHg. If the patient improves to the point that the FiO2 requirement is ≤ 40%, treatments will be resumed. However, if O2 requirements again increase to FiO2 > 50%, treatments are permanently terminated. Likewise, if PEEP requirements are > 10 cm of water, HBO2 treatments are temporarily discontinued. If requirements become < 6 cm of water, HBO2 treatments are resumed. However, if PEEP requirements again increase to > 10 cm of water, treatments are permanently terminated. Daily chest radiography is performed, and if there are changes suggesting O2 toxicity, treatment is temporarily discontinued until the chest x-ray improves. Adhering to these guidelines, permanent O2 induced injury to the lungs has not occurred.

Cerebral O2 toxicity could potentially manifest itself as seizures. Severe TBI patients are susceptible to seizures and all patients are loaded with prophylactic phenytoin sodium and started on maintenance doses to achieve and maintain therapeutic levels for 7 days. No patient at our institution has had a seizure occur during the HBO2 treatment using this protocol.

There are many details requiring special attention prior to the placement of the patient in the HBO2 chamber (Gossett 2010, Weaver 1999). All clinical sites expected to participate in the HOBIT Trial have trained personnel who are very cognizant of these critical procedures. The EC also will maintain strict oversight of protocol and assessment adherence at each participating

clinical site. The procedures include ensuring that: chest tubes are connected to a Heimlich valve and drained passively into a sterile receptacle such as a Foley drainage bag or a sterile glove; the air from the endotracheal tube cuff is completely evacuated and replaced with sufficient normal saline to achieve an appropriate seal with a minimum pressure; gastric tubes are attached to a sputum trap or drainage bag; and, subdural Jackson-Pratt drains are securely occluded for the duration of treatment. In the monoplace chamber, all intravenous (IV) lines in use must have specialized hyperbaric tubing extensions. Each IV line requires its own pump, and only one line can be used for each penetration. IV check valves are positioned inside the chamber door on each line.

The patients are connected to the hyperbaric ventilator at least 15 minutes prior to being pressurized in the HBO2 chamber. Ventilatory parameters are set and stabilized, and arterial blood gasses are checked to verify that the ventilator parameters are appropriate. If secretions are present, the patient is suctioned thoroughly prior to the HBO2 treatment. Suctioning the patient during a treatment is easily accomplished in a multiplace chamber. If suctioning is required during a monoplace treatment, however, the chamber must be decompressed, the patient suctioned, and the chamber recompressed. This suctioning is rarely required. Bilateral myringotomy is performed prior to the first HBO2 treatment. The myringotomy can be accomplished with an 18-guage spinal needle in the anterior inferior quadrant of the tympanic membrane. The tympanic membrane should be checked each day to assure patency of the myringotomies. This procedure reduces middle ear barotrauma and thus avoids the painful stimulation which raises ICP (Rockswold 1992). A myringotomy will not be performed if there is blood in the external canal or otorrhea present. A hyperbaric pretreatment checklist is maintained and all items performed and checked off prior to the patient entering the HBO2 chamber ***(Appendix D).***

10.2.2 ***Monitoring of the Severe TBI Patient During HBO2 Treatment.*** Patient monitoring and safety within the HBO2 chamber is of the utmost importance (Gossett 2010, Rockswold 1985, Weaver 1988, Weaver 1999, Weaver 1999). The hyperbaric chamber becomes an extension of the critical care environment. Routine systemic monitoring of the patient includes continuous heart rate, blood pressure, electrocardiogram, and central venous or pulmonary wedge pressures as needed. Intracranial monitoring, including ICP and brain temperature, continue throughout the HBO2 treatment. Brain tissue PO2 monitoring will be optional. ICP will be monitored using an intraventricular catheter. In the case of a monoplace chamber, a pressure transducer is connected to the ventriculostomy line inside the HBO2 chamber. Cerebrospinal fluid (CSF) is allowed to flow from the ventriculostomy to the transducer which converts the fluid pressure to a digital signal. This signal is transmitted through the chamber door to the outside monitors via electrical penetrations. A system will allow the attendant on the outside of the monoplace chamber to turn the ventriculostomy stopcock valve either open for draining (if ICP is elevated) or closed for intermittent ICP monitoring.

10.2.3 ***Management of the Severe TBI Patient in the HBO2 Chamber***

Monoplace Chamber

Adequate mechanical ventilation throughout the hyperbaric treatment is essential for TBI patients with severe injury (Gossett 2010). Monoplace ventilators are generally kept on the outside of the chamber. The monoplace ventilator has to overcome the pressure differential between the outside and the inside of the chamber in order to properly ventilate the patient. A common problem with monoplace ventilators is that at any set tidal volume the delivered tidal volume decreases during compression and increases during decompression (Weaver 1988, Weaver 1999). This fluctuation is because the volume of gas changes inversely with pressure

(Boyle's Law V=1/P). Therefore, respiratory rate, tidal volume, inspiratory to expiratory ratio, and peak inspiratory pressures is monitored closely throughout the hyperbaric treatment with particular vigilance during pressure changes. Arterial blood gasses can be obtained during HBO2 treatment and are especially important in patients with borderline pulmonary function (Ratzenhofer-Komedna 2003, Weaver 1994).

There are special requirements for delivering IV fluids and medications to a patient in the monoplace chamber. In a monoplace chamber, IV fluids which are delivered to the patient through the chamber door are significantly decreased during compression in the chamber. This decrease is particularly true at slow rates of IV delivery (Ray 2000, Weaver 2005). Using hard pressure tubing between the IV pump and the chamber hatch allows more rapid stabilization of the IV delivery rate at treatment pressure. During decompression, there is a potential of increased IV drip. This situation is obviated by hand administering the drug during compression and slowing the drip during decompression. High pressure IV pumps permit the controlled delivery of IV fluids.

Proper sedation or paralysis is important for proper control of the patient in the monoplace chamber. Most severe TBI patients are sedated as a routine part of their ICP management. Elevated ICP or a decrease in cerebral perfusion pressure (CPP) is treated during HBO2 in standard fashion. This treatment includes CSF drainage and administration of osmotic therapy or moderate hyperventilation. Blood pressure is supported with appropriate vascular volume expansion and/or vasopressors.

Multiplace Chambers

The ventilator in the case of the multiplace chamber is inside the chamber during treatment. Respiratory function is monitored as described for the monoplace chamber. Ventilator settings are verified with blood gasses prior to initiating treatment and rechecked as needed during treatment. Administration of IV fluids and medications present no special problem inside the multiplace chamber. ICP and sedation management in the multiplace is accomplished without modification of ICU protocols.

10.2.4 ***Personnel Safety.*** Medical personnel are not exposed to hyperbaric conditions when a monoplace chamber is utilized. In the case of the sites using multiplace chambers, all medical personnel who will attend to the patients in the multiplace chamber must undergo medical clearance according to the standards of the Undersea and Hyperbaric Medical Society (UHMS). The various HBO2 treatment paradigms to be evaluated in the HOBIT trial are well within the normal limits of HBO2 treatments utilized for standard indications.

## 10.3 **Concomitant Interventions**

ICP will be monitored continuously during HBO2 treatments with 15-minute means recorded. Licox brain tissue PO2 monitoring is optional.

## 10.4 **Protocol Adherence Assessment**

10.4.1 ***Management Guidelines***. It is critical that a uniform management plan among the enrolling sites is instituted. Treatment variability among enrolling sites is thought to have been a significant factor in the failure of previous multisite clinical trials involving severe TBI. David Wright, M.D., PI for the Progesterone for the Treatment of Traumatic Brain Injury (ProTECT) III trial, has agreed to allow the HOBIT Trial to utilize the CSG developed for the ProTECT Trial. This is important for two reasons. 1) The ProTECT III CSGs were developed by a national

committee of experts in neurosurgery, trauma surgery, neuro critical care, and emergency medicine. They are based on both their expertise as well as the Guidelines for the Management of Severe TBI (Brain Trauma Foundation 2007). Therefore, they represent the "state-of-the-art" and would be hard to improve upon. 2) Since there are eight enrolling sites that participated in the ProTECT III trial, the management of the patients will be standard care. The guidelines developed by the ProTECT III Clinical Standardization team follow a Goal-Directed Therapy approach. Since all of the potential enrollees in the HBO2 study have suffered severe TBI, all patients will require ventriculostomy and ICP monitoring. ***(See Appendix E: Clinical Standardization Guidelines).***

10.4.2 ***Treatment Variability.*** The major concern of any clinical trial of a potential therapy is maintenance of consistent management within and across clinical sites. Otherwise, variations in management will tend to obscure evidence of benefit from the experimental therapy. Every effort must be made to assure that each patient enrolled in this study will receive consistent, state-of-the-art treatment. Uniform management will assure that the only meaningful difference in treatment between patients randomized to receive HBO2 versus HBO2 sham treatments will be the administration of HBO2 itself.

We have carefully examined problems with previous clinical trials and discussed the challenges with our ESC who have conducted a number of these trials. To that end, we have incorporated the following in the HOBIT Trial.

