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

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Strategies to Innovate EmeRgENcy Care Clinical Trials Network (SIREN) Central Institutional Review Board (CIRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the CIRB before the changes are implemented to the study. In addition, all changes to the consent form will be CIRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

PROTOCOL SIGNATURE PAGE

I have read the attached clinical protocol titled Hyperbaric Oxygen in Brain Injury Treatment Trial Version 5, dated April 5th, 2019. My signature assures that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality.

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Principal Investigator's Signature Date of Signature

I have read this protocol and agree that it contains all necessary details for carrying out the study as described.

I will conduct this protocol as outlined herein, including all statements regarding confidentiality. I will make all reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all study information to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the intervention and the study. I understand that the study may be terminated or enrollment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the interests of the study subjects.

I agree to conduct this study in full accordance with all applicable regulations and Good Clinical Practices (GCP).

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Investigator's Signature Date of Signature

ABBREVIATIONS

ABMS	American Board of Medical Specialties
AC	Analytical Center
ADL	Activities of daily living
AE	Adverse Event
AIS	Abbreviated Injury Score
CCC	Clinical Coordinating Center
CFR	Code of Federal Regulations
CIRB	Central Institutional Review Board
CONSORT	Consolidated Standards of Reporting Trials
CPC	Clinical Project Coordinator
CPP	Cerebral perfusion pressure
CRF	Case Report Form
CT	Computerized tomography
DCC	Data Coordinating Center
DM	Data Manager
DNR	Do Not Resuscitate
DSMB	Data and Safety Management Board
EC	Executive Committee
ESC	External Steering Committee
FDA	Food and Drug Administration
FM	Financial manager
GCP	Good Clinical Practices
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
GOSE	Glasgow Outcome Scale Extended
HBO	Hyperbaric oxygen
HCMC	Hennepin County Medical Center
HIPAA	Health Information Portability and Accountability Act
HOBIT	Hyperbaric Oxygen Brain Injury Treatment
ICU	Intensive Care Unit
IDE	Investigational device exemption
IMSM	Independent medical safety monitor
IQR	Internal quality reviewer
ISS	Injury Severity Score
ITT	Intention to treat
LAR	Legally authorized representative
MAP	Mean Arterial Pressure
NBH	Normobaric hyperoxia

NCI	National Cancer Institute
NFPA	National Fire Protection Association
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NINDS	National Institutes of Neurological Disorders and Stroke
OTU	Oxygen toxicity unit
PEEP	Positive end expiratory pressure
PI	Principal Investigator
ProTECT	Progesterone for Traumatic Brain Injury Experimental Clinical Trial
RAR	Response adaptive randomization
SAE	Serious adverse event
SC	Study Coordinators
SCC	Scientific Coordinating Center
TBI	Traumatic brain injury
TIL	Therapeutic intensity level
UHMS	Undersea and Hyperbaric Medical Society