1. The HOBIT trial has adapted the ProTECT III CSGs developed by a multidisciplinary team of experts in the management of severe TBI. These guidelines are straightforward and are in use in most major TBI treatment centers and follow a goal-direct therapy approach.
2. *An ESC made up of a group of experts including Drs. Ross Bullock,* Lori Shutter, Lindell Weaver, and David Wright will help ensure standardization of TBI care.
3. The EC plans to conduct *a 2-day course in the management of severe TBI patients in both monoplace and multiplace chambers prior to enrolling patients* with the lead staff at the enrolling sites.
4. The EC will implement a protocol based online examination through the WebDCU which will be required for all personnel involved in patient care prior to participation in the study.
5. The SDMC has had a great deal of experience in tracking performance based on key data elements entered daily into the study database to monitor each site's adherence to the management protocol. The system will alert the PI and other appropriate EC members to violations and deviations.
6. The EC will assess site quality and performance via a site Report Card that will be generated on a regular basis with pre-determined minimal site guidelines for patient care and adherence to the protocol. As part of the "Report Card" process, there are provisions to drop a participating clinical site if a pattern of willing disregard for the protocol is identified at any site.
7. Periodic ongoing onsite visits by the PI and CPC will be conducted to ensure quality assurance throughout the trial.
8. The HOBIT trial statistical plan includes randomization adjusted for enrolling sites.
9. The EC has secured written assurances of cooperation from our research partners at each enrolling site.

## 10.5 **Protocol and Safety Monitoring**

10.5.1 ***Data Safety Monitoring Board.*** The DSMB will review study mortality rates, center performance, AEs and SAEs data semiannually. This review will identify any clinical, operational, or other data issues that might require changes or adjustments in the way in which the trial is conducted as well as any safety issues that may need to be addressed. In order to accommodate this, the SDMC will generate safety monitoring reports ***quarterly*** as well as a comprehensive statistical report semi-annually for the DSMB. These reports will contain compiled data on enrollment (expected and actual), demographic and baseline characteristics, eligibility and protocol violations, safety data, concomitant medications and surgical procedures, and data quality (e.g., timeliness of data entry, and number of data clarification requests generated and resolved). All coded AEs and SAEs will be summarized in terms of frequency of the event, number of subjects having the event, timing relative to randomization, severity and relatedness to treatment. The comprehensive report that coincides in timing with the planned interim analysis also contains the results of the analysis for overwhelming efficacy and futility. The content of the reports is partially unblinded with treatment groups identified with a letter A, B, C . . . I. If the DSMB wishes to be completely unblinded for these comprehensive reports, a sealed treatment identification envelope will be provided to the NINDS DSMB Liaison; this envelope can be opened at the discretion of the DSMB.

10.5.2 ***Protocol Adherence Monitoring*****.** Although the clinical sites that have been identified to participate in the HOBIT Trial all have personnel very experienced with HBO2 treatment administration, there may be some variation in the actual administration of the intervention required by the HOBIT protocol. In an effort to reduce the variability among the participating clinical sites, the EC will institute an oversight process that will help to ensure "standardization" of the intervention and adherence to the HOBIT protocol. Prior to starting the trial, each participating clinical site will be advised of the elements of a "report card" by which their clinical site performance and protocol adherence will be measured. By identifying the criteria at the start of participation in the trial, clinical site personnel will not be surprised by the expectations of the EC.

The SDMC working with the EC will develop a mechanism to allow review of the performance of participating clinical sites in terms of both "best practices" and protocol adherence. The SDMC will generate clinical care profiles and provide access to pertinent data that allows the EC to make assessments of the "best practices" principles of care. Examples of relevant data that may be included in the profiles are the medical history, baseline GCS scores, lab values, and vital signs.

With regard to protocol adherence, there will be a two-part process. The EC, on a regular basis, will review a summary of the data entered in the HOBIT WebDCU$^{TM}$ database by the participating clinical sites to identify deficiencies in data collection and/or entry. This summary will be the result of the ongoing review by the SDMC Data Manager (DM) of data entered by all participating clinical sites. A second concurrent review process for protocol adherence will be conducted by the SDMC PM (working with the DM) and the IMM to determine protocol violations and deviations.

At regular intervals, the EC will review the material and discuss, among other items, any concerns regarding the principles and intensity of the overall care at particular sites and aggregations of protocol violations/deviations at particular sites. The EC may recommend that individual sites be contacted to discuss the issues identified at those sites and potential remedial measures. As a result of these reviews, the EC may make recommendations for protocol changes if serious safety concerns arise or there is an overarching issue with implementation of the protocol.

# 11 CLINICAL, LABORATORY EVALUATIONS

## 11.1 Schedule of Evaluations

| Evaluations | Baseline | Randomization Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | 30 days | 3 months | 6 months | End of Study |
|---|---|---|---|---|---|---|---|---|---|---|
| Screening | X | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | | | | | |
| Demographics | X | | | | | | | | | |
| Medical History | X | | | | | | | | | |
| Pre-hospital Events | X | | | | | | | | | |
| Informed consent | X | | | | | | | | | |
| Pupil Reactivity | X | X | X | X | X | X | X | | | |
| Hypotension (systolic BP < 90) | X | X | X | X | X | X | X | | | |
| Hypoxia (O2 saturation [SpO2] < 90%) | X | X | X | X | X | X | X | | | |
| GCS | X | X | X | X | X | X | X | | | |
| AIS | X | | | | | | | | | |
| ISS | X | | | | | | | | | |
| Revised Trauma Score | X | | | | | | | | | |
| Randomization | | X | | | | | | | | |
| Enrollment Head CT | X | | | | | | | | | |
| Marshall CT Score | X | | | | | | | | | |
| tSAH or CT | X | | | | | | | | | |
| Epidural Mas on CT | X | | | | | | | | | |
| ICP Monitor Insertion | X | | | | | | | | | |
| Licox Monitor Insertion Option | X | | | | | | | | | |
| Check Licox Monitor Function q $HBO_2$ Rx | X | X<br>X | X<br>X | X<br>X | X<br>X | X<br>X | | | | |
| Head CT to Check Placement | | X | | | | | | | | |
| 1st HBO2 Rx | | X | | | | | | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| HBO2 Rxs | | X | X<br>X | X<br>X | X<br>X | X<br>X | | | | |
| ICP Monitoring | | X | X | X | X | X | | | | |
| Licox Monitoring Option | | X | X | X | X | X | | | | |
| TILS Recording | | X | X | X | X | X | | | | |
| *FiO2 Levels q1h* | X | X | X | X | X | X | | | | |
| Vitals | X | X | X | X | X | X | | | | |
| Labs | | X | X | X | X | X | | | | |
| Glucose (3-20 mmol) | X | | | | | | | | | |
| Hb (6-17 gldL) | X | | | | | | | | | |
| Concomitant Medications | | X | X | X | X | X | | | | |
| Hospital Discharge | | | | | | | X | | | |
| Surgical Procedures | | X | X | X | X | X | X | | | |
| GOS-E | | | | | | | X | X | X | |
| AE (only SAEs after Day 5/Discharge) | | X | X | X | X | X | X | X | X | |
| End of Study | | | | | | | | | | X |

## 11.2 **Timing of Evaluations**

Extensive data will be collected in this clinical trial. Data collection is grouped in the following three sections. *See the accompanying SDMC application regarding NIH TBI common data elements.*

1. ***Screening and Enrollment***
   a. ***Baseline:*** The data collected during the Baseline phase of the trial is used to validate eligibility for enrollment into the trial, including, but not limited to, the inclusion/exclusion criteria. Additionally, demographic information and a medical history are collected to identify pre-existing conditions and other information that may prove to be relevant to later treatment decisions. Information related to the accident (e.g., mechanism of injury, medications and fluids administered, transport mode) also is collected to ensure that all relevant information is available for assessments of the patients and their injuries. If a patient is not randomized, the reason is captured on the Screen Failure Log.
   *b.* ***IMPACT Prediction Data:*** *Specific data to predict outcome will be collected on admission; age, motor score, pupils, CT classification, tSAH on CT, epidural mass on CT, hypoxia (SpO2 < 90%), hypotension (systolic BP < 90), glucose, and hemoglobin.*
   c. ***Consent:*** A written, signed, and dated informed consent document is required for this trial and will provide documentation of the date and time of the LAR's agreement to allow the patient to be a participant in the trial.
   d. ***CT scans:*** The Baseline CT scan will be sent to the HCMC for review.

e. ***Prognostic Scoring:*** The Abbreviated Injury Score (AIS), Injury Severity Score (ISS), and the Revised Trauma Score are collected to allow quantitative and consistent characterization of associated injuries. **(Table 2)**.

2. ***Treatment (Randomization/Day 1 through Discharge)***
   a. ***Treatment:*** Data are collected to document all treatments, including ICP and CPP management, nutrition, and pentobarbital-induced coma.
   b. ***Monitoring:*** Records ICP and Licox monitor and insertion procedures for the first 5 days post injury. Records ICP and brain tissue PO2 for the first 5 days post injury.
   c. ***Therapeutic Intensity Level Score:*** Documents the level of therapies used to control ICP and will be tracked for the first 5 days post injury (**Table 3**).
   d. ***Surgical Procedures:*** All surgical procedures performed until Day 5 or Discharge (whichever occurs first) are documented in the database.

**3.** ***Follow up (Discharge through End of Study)***
   a. ***Adverse Events:*** All AEs will be recorded through 5 days following the last treatment or discharge (whichever occurs first). All SAEs will be recorded through the end of study.
   b. ***Outcome/GOS:*** The GOS-E score will be obtained at 3 and 6 months by telephone interview by trained registered nurse site coordinators (SC).

### 11.3 Off-Intervention Requirements

All subjects are followed using the intent-to-treat (ITT) principle. Thus, for all subjects, follow-up procedures will be performed according to the standard schedule. After the final intervention, the subject is monitored for all AEs for an additional five days or the day of hospital discharge, (if sooner), and SAEs until the end of the study. The best standard of care applies to all subjects.

### *11.4 Outcome Evaluations*

*The International Mission for Prognosis and Analysis of Clinical Trials (IMPACT) in TBI funded by NIH has developed a prognostic model as a means of risk adjustment and outcome prediction for use in trial design and analysis (Steyerberg 2008). Prospectively collected individual patient data were analyzed from 11 studies of severe TBI. It was determined that the strongest predictors of outcome were age, motor score, pupillary reactivity and CT characteristics. The predictive performance could be improved if secondary insults (hypotension and hypoxia) and laboratory parameters (glucose and hemoglobin) were considered. External validation confirmed that the discriminative ability of the model was adequate (AUC 0.80). Further validation of this prognostic tool has been carried out at other centers (Lingsma 2013, Panczykowski 2012, Roozenbeek 2012). Following resuscitation, the clinical, CT, secondary insults, and laboratory parameters will be recorded and used in the longitudinal modeling of the HOBIT trial. In addition, 30-day mortality will be included. At 3 and 6 months a structured interview for the GOS-E will be carried out by trained interviewers who are not part of the treatment team and are blinded to the treatment paradigm or control group the patient was assigned to (Weir 2012, Wilson 1998).*

*The GOS-E reflects disability and handicap rather than impairment; that is, it focuses on how the injury has effected functioning in major areas of life rather than on the particular deficits and symptoms caused by the injury (Wilson 1998). It is of particular value in allowing the outcome of different groups of patients to be compared in a simple and easily interpreted fashion (Narayan 2002, Choi 2001). It has been widely adopted as a measure of outcome for clinical trials. The advantages of the GOS-E remain its simplicity, wide recognition, and the fact that differences in disability are clearly meaningful. The GOS shows a consistent relationship with other measures including subjective reports of health outcome. It remains a useful overall summary assessment of outcome of*

*head injury (Wilson 1998). Sliding dichotomy methodology takes into consideration the severity of the initial injury when determining a favorable outcome.*

# 12 MANAGEMENT OF ADVERSE EXPERIENCES

## 12.1 Definition of Adverse Events and Serious Adverse Events

12.1.1 ***Adverse Event Definition.*** An AE is any symptom, sign, illness, or experience which develops or worsens during the course of the study, whether or not the event is considered related to the study treatment.

Some examples of AEs are:

- A change, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition (for purposes of the trial, we will record only pre-existing conditions that worsen in severity after randomization).
- Deterioration in the subject's condition due to the subject's primary disease or a pre-existing condition.
- Development of any intercurrent illness during the study.
- Development of symptoms which may or may not be related to the treatment.
- Appearance of abnormal laboratory results or significant shifts from baseline, that may still be within the reference ranges, following treatment, and that the Investigator considers to be clinically significant.

## 12.2 Other Adverse Events

Each AE is a unique representation of a specific event used for medical documentation and scientific analysis. AEs encountered during the time of intervention plus an additional five days will be recorded. SAEs will be reported from randomization through the end of the 6-month study visit. Specific clarifications for reporting other events are provided below.

12.2.1. ***Pre-existing medical conditions or unchanged, chronic medical conditions.*** Pre-existing medical conditions or unchanged, chronic medical conditions consistent with natural disease progression are NOT considered AEs and should not be recorded on AE case report forms (CRF). These medical conditions should be adequately documented on the medical history and/or physical examination CRFs. In the HOBIT Trial, any medical condition not present prior to consent and randomization but that emerge after randomization are considered AEs. All medical conditions present upon arrival to the hospital and prior to randomization are considered pre-existing conditions and should be recorded on the medical history CRF.

12.2.2. ***Exacerbation of Pre-existing medical conditions.*** A pre-existing medical condition (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character is considered an adverse event and reported through the time of intervention plus an additional five days or date of hospital discharge (if sooner). If the judgment is that it is a SAE, it is reported through the end of the 6-month study visit.

All AEs will be recorded during the time of intervention plus an additional five days or date of hospital discharge (if sooner). Investigators should define AEs and grade their severity according to the Common Terminology Criteria for Adverse Events. Adverse events will be submitted online through the SDMC database and categorized by Med DRA.

## 12.3 **Serious Adverse Events**

### 12.3.1 **Serious Adverse Event Definition**

A SAE is defined as any AE that occurs during the course of the trial that results in any of the following outcomes:

- death;
- a life-threatening adverse experience;
- prolongation of existing hospitalization or inpatient hospitalization subsequent to initial hospital discharge; or
- a persistent or significant disability/incapacity

12.3.2 **Serious Adverse Events.** *Particular attention will be paid to potential complications of HBO2 treatment as listed below.* Patients with severe TBI have an average of 3 critical complications per patient. This subpopulation of the most severely injured patients has a mortality rate of 40%.

- Subcutaneous emphysema
- Pneumothorax
- Ruptured tympanic membrane
- Signs of pulmonary dysfunction, including FiO2 $\geq$ 60 to maintain partial pressure of arterial oxygen (PaO2) levels > 90 mmHg, and PEEP > 10 cm of water to maintain PaO2 levels > 80 mmHg
- Pneumonia
- Adult Respiratory Distress Syndrome
- Critical decreased CPP (< 50 mmHg)
- Hypotension (mean arterial pressure [MAP] < 70 mmHg)
- Seizures

An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include (but are not limited to): an intracerebral hematoma secondary to ventriculostomy insertion which requires evacuation or a pneumothorax requiring a chest tube caused by an HBO2 treatment.

This category also includes any event the clinical site PI or IMM judges to be serious or which would suggest a significant hazard, contraindication, side effect or precaution.

12.3.3 ***Reporting Serious Adverse Events.*** Reports of SAEs, as defined above, require submission to the WebDCU™ within 24 hours of the site personnel awareness of the event, whether or not the clinical site PI believes that the experience is related to the study treatment or an expected event. Additionally, study personnel will evaluate subjects daily for the presence of SAEs while in the hospital and subsequently at each telephone communication and follow up. SAEs will be reported and recorded throughout the course of the subject's participation in the trial (6 months). The IMM will be responsible for reviewing and coding AEs and SAEs prior to being forwarded to the MSM. The IMM will also assist the PI, CPC and SDMC in monitoring protocol compliance.

The external MSM conducts independent blinded reviews of all SAEs entered into the WebDCU™. Should the IMM or MSM need additional subject data to conduct the review, those data may be accessed on the WebDCU™. The MSM also may contact the site personnel for

more information or discussion. The MSM submits their opinion on whether the AE was a) serious, b) unexpected, or c) related to the study treatment within 72 hours of notification of the SAE. Any MSM report that identifies a possible relationship to the study treatment will be sent immediately to the HOBIT trial PI and the project manager (PM). The determination of a probable or possible relationship to the HBO2 treatment will be discussed with the EC and the NINDS liaison to the DSMB to determine what, if any, action should be taken with regard to continuation of the trial. Following that determination, the PM will distribute all appropriate information to the clinical site PIs and study coordinators. The PI at each participating center is responsible for ensuring appropriate reporting or safety events to their individual IRB according to the procedures and requirements established by that IRB.

Should there be a disagreement between the investigator and the MSM regarding the nature of the SAE, the SAE will be reviewed by the second MSM, the MSM not conducting the original review, who will act as arbiter.

12.3.4 ***Follow-Up Reporting of Serious Adverse Events.*** After the submission of the initial SAE (and possible safety report), the clinical site staff is responsible for obtaining any follow-up information about the SAE. All follow-up information should be actively sought by the clinical site staff and must be submitted to the WebDCU™ as soon as the information becomes available. The PM also distributes information regarding follow up reports of serious, unexpected, and adverse events to the DSMB (through the NINDS DSMB Liaison), and the clinical site PIs and SCs. As with initial reports, each clinical site PI is responsible for reporting to their individual clinical site IRB per local requirements.