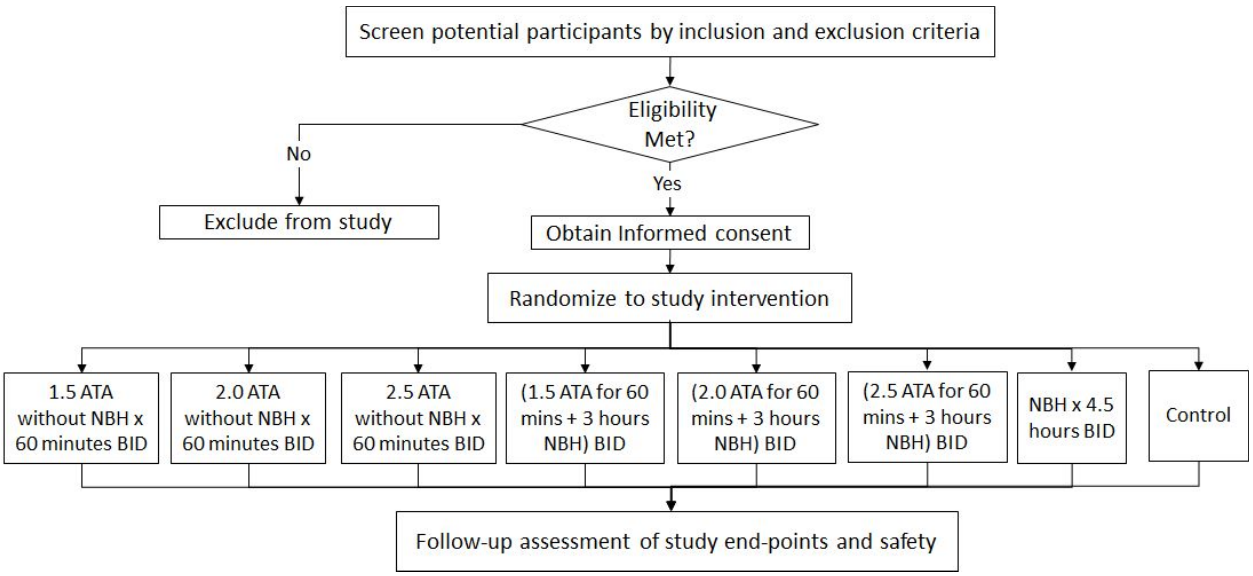
1 Protocol Summary

1.1 Synopsis

Title:	Hyperbaric Oxygen Brain Injury Treatment (HOBIT) Trial: A Multicenter, Randomized, Prospective Phase II Adaptive Clinical Trial Evaluating the Most Effective *Hyperbaric Oxygen* Treatment Paradigm for Severe Traumatic Brain Injury
Study Description:	There continues to be an overarching problem of high mortality and poor outcome for victims of severe traumatic brain injury (TBI). Preclinical and clinical investigations indicate that hyperbaric oxygen (HBO) has a positive impact on reducing brain injury and improving outcomes in severe TBI. By markedly increasing oxygen (O2) delivery to the traumatized brain, HBO can reverse the lack of O2 that precipitates cellular energy failure and subsequent brain cell death. However, prior to a formal phase III definitive efficacy study, important information is required regarding optimizing the HBO treatment schedule to be instituted in terms of pressure, frequency and other parameters. The lungs in severe TBI subjects have frequently been compromised by direct lung injury and/or acquired ventilator pneumonia and are susceptible to O2 toxicity. It is essential to determine the most effective HBO dose schedule without producing O2 toxicity and clinical complications. This proposed adaptive clinical trial is designed to answer these questions and to provide important data to plan a definitive phase III efficacy trial.
Objectives:	**Objective 1**: (Signal of efficacy) To determine, in subjects 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. **Objective 2**: (Dose selection) To select, in subjects with severe TBI, the combination of treatment parameters (pressure +/- 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.
Endpoints:	**Primary Endpoint**. The primary analysis will use the intention to treat (ITT) sample to compare the proportion of favorable outcomes in the 6-month dichotomized, severity adjusted, GOS-E (section 11.1 of the SAP) in each treatment arm to control dose regimen. Favorable outcome for an individual subject is defined according to a sliding dichotomy (Murray, 2005), where the definition of favorable outcome varies according to baseline prognosis. Prognosis will be defined according to the probability of poor outcome predicted by the IMPACT Core Model (Steyerberg EW, 2008); see section 11.1.2.1 of the SAP). The favorable outcome definition