## 13 STATISTICAL CONSIDERATIONS

***13.0 Background.*** *This statistical analysis plan (SAP) is for the HOBIT trial and describes it as a phase II clinical trial adaptive design for selecting the combination of hyperbaric oxygen (hyperoxia) treatment dose parameters - pressure and intervening normobaric hyperoxia [NBH]) that provides the greatest improvement in the rate of good neurological outcome versus standard care for subjects with severe traumatic brain injury (TBI). A second goal of this phase II trial is to determine if there is any factor combination of hyperoxia treatment that has at least a 50% probability of demonstrating improvement in the rate of good neurological outcome versus a control (i.e. standard care) in a subsequent phase III confirmatory trial, assuming to be 500 in the control and 500 in the novel arms (Gajewski 2016).*

### *13.1 Treatment Arms*

*There are eight treatment arms in the trial:*

| | *Arm* | *Dose (Oxygen Toxicity Units, $\nu_a * 100$)* |
|---|---|---|
| *1.* | *Control (1.0 ATA)* | *0* |
| *2.* | *1.5 ATA* | *260* |
| *3.* | *2 ATA* | *416* |
| *4.* | *NBH (100% FiO2 at 1.0 ATA)* | *540* |
| *5.* | *2.5 ATA* | *592* |
| *6.* | *1.5 ATA+NBH* | *620* |
| *7.* | *2 ATA+NBH* | *776* |
| *8.* | *2.5 ATA+NBH* | *952* |

*We label the control arm as a = 1, and the experimental arms as a = 2, 3, 4, 5, 6, 7, and 8 respectively. $\nu_a$ is the dose of that arm in 100 Oxygen Toxicity Units and is used in the normal dynamic linear model.*

***13.2 Primary Endpoint.*** *The primary endpoint is the six-month GOS-E response (success or failure). Additionally each patient will have earlier, possibly associated outcome of 1-day, 1-month, and 3-month predictions of GOS-E response. We label the six-month GOS-E response as $Y_6$. The one-day, 1-month, and 3-month prediction response values are $Y_0$, $Y_1$, and $Y_3$, respectively.*

***13.3 Primary Analysis.*** *The primary analysis is of the six-month sliding dichotomized GOS-E response. The primary analysis will be that a treatment arm is superior to the control arm, meaning that the rate of response with GOS-E is greater for one experimental arm compared to the control arm. The final analysis will also identify the best treatment arm to advance to a future Phase III trial for* ***confirmation of superiority to the control arm****. Specifically, the currently proposed Phase II trial will be considered conclusive if one of the three following cases occur:*

1. *Early Success: If at any interim analysis the most likely arm has at least a 0.935 posterior probability of being better than control.*
2. *End of Enrollment Success: If at the conclusion of accrual, the most likely arm has at least a 0.9 posterior probability of being better than control and this same best arm has at least a 0.5 posterior probability of leading to a successful Phase III trial. Minimum subjects enrolled before the study can stop for early success is 100.*
3. *Early Futility: If at any interim analysis the most likely arm has at most a 0.5 posterior probability of being better than control. Minimum subjects enrolled before the study can stop for early futility is 53.*

***Future Phase III trial.*** *Phase II information will be used to predict the probability of a successful Phase III clinical trial (equally randomized to usual care or novel treatment) to confirm the efficacy of novel treatment to increase response and confirm the safety of treating severe TBI with optimal hyperoxia compared to usual care. The primary outcome for the Phase III trial will be the same as in Phase II (sliding dichotomized GOS-E at 6 months). The primary analysis in Phase III investigates, with two sample proportions test (chi-square test), whether there is a simple difference between usual care and novel treatment. The sample size for Phase III is assumed to be 500 in control and 500 in the novel treatment (total n=1000), and alpha =.05 2-tailed).*

***13.4 Analysis Populations.*** *The following subject groups or analysis populations. We will use the Intent-to-treat patient population (ITT). The ITT patient population will include all patients randomized, where patients will be classified by the group in which they are randomized, regardless of the treatment received.*

***13.5 Adaptive Design.*** *The design is a Phase II adaptive design. The purpose of the trial is to explore the different active treatment arms for relative efficacy and comparison to the control arm. The trial will utilize response adaptive randomization to favor the better performing experimental arms. If there is at least one experimental treatment arm promising enough it will advance to a Phase III trial and be compared for superiority to the control arm.*

***Phase II trial:***

1) *Burn-in Phase: An initial burn-in period of 53 subjects is used in which these patients are enrolled in a fixed randomization to the control and each of the experimental arms. A ratio of 11:6:6:6:6:6:6:6 will be used for the burn-in period.*
2) *Response Adaptive Randomization Phase: After the initial burn-in period response adaptive randomization will be utilized. A vector of probabilities, $\mathbf{q}=(q_2, q_3, q_4, q_5, q_6, q_7, q_8)$, is created for randomizing to the experimental arms. A constant proportion of 20% of patients will be enrolled to the control arm through Phase II. Interim analyses will take place quarterly to adjust the randomization probabilities based on the current data. This means that since the interim analyses will be done quarterly and so 21 new patients are enrolled on average. The probabilities will be set to be proportional to the "information" in each arm. The "information" is the square root of the probability each experimental arm is the maximally effective treatment arm multiplied by the variance of the posterior response divided by the number of patients currently enrolled plus one.*
3) *The final analysis will be conducted after all subjects have completed six-month GOS-E response.*

***2.0 Statistical Modeling.*** *This section describes the statistical modeling used in the adaptive design and the primary analysis. The modeling is Bayesian in nature.*

***2.1 Dose-Response Model for Six-Month GOS-E Response.*** *The primary outcome is six-month sliding dichotomized GOS-E response. We label the observations of the six-month GOS-E response for subject i, at the six-month visit as $Y_{i,6}$. We model the six-month primary outcomes as Bernoulli distributed. The model is a normal dynamic linear model:*

$$[Y_{i,6}] \sim \text{Bernoulli}(\theta_{a_i}),$$

*where $a_i$ is the treatment arm for subject i.*

*We label the six-month GOS-E response for arm a as $\theta_a$. Based on prior studies, it is expected GOS-E response for control group and novel treatment have the following prior distributions:*

$$\text{logit}(\theta_1) \sim N(-.41, .75^2), \text{ the control arm (a=1),}$$

$$\text{logit}(\theta_a) \sim N(\theta_{a-1}, \tau^2_{a-1}), \text{ novel treatments a=2,3,4,…,8,}$$

$$\tau^2_{a-1} = \tau^2(v_a - v_{a-1}), \text{ and } \tau^2 \sim IG\left(\frac{1}{2}, \frac{1}{2}\right).$$

*According to the previous clinical trials with the same endpoint, the control arm's prior on the response scale ($\theta_1$) has a median of 0.40. If simulated data is fitted to a Beta distribution, the control arm's prior is equivalent to eight patients i.e. $\alpha_0+\beta_0 \approx 8$, where $\alpha_0$ and $\beta_0$ are Beta parameters.*

***2.2 Longitudinal Model.*** *At each interim analysis there will be subjects who could have complete or incomplete information. Some subjects will have complete information on their six-month observation, $Y_{i,6}$. These subjects may also have their interim value, $Y_{i,0}$, $Y_{i,1}$, and/or $Y_{i,3}$. There will be subjects with interim observations response, but no six-month value. There will be subjects with no observations.*

*We utilize the information from subjects with incomplete information to the extent that the interim values are predictive of the final six-month values. A Bayesian model is built to learn from the*

*accruing information (those subjects with complete six-month data) in the early response values to the final endpoint of six-month response.*

*Estimate transition probabilities from outcome at early time point to final outcome. The number of transitions to final outcome given early outcome is distributed as Binomial. Let p21 and p22 be conditional on a patient showing early response, the respective final probabilities of response and not responsive. For these we use a Beta prior on transition probabilities, (p21,p22)~Beta(2,1). Similarly for a patient that shows no response early, the final prior probabilities are (p31,p32)~Beta(1,2). These are fairly diffuse, each having a prior sample size equivalent to 3 patients. This allows the model to learn as we go along in this trial and does not heavily rely on previous information.*

***2.3 Bayesian Quantities.*** *The following Bayesian quantities are calculated at each interim analysis. These quantities are used in the adaptive design.*

*2.3.1 Most Likely Maximum Effective Duration. From the joint posterior distribution the posterior probability that each arm, a=2,3,4,….,8 is the maximally effective arm,* $P_a^{\max}$*, is calculated. The arm with the largest* $P_a^{\max}$ *is labeled the most likely maximum effective novel treatment.*

*2.3.2 Posterior Variance. The posterior mean and variance for each GOS-E response rate is calculated. We label* $V(\theta_a)$ *as the posterior variance of the parameter* $\theta_a$*.*

*2.3.3 Posterior probability superior to the control. For GOS-E response rate the posterior probability that each arm is superior (larger response rate) to the control arm is calculated:*

$$Pr(\theta_a > \theta_1 | data), \text{ where } a=2,3,4,\ldots,8.$$

*Each of these Bayesian quantities are calculated at each interim analysis point. Each of these quantities are calculated using the data from all subjects in the trial—those with complete data and those with interim data.*

*2.3.3 Posterior predictive probability phase III success. Taking the maximum arm from Phase II trial simulations we calculated the posterior predictive probability whether there is a >50% probability of hyperbaric treatment demonstrating improvement in the rate of good neurological outcome versus placebo in a subsequent Phase III confirmatory trial.*

***2.4 Adaptive Randomization.*** *During the defined burn-in period (53 subjects) the allocation is set at 11:6:6:6:6:6:6:6 for arms 1,2,3,…..,8, respectively. During the adaptive allocation in Phase II randomization will be used in which the allocation probabilities are updated monthly to favor those durations most likely to be the maximum effective treatment arm.*

*The specification of the vector of probabilities for randomization is defined in this section. The randomization vector is created by selecting a vector based on the posterior distribution of the GOS-E response for each arm.*

*Let the number of subjects enrolled in arm a be* $n_a$*. The goal of the adaptive randomization is to allocate subjects to the arms most likely to be the maximum effective arm. In addition, the goal is to learn how good the effective maximum arm is relative to the control arm.*

*A component, labelled as $V_a$, is constructed for each arm. Set $V_1$=1, assuring 1/5 probability for control arm throughout the trial. The component for arms a=2,3,4,…,8 is $V_a=4\left(\frac{P_a^{max}Var(\theta a)}{n_a+1}\right)^{1/2} / \left\{\sum_{a=2}^{8}\left(\frac{P_a^{max}Var(\theta a)}{n_a+1}\right)^{1/2}\right\}$ for a=2,3,4,…8. The randomization vector, **q**, is set as $q_a=V_a/5$ for a=1,2,3,4…,8.*

***3. Software and Computations.*** *Computations were performed using software: Fixed and Adaptive Clinical Trial Simulator (FACTS) (Berry 2010). FACTS is a software program designed to rapidly design, compare, and simulate both fixed and adaptive trial designs. It is built on compiled low-level languages such as Fortran and C++, it is very fast. The simulations take into account all of the testing that is done at each of the interim analysis and are accounted and tallied in the chances of stopping early or late. The scenario where the effect of novel treatment is none (see below) is where we tally the false positives under the null hypothesis which is the Type I error. We changed the early and late stopping rules for success to achieve an acceptable Type I error rate of approximately 20%.*

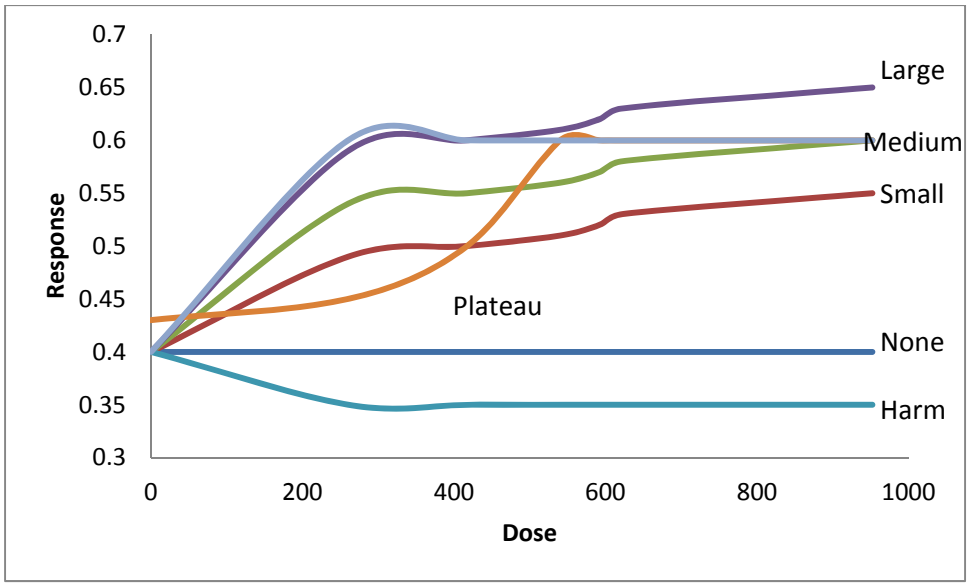
***4. Operating Characteristics.*** *In this section we summarize the results of several simulation cases and an additional scenario of a null scenario in order to ensure type I error control of the design. For each of the cases 1,000 trials are simulated. We present the results as a function of the final six-month GOS-E response for each of the arms.*

*For all simulations in this section we assume an accrual rate of 1.6 subjects per week. No drop outs are assumed.*

*Several cases are presented in Table 1 (for longitudinal assumptions see Appendix H). The value in each cell is the GOS-E response at six-months. The first case is referred to as the null hypothesis as each of the arms have identical GOS-E responses—the novel treatment has no effect on GOS-E response relative to the control arm. The remaining six cases explore scenarios with different GOS-E responses for the experimental arms, including one case where harm is exhibited. The six cases involved are small, medium, and large increases as well as plateau and flat cases.*

| Case | Control | 1.5 ATA | 2.0 ATA | NBH (100% O2 at 1.0 ATA) | 2.5 ATA | 1.5 ATA + NBH | 2.0 ATA + NBH | 2.5 ATA + NBH |
|---|---|---|---|---|---|---|---|---|
| 1. None | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 |
| 2. Small | 0.4 | 0.49 | 0.5 | 0.51 | 0.52 | 0.53 | 0.54 | 0.55 |
| 3. Medium | 0.4 | 0.54 | 0.55 | 0.56 | 0.57 | 0.58 | 0.59 | 0.60 |
| 4. Large | 0.4 | 0.59 | 0.60 | 0.61 | 0.62 | 0.63 | 0.64 | 0.65 |
| 5. Harm | 0.4 | 0.35 | 0.35 | 0.35 | 0.35 | 0.35 | 0.35 | 0.35 |
| 6. Plateau | 0.43 | 0.45 | 0.5 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 |
| 7. Flat | 0.4 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 |

*Table 1: The seven cases used to evaluate the trial design. For each treatment arm, the six-month GOS-E response is reported.*




**4.1** ***Results for Cases.*** *We performed seven sets of trial simulations based on the various cases of response to calculate the trial operating characteristics, i.e. power, futility probability, sample size, duration, and subject allocation, which are presented in Table 2. The first four cases range from no effect (null), to large treatment effect. We could clearly see an increase in power (starting with a 19% type I error rate) but a decrease in futility rates as the effect increases. Because the null trial has a higher chance to stop for futility, the balance switches in a higher probability to stop for success as the benefit moves to large. Both the sample size and duration increase from null hypothesis to medium treatment effect then go down in large treatment effect. The fifth case has explored characteristics, including the futility with a high rate, of the harmful treatment effect. The plateau and flat cases each exhibits strong power, small in size, fast in duration, and appropriate percentage in the top three of the arms. If the accrual is much slower than anticipated, say 1.2 patients/week, instead of 1.6, then we very slight improvement in the power, futility, size and percentage in top three arms. The only noticeable change is that the trial will take longer to finish but still within three years from first accrued patient to final endpoint (Table 3). In the expected accrual case we also checked to see how the design would perform if in the unlikely case that there ended up being no relationship between early and late responses in the longitudinal model (Table 4. Then there is a slight drop in power but nothing alarming, for example in the large case the power drops from 0.97 to 0.94. We also investigated taking out the early stopping rule. While there is an increase in the percentage of patients in the top 3 arms, the power is not much larger but with larger sample size and the trial taking longer. Of note, the estimated sample size of a fixed trial is 325 and would give similar power but would be substantially larger.*

| Case | Power (best arm + Phase III Success) | Futility Prob. | Size (n) | Duration (wks) | %n top 3 arms |
|---|---|---|---|---|---|
| 1. None | 0.19 | 0.53 | 135 | 97 | 36% |
| 2. Small | 0.76 | 0.11 | 152 | 118 | 37% |
| 3. Medium | 0.91 | 0.03 | 142 | 113 | 37% |
| 4. Large | 0.97 | 0.02 | 129 | 106 | 37% |
| 5. Harm | 0.07 | 0.72 | 115 | 80 | 35% |
| 6. Plateau | 0.87 | 0.07 | 136 | 109 | 39% |
| 7. Flat | 0.93 | 0.02 | 136 | 110 | 36% |

Table 2: Simulated trial operating characteristics, accrual is as expected **1.6 patient/week.**

| Case | Power (best arm + Phase III Success) | Futility Prob. | Size (n) | Duration (wks) | %n top 3 arms |
|---|---|---|---|---|---|
| 1. None | 0.20 | 0.52 | 135 | **126** | 36% |
| 2. Small | 0.79 | 0.10 | 143 | **143** | 38% |
| 3. Medium | 0.89 | 0.05 | 133 | **136** | 37% |
| 4. Large | 0.97 | 0.01 | 124 | **129** | 37% |
| 5. Harm | 0.07 | 0.75 | 112 | **100** | 35% |
| 6. Plateau | 0.90 | 0.06 | 132 | **134** | 40% |
| 7. Flat | 0.94 | 0.02 | 129 | **132** | 36% |

Table 3: Simulated trial operating characteristics, accrual is slow **1.2 patient/week.**

| Case | Power (best arm + Phase III Success) | Futility Prob. | Size (n) | Duration (wks) | %n top 3 arms |
|---|---|---|---|---|---|
| 1. None | 0.21 | 0.56 | 134 | 95 | 36% |
| 2. Small | 0.71 | 0.15 | 155 | 119 | 37% |
| 3. Medium | 0.86 | 0.09 | 146 | 115 | 37% |
| 4. Large | 0.94 | 0.05 | 138 | 111 | 37% |
| 5. Harm | 0.06 | 0.76 | 114 | 78 | 36% |
| 6. Plateau | 0.85 | 0.11 | 143 | 112 | 39% |
| 7. Flat | 0.91 | 0.06 | 142 | 112 | 36% |

*Table 4: Simulated trial operating characteristics, accrual is as expected **1.6 patient/week, but predictive power of longitudinal model is weak.***

| Case | Power (best arm + Phase III Success) | Futility Prob. | Size (n) | Duration (wks) | %n top 3 arms |
|---|---|---|---|---|---|
| 1. None | 0.20 | 0.53 | 141 | 101 | 36% |
| 2. Small | 0.79 | 0.11 | 188 | 140 | 38% |
| 3. Medium | 0.92 | 0.03 | 196 | 148 | 38% |
| 4. Large | 0.97 | 0.02 | 198 | 149 | 38% |
| 5. Harm | 0.08 | 0.72 | 117 | 81 | 35% |
| 6. Plateau | 0.88 | 0.07 | 190 | 143 | 42% |
| 7. Flat | 0.94 | 0.02 | 197 | 148 | 36% |

*Table 5: Simulated trial operating characteristics, accrual is as expected **1.6 patient/week, but no early success.***

***4.2. Secondary Aims Analysis.*** *We will perform a follow-up heterogenous treatment effect by using the final data to use the normal dynamic linear model to identify optimal dose whether or not patients undergo TBI-related surgery. This study, in addition to identifying the optimal dose, offers the opportunity to explore the treatment effect in other important outcome domains using ICP, TIL scores and brain tissue PO2. These analyses will allow us to further support a go/no-go decision regarding a subsequent definitive efficacy trial. Based on our previous work, we anticipate brain tissue PO2 would have better power than ICP (Rockswold 2010, Rockswold 2013). Additionally, (1) the therapeutic intensity level (TIL) scores for controlling intracranial pressure (ICP) in hyperoxia-treated patients will be compared to controls; and (2) in centers utilizing Licox brain tissue PO2 monitoring, the level and duration of brain tissue hypoxia (brain tissue PO2 < 20 mmHg) in hyperoxia-treated groups versus control will be analyzed. Both of*

*these analyses will be modeled using two continuous versions of the normal dynamic linear model.*

13.5.0 **Safety analysis**

13.5.1 **Mortality at *30 days and* at 3 and 6 months**

For the final analysis of the primary safety outcome, Bayesian survival curves will be generated for deaths from any cause within *30* days and at 3 and 6 months.

13.5.3.2 **Safety Monitoring**

The review of safety data will focus on the following AEs, SAEs potentially caused by HBO2 treatment:

- Subcutaneous emphysema
- Pneumothorax
- Ruptured tympanic membrane
- Signs of pulmonary dysfunction, including FiO2 $\geq$ 60 to maintain PaO2 levels > 90 mmHg, and PEEP > 10 cm of water to maintain PaO2 levels > 80 mmHg
- Pneumonia
- Adult Respiratory Distress Syndrome
- Critical decreased CPP (< 50 mmHg)
- Hypotension (mean arterial pressure [MAP] < 70 mmHg)
- Seizures

All AEs and SAEs are summarized by preferred term and associated system-organ class according to the MedDRA adverse reaction dictionary and by treatment group in terms of frequency of the event, number of subjects having the event, time relative to randomization, severity, and relatedness to the treatment. Accumulative incidences of the specific SAEs related to HBO2, as well as all SAEs, will be compared across arms using a main effects model. Additional evaluation of safety events will be conducted adjusting for relative baseline co-variants, such as age at baseline and GCS score.

13.5.2 **Handling of Missing Data**

Under the ITT principle, all patients who are randomized are included in the analysis. Therefore, missing data, especially in the outcome measure, can be problematic. Extensive efforts will be made to keep all missing data, particularly the 6 month GOS assessment, to a minimum and minimize loss to follow-up. However, it is likely that there will be some missing data. As our primary approach to handling missing data, we will use the multiple imputation method. This approach incorporates uncertainty in the imputed value and so is less biased than other approaches. A distribution for the primary outcome will be derived from a logistic regression that accounts for clinically relevant baseline covariates (age, gender, baseline GCS score, Marshall scores 3 and 4 versus 5 and 6), treatment, and some post-treatment data, and a random sample from this distribution is used to impute values for missing primary outcomes. Multiple sample data sets with complete 6 month GOS scores will be generated, and each of the data sets will be analyzed as described above. The results for each sample are combined and analyzed to produce valid statistical inference about the treatment effect. As a sensitivity analysis, we will impute missing primary outcome data 1) using only those with complete GOS scores at 6 months and 2) assuming missing outcomes to be unfavorable. If the treatment effect is robust, we expect analysis using these imputation methods will yield similar inferences, particularly if the missing data are minimal (<5%). We plan to implement the multiple imputation method using the Bayesian longitudinal model.

Since this study is an ITT trial, data that have been collected up to the time of withdrawal of consent will remain in the database; however, no additional data will be collected from that subject. It would be unusual for a study subject's participation in the study to be terminated by a site study team member unless it was in the interests of subject safety or there was a loss of funding for the study.

## 14 ***DATA COLLECTIONS AND SITE MONITORING***

### 14.1 **Records to be Kept**

In June 2005, Federal law extended the statute of limitations to six years to bring forward an allegation of research misconduct. In response to this extension, research records must be retained for a sufficient period to investigate an allegation of research misconduct - - a minimum period of six years.

Additionally, existing Federal regulations [56 CFR 56.115(b)] require that IRB records be retained for at least 3 years after completion of the research. All records must be accessible for inspection and copying by authorized representatives of HHS and Food and Drug Administration at reasonable times and in a reasonable manner. At the end of the three year period, the IRB records may be boxed, labeled and sent to central storage for an additional 3-10 years. A log of stored records is maintained in the IRB office for retrieval if files are needed for audit or other purposes.

An agreement must be in place between the clinical site PI and the PI regarding records that may be destroyed.

Records will be maintained in a de-identified manner in a locked location to ensure confidentiality.

### 14.2 **Role of Data Management**

14.2.1 ***Data Management Overview.*** Data management will be handled by the SDMC, which is housed in the Division of Biostatistics and Epidemiology in the Department of Medicine at the Medical University of South Carolina. All activities will be conducted in coordination with the multiple PIs, the sites, and the EC. The data validation procedure will be implemented in two stages. First, the automated data checks will flag items that fail a rule, and the rule violation message will appear on the data entry screen at the time of data entry. The site coordinator (SC) at a site will see these rule violations and will be requested to address it. His/her choices are to: (1) correct the entry immediately; (2) correct the entry at a later time; or (3) if the entered data are confirmed to be correct, dismiss the rule by checking that option provided by the WebDCU™ system. Any changes made to the data will have a full audit trail. Secondly, for some checks that are more complicated, additional consistency checks will be run periodically after data entry occurs at the site. All data items that fail the programmed consistency checks will be queried via the data clarification request (DCR) process initiated by the SDMC data manager (DM).

Site Monitors will also be able to generate DCRs when discrepancies are found during source to database verification. The DCRs will be generated, communicated to the sites, and resolved on the secure study website. In addition to the study database, the SDMC will provide the site staff password protected access to a standard set of web-enabled tools, including subject visit

calendar, subject accrual status, CRF completion status, and outstanding DCR status pertaining to their respective sites.

14.2.2 ***Data Acquisition and Central Study Database.*** The entire study will be conducted using an electronic data acquisition method where all clinical data on enrolled subjects will be data entered (single-keyed) by the site personnel into a web-based data management system, WebDCU™. In order to provide user-friendly and easy-to-navigate interfaces, the WebDCU™ data capture screens are designed based upon individual CRFs. Prior to the start of the trial, the system is validated to ensure the data entry screens mirror the CRFs and that the pre-programmed data rules appropriately detect incorrect data. The data will be managed after data entry via data queries from the SDMC. The latest version of each CRF will be available as a PDF file on the HOBIT Trial WebDCU™ website for use as worksheets and source documents by study personnel. This process facilitates version control of these study related documents, particularly since documents may evolve over the course of the trial. This user friendly web-based database system, developed and validated by the SDMC, will be used for subject randomization, data entry, data validation, project progress monitoring, subject tracking, user customizable report generation and secure data transfer.

14.2.3 ***Core Trial Database.*** The SDMC programmers will maintain the core clinical database. The relational database was developed based on the approved CRFs using Microsoft SQL Server. The study database has extensive consistency checks programmed into the forms (*e.g.,* data type, range and logic checks). During the development of the database, these checks were incorporated into the underlying program to flag potential data entry errors, including missing required data, data out of pre-specified range, and data conflicts and disparities within each CRF and across different CRFs. All validation parameters are outlined in the Data Management Plan maintained by the SDMC.

14.2.4 ***Randomization Module.*** The SDMC developed a web-based Randomization Module that will be used by all authorized site personnel for the purpose of randomizing eligible patients. A study team member will log onto the WebDCU™ HOBIT web-based system using a unique username and confidential password. When a subject is deemed eligible, WebDCU™ will generate a unique subject identification without storing any personal identifying information. The study team member will then enter the required subject information, including GCS, age, and inclusion/exclusion criteria. The computer program will check for accuracy and completeness of this information prior to selecting the treatment assignment to be assigned to that subject. The subject is considered randomized at the time treatment is assigned. An automatic e-mail notification of randomization will be sent to the appropriate parties (e.g., EC members, the NINDS Project Scientist, the CCC, and SDMC staff).

If, under rare circumstances, the web system is not available, the site should follow the emergency randomization procedures outlined in the Manual of Procedures.

14.2.5 ***Reporting Module.*** The WebDCU™ system also has a real-time reporting component that allows authorized users to view protocol specific reports as data listings and in a summary format, overall and by site, at any time during the study via the password protected system. The Reporting Module is developed based on input from the EC and includes reports on enrollment, SAEs, CRF processing, and subject progress. The reports are presented in a manner that protects the integrity of the study. The SDMC will provide the *EC* and authorized study personnel access to a standard set of web-enabled tools on the WebDCU™. These tools allow the authorized research personnel to receive regular updates on accrual status and CRF status of enrolled subjects. Examples of available reports include subject enrollment logs, basic

subject demographics, CRF completion rate and number of data queries outstanding and resolved.

14.2.6 ***Security, Privacy, and Confidentiality.*** The SDMC employs several layers of data protection to ensure data security. The first part of security is physical protection of the hardware systems employed by the SDMC. The facility housing the SDMC hardware is protected 24/7 by multiple layers of security, including electronic building & facility access secured by magnetic locks, onsite-personnel, monitored and recorded closed-circuit television, person-traps, and mandatory identity logging of all outside visitors. By limiting access, ensuring only authorized personnel have access, and tracking all entry, we can ensure this risk is minimal.

The network and system security is ensured by implementing multiple layered firewalls and a network intrusion prevention system for identifying and blocking malicious network activity in real time. Vulnerability scans are also run daily to ensure server and network hardening preventing known application and operating system vulnerabilities. Antiviral, Trojan and worm protection is achieved by using Microsoft Forefront, updated on a daily basis. All communication with the web server and client is encrypted via SSL to make certain network traffic 'sniffing' poses no threat.

14.2.7 ***Audit Trail Function for WebDCU$^{TM}$***. To maintain electronic records in the database as adequate and accurate, WebDCU$^{TM}$ system tracks all changes made to any study patient-related and dynamically managed electronic records. This audit-trail information is created with a computer generated time-stamp and the user name in chronological order, when the original data is modified or deleted.

14.2.8 ***Data Redundancy.*** The Volume Shadow Copy Service is enabled for all SDMC file servers and web servers used in the storage of clinical trial related documents and website files in order to provide a quick recovery solution of lost data. This allows for "point-in-time" copies of all edited files to be maintained in a hidden file space on the server. The copies or "snapshots" of edited files are taken 3 times daily.

14.2.9 ***Backup (Disaster Recovery).*** The databases housed in the WebDCU$^{TM}$ are backed up in two steps. The Microsoft® SQL server maintenance plans are set up to initiate the internal data integrity check up procedures and to produce off-line backup copies of the database prior to IBM® Tivoli Storage Manager (TSM) backup. The TSM then delivers the full data backup to all Data Coordinating Unit (DCU) servers used in the storage of database at daily basis. The TSM completely backups all system files (i.e., system registry, operating system, software, etc) and user data files on the server. In the event of a weather related emergency or other situations where the university implements emergency procedures, the SDMC also begins emergency full backup of all servers and other procedures in accordance with the SDMC's Emergency Operation Standard Operating Procedure (SOP).

## 14.3 Quality Assurance

To ensure monitoring responsibilities are performed to the fullest extent possible, industry experienced independent clinical research associates (CRAs/monitors) will perform on-site data verification for the trial. For the first subject enrolled at any site, 100% of the data will be verified to source documents. For subsequent subjects, a checklist of key outcome and safety data variables requiring source document verification has been developed based on the trial's safety and efficacy endpoints. The check list ensures that a target of no less than 40% of the clinical data submitted to the HOBIT database are verified against source documents at the

performance sites prior to finalization of the database. Of the data on the checklist, the safety and efficacy variables represent approximately half of the data to be verified. The remaining half of source monitored data include: 100% of deaths and 100% of SAEs and all EC-requested source data reviews based on the per-subject evaluation of safety parameters defined in the protocol. All data monitored on site are verified for accuracy and thoroughness using the most appropriate source documents for all subjects.

In addition, 100% of subjects enrolled are monitored for the presence and adequacy of signed informed consent and Health Insurance Portability and Accountability Act documentation.

Additional onsite monitoring verification includes: ongoing evaluation of the adequacy of site facilities and staff, site recruitment, subject randomization, the presence of regulatory documents, and specific review of documents and data as requested by the *EC.* The initial performance monitoring visit to a site takes place after the first subject is enrolled. Thereafter, it is expected that each site will be monitored at least twice a year. Sites are evaluated in an ongoing manner by site monitors and the SDMC staff to determine if there is a need to monitor more frequently or more thoroughly. During the monitoring visit, any omissions and corrections to data submitted to the database are noted and queries are generated by the monitor on site or within 48 hours via the WebDCU™ system.

A close-out monitoring visit by a monitor takes place at the completion of subject enrollment at the performance site. At that visit, the monitor again reviews the presence of a regulatory file and verifies documents for currency and completion as directed by the SDMC staff. Sites are instructed in the record retention of all trial documents. Principal Investigators are directed to close the trial and issue a final report to the IRB. Finally, any additional special considerations for the auditing of any additional safety issues are made during this final monitoring visit.

CRA/monitor training will take place at or prior to the initial Investigators' Meeting. The CRAs/monitors will be included in any re-training meetings that occur during the trial.

## 15 HUMAN SUBJECTS

### 15.1 Institutional Review Board Review and Informed Consent

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB responsible for oversight of the trial at each participating clinical center. A signed consent form will be obtained for every subject. Since subjects in this trial cannot consent for themselves, a LAR, or person with power of attorney, must sign the consent form. 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 LAR, and this fact will be documented in the subject's record. A sample Informed Consent template is attached as **Appendix *F.***

### 15.2 Subject Confidentiality

All CT scans, evaluation forms, reports, and other records required by the HOBIT Trial that leave the site will be identified only by the Study Identification Number (SID) to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using SIDs only. Clinical information will not be released without written permission of the *LAR or the* subject, except as necessary for monitoring by IRB, the NINDS, or the Office of Human Research Protection (OHRP).

### 15.3 **Study Modifications/Discontinuation**

The study may be modified or discontinued at any time by the NINDS, the OHRP, or other government agencies as part of their duties to ensure that research subjects are protected. An individual IRB may discontinue the study at the clinical site it oversees, but the action is limited to that individual site.

## 16 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the EC. The Publication Policy will be fully compliant with the voluntary NIH Public Access Policy mandated by the Consolidated Appropriations Act of 2008 (Division G, Title II, Section 218 of PL 110-161). The EC will follow NIH policies on data-sharing (as described at the site: http://grants2.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm and any updates thereto).

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**Table 1. Diagnostic Categories of Types of Abnormalities Visualized on CT Scanning**

| Category | Definition |
|---|---|
| Diffuse Injury I (no visible pathology) | No visible intracranial pathology seen on CT scan |
| Diffuse Injury II | Cisterns are present with midline shift 0-5 mm and/or:<br>Lesion densities present<br>No high- or mixed-density lesion > 25 cc<br>May include bone fragments and foreign bodies |
| Diffuse Injury III (swelling) | Cisterns compressed or absent with midline shift 0-5 mm, no high- or mixed-density lesion > 25 cc |
| Diffuse Injury IV (shift) | Midline shift > 5 mm, no high- or mixed-density lesion > 25 cc |
| Evacuated mass lesion V | Any lesion surgically evacuated |
| Non-evacuated mass lesion VI | High- or mixed-density lesion > 25 cc, not surgically evacuated |

**Table 2.**

| AIS Score | Injury |
|---|---|
| 1 | Minor |
| 2 | Moderate |
| 3 | Serious |
| 4 | Severe |
| 5 | Critical |
| 6 | Un-survivable |

| ISS Region | Injury Description | AIS | Square Top Three |
|---|---|---|---|
| **Head & Neck** | Cerebral contusion | 3 | 9 |
| **Face** | No injury | 0 | |
| **Chest** | Flail chest | 4 | 16 |
| **Abdomen** | Minor contusion of liver<br>Complex rupture spleen | 2<br>5 | 25 |
| **Extremity** | Fractured femur | 3 | |
| **External** | No injury | 0 | |
| | | **Injury Severity Score:** | **50** |

**Revised Trauma Score[a]**

| GCS | SBP | RR | Coded Value |
|---|---|---|---|
| 13-15 | > 89 | 10-29 | 4 |
| 9-12 | 76-89 | > 29 | 3 |
| 6-8 | 50-75 | 6-9 | 2 |
| 4-5 | 1-49 | 1-5 | 1 |
| 3 | 0 | 0 | 0 |

[a]RTS = 0.9368 $GCS_c$ + 0.7326 $SBP_c$ + 0.2908 $RR_c$ where the substrict c refers to coded

**Table 3. Therapeutic Intensity Level Scale (TILS)**

**TILBasic = TIL Basic**

| | |
|---|---|
| **1. CDE Variable** | TILBasic = TIL Basic; Global summary measure of therapy intensity level for control of intracranial pressure (ICP). |
| **2. CDE Definition** | This summary measure captures a global categorization of therapy intensity over a given period. This may be assessed on a daily basis or represent a single summary measure over the entire ICU period. |
| **3. Recommended instrument for assessment** | Chart review by investigator or trained research assistant. |
| **4. Description of measure** | Categorical measure; unique entry |
| **5. Permissible values** | **TIL 0:** No specific ICP directed therapy<br>**TIL 1 – basic ICU care**<br>- Sedation for ventilator/endotracheal tube tolerance<br>- Volume/vasopressors for non-CNS cause (e.g. sepsis, myocardial injury)<br>- Head up positioning (ventilator bundle)<br>- Normocapnia (PaCO2 ≥ 40mmHg)<br>**TIL 2 – Mild**<br>- Higher levels of sedation<br>- Vasopressors/volume for CPP support<br>- Low dose osmotic therapy<br>- Mild hypocapnia (PaCO2 4.6-5.3 kPa; 35-40 mmHg)<br>- CSF drainage < 120 ml/day (<5 ml/hour)<br>**TIL 3 – Moderate**<br>- Higher doses of osmotic therapy<br>- Moderate hypocapnia (PaCO2 4.0-4.5 kPa; 30-35 mmHg)<br>- Mild hypothermia (> 35oC)<br>- CSF drainage ≥ 120 ml/day (>5 ml/hour)<br>**TIL 4 – Extreme**<br>- Profound hypocapnia (PaCO2 < 4.0 kPa; < 30 mmHg)<br>- Hypothermia < 35 oC<br>- Metabolic suppression for control of ICP<br>- Surgery for refractory ICP (decompression, lobectomy) |
| **6. Classification: Basic/Intermediate/Advanced** | Basic |
| **7. Procedure** | A judgement of the basic TIL for a given period should be recorded by the investigator or a trained research assistant and entered as a single data entry for that period. |
| **8. Comments/Special instructions:**<br>Interpretation of data on ICP is difficult without some reference to the intensity of therapy directed at control of ICP. Therapy Intensity Level can be documented in great detail. The aim of the basic-TIL classification scheme is to broadly categorize treatments into different levels.<br>***Level 0:*** no specific ICP directed therapy<br>***Level 1:*** this category includes any intervention required for general ICU care. This can include sedation. The dose of sedation is not specified, since sedation requirements and specific drug use are known to vary between centers and patients; the requirement is that sedative use in this category is not targeted to control ICP. Similarly, the use of vasoactive drugs (e.g. for sepsis) may vary between centers, but at this level they would not be used to support CPP. The underlying implication is that ICP and compliance are **not** a concern in this group of patients. | |

***Level 2:*** this category includes interventions that are relatively modest – the key issue is that they are targeted to ICP/CPP control. The implication is that ICP and pressure volume relation **are** a concern in this group. Thus, with sedation, dose and drugs may vary but the intention is that they are being used to modulate ICP. Similarly, this category would include the use of vasoactive agents, which are being used to support a CPP target. The use of osmotic agents is included in this category, but only for the control of moderate or transcient elevations of ICP, that respond readily to therapy. Arbitrarily, a threshold over a 24 hour period could be set at 2 gr/kg Mannitol or 0.3 gr/kg Hypertonic saline. For estimating the intensity of hyperosmolar therapy, the total osmolar load of all agents given should be taken into consideration.
***Level 3:*** this level includes most patients who have major problems with ICP/CPP management, but in common clinical practice, are not 'refractory' to common therapies.
***Level 4:*** this level includes therapies that are used in patients with refractory intracranial hypertension. Allocating the use of sedative agents to this level requires that the agent
(typically pentobarbital or thiopental, but sometimes propofol, ethomydate or other agents) is being used with the aim of substantially reducing cerebral oxygen utilization, often with monitoring of brain electrical activity and titration of sedation to burst suppression. Surgery for refractory ICP and hypothermia < 35 oC would always warrant classification at level 4.

***Note***: The TIL Basic only provides a broad, but nevertheless highly relevant, categorization of therapy intensity. It is simple to assess, but a drawback is that it is inherently flawed by subjectivity and regional variations in opinions about what constitutes a more or less intense therapy. For example, CSF drainage is seen as an early intervention in centers who monitor
ICP by means of ventriculostomy, but will constitute a later invention in centers where parenchymal probes are routinely used for ICP monitoring.
The more detailed summary TIL as presented in the intermediate/advanced modules can be collapsed into an approximation of the TIL Basic, according to the following conversion table:

| **TIL Basic** | **Summary score full TIL** |
|---|---|
| TIL 1 | 0-3 |
| TIL 2 | 4-6 |
| TIL 3 | 8-10 |
| TIL 4 | ≥ 11 |

This proposal for conversion/collapsing the full summary TIL into the TIL basic constitutes no more than expert opinion recommendations of the working group and should be subjected to field testing prior to any uncritical use.

**9. Rationale/justification:**
ICP is often regarded as a surrogate endpoint in TBI and considered a surrogate for the intensity of a range of pathophysiological processes. Interpretation of ICP is however not possible without knowledge of the intensity of therapy directed at ICP/CPP control. Modern, neuro-ICU practices have substantially blunted our ability to use ICP as a surrogate marker. It is possible to control ICP by intensifying ICP/CPP therapies, until the system terminally decompensates and intracranial hypertension becomes refractory to therapy. In this context, the intensity of ICP/CPP targeted therapy may be a more sensitive measure of the severity of pathophysiology, and the ability of a novel intervention to modify such pathophysiology.

**Table 4. Indications for HBO2 Reimbursed by Medicare and Commercial Insurance Companies**

- Air or gas embolism
- Carbon monoxide poisoning and carbon monoxide poisoning complicated by cyanide poisoning
- Clostridial myositis and myonecrosis (gas gangrene)
- Crush injury, compartment syndrome, and other acute traumatic ischemias
- Decompression sickness
- Enhanced healing of selected problem wounds
- Exceptional blood loss anemia
- Necrotizing soft tissue infections
- Osteomyelitis (refractory)
- Delayed radiation injury (soft tissue and bony necrosis)
- Skin grafts and flaps (compromised)
- Thermal burns
- Intracranial abscess

*Table 5. Enrolling Site Experience with Emergent HBO2 Treatment*

| *Enrolling Site* | *HBO2 2/47 Availability* | *No. of Annual Intubated/Critical Care HBO2 Treatments* | *Location of HBO2 Chamber Relative to ICU* | *No. of Annual Emergent HBO2 Patients / Treatments* |
|---|---|---|---|---|
| *HCMC* | *Yes* | *94* | *Dedicated elevator 7th → 1st floor* | *411* |
| *Duke* | *Yes* | *15* | *Hallway - 5 mins from ICU* | *379* |
| *University of Utah* | *Yes* | *31* | *Monoplace in ICU* | *250* |
| *University of Maryland* | *Yes* | *110* | *In Shock Trauma Tower with dedicated elevator* | *600* |
| *University of Iowa* | *Yes* | *23* | *Adjacent to ICU and OR* | *105* |
| *Medical College of Wisconsin* | *Yes* | *20* | *5th → 1st floor by dedicated elevator* | *84* |
| *Ohio State University* | *Yes* | *30* | *4th → 1st floor by dedicated elevator* | *110* |
| *University of Kentucky* | *Yes* | *16* | *6th → 1st floor by dedicated elevator* | *64* |
| *University of Pittsburgh* | *Yes* | *10* | *6th → 1st floor by dedicated elevator* | *103* |
| *Mass General Hospital* | *Yes* | *35* | *ICU → HBO via dedicated elevator and indoor bridge to 2nd floor (10 mins)* | *138* |
| *University of Nebraska* | *Yes* | *47* | *1st → 2nd floor via dedicated elevator* | *246* |
| *Hamilton* | *Yes* | *40* | *Adjacent to ICU* | *94* |
| *Loma Linda* | *Yes* | *24* | *2nd → 1st floor by dedicated elevator* | *202* |
| *University of Texas Houston* | *Yes* | *44* | *4th → 2nd floor by dedicated elevator* | *152* |