	is more stringent for subjects predicted to do well (i.e. a low probability of poor outcome), as outlined in the Table in Section 9.1. The IMPACT core score will be based on the covariate as known at randomization. The primary endpoint will analyze the GOS-E at 26 weeks; intermediate measurements will be taken at 4, 13 weeks. **Secondary Endpoints**: 1. To analyze the level and duration of intracranial hypertension (> 22 mmHg) in hyperoxia-treated versus control groups. 2. To analyze the therapeutic intensity level (TIL) scores for controlling intracranial pressure (ICP) in hyperoxia-treated subjects compared to controls. 3. At sites utilizing brain tissue PO2 monitoring, analyze the level and duration of brain tissue hypoxia (brain tissue PO2 < 20 mmHg) in HBO-treated groups versus control (van den Brink 2000). 4. To compare the type and rate of serious adverse events (SAEs) between hyperoxia treatment arms and control. 5. To examine the association between peak brain tissue PO2 during hyperbaric treatment and favorable outcome at 6-months (measured by the GOS-E).
Study Population:	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. Subjects with a GCS score of 7 or 8 with a Marshall CT score = 1 are excluded. Subjects with a GCS score of 3 AND bilateral mid-position, nonreactive pupils are excluded because of their grim prognosis and the fact that it is doubtful any treatment could have a neuroprotective effect.
Phase:	II
Description of Study Intervention:	There are eight treatment arms. Participants will be randomized to one of six hyperbaric oxygen (HBO) treatment groups, one normobaric hyperoxia (NBH) treatment group, or one control (no hyperoxia treatment) group. The six hyperbaric oxygen treatment groups are: 1.5 Atmospheres Absolute (ATA) for 60 minutes twice a day; 2.0 ATA for 60 minutes twice a day; 2.5 ATA for 60 minute twice a day; 1.5 ATA for 60 minutes followed by NBH for 3 hours twice a day; 2.0 ATA for 60 minutes with NBH for 3 hours twice a day; 2.5 ATA for 60 minutes with NBH for 3 hours twice a day, and NBH for 4.5 hours twice a day.
Study Duration:	Anticipated 60 months
Participant Duration:	6 months

1.2 Schema



1.3 Data Collection Schedule

Form #	CRF	Baseline	Randomization	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Hospital Discharge	Day 30 +/- 7 days	Day 90 +/- 14 days	Day 180 +/- 21 days	End of Study
N/A	Subject Enrollment	X												
F138	Glasgow Coma Scale	XM		XM	XM	XM	XM	XM	XM					
F101	Inclusion and Exclusion Criteria	XM												
F102	Randomization		X											
F106	Medical History	X												
F274	Pre hospital Events	X												
F286	Pupil Reactivity	X		X	X	X	X	X	X					
F117	Vital Signs	X												
F105	Laboratory Tests	X		X	X	X	X	X	X					
F271	CT Scan	X		X										
F272	CT Scan - Central Reader	X		X										
F501	Hourly Monitoring			XM	XM	XM	XM	XM	XM					
F275	Study Therapy			XRM^{C1}	XRM^{C1}	XRM^{C1}	XRM^{C1}	XRM^{C1}	ORM^{C1}					
F287	Therapy Intensity Level Scale			X	X	X	X	X	X					
F502	Ventilatory Parameters			XM	XM	XM	XM	XM	XM					
F112	Concomitant Medications			X	X	X	X	X	X					
F172	Surgical and Procedural Interventions									X				
F123	Hospital Discharge									XM				
F156	Glasgow Outcome Scale - Extended										XM	XM	XM	
F104	Adverse Event			OR	OR	OR	OR	OR	OR	OR	OR	OR	OR	
F127	MedWatch			XR^{C2}	XR^{C2}	XR^{C2}	XR^{C2}	XR^{C2}	XR^{C2}	XR^{C2}	XR^{C2}	XR^{C2}	XR^{C2}	
F126	End of Study													XM
F269	Abbreviated Injury Scale													X

X = Required
O = Optional
R = Repeatable
C1 = Non control subjects
C2 = MedWatch is required per IMSM

2 Introduction

2.1 Study Rationale

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 subject population was “front-loaded” with subjects who have a relatively good prognosis (Narayan 2002). If one pools the subjects from three large multisite trials, approximately 50% of the subjects 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 subjects had a “diffuse injury” or a Marshall CT score of 2 (Marshall 1991). These subjects had a favorable outcome on the dichotomized Glasgow Outcome Scale (GOS) score in the 70-80% range. However, in the more recently completed Progesterone for Traumatic Brain Injury Experimental Clinical Trial (ProTECT), Subjects with a Marshall CT score of 2 or greater with GCS of 7-8 had favorable outcomes only 55% of the time.

In our phase II clinical trial evaluating HBO in the treatment of severe TBI subjects, 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 Data Coordinating Center (DCC) at the Medical University of South Carolina, it was determined that if all subjects 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 HBO-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 (subjects 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 Glasgow Outcome Scale Extended (GOSE). Although the n is too small to produce statistical significance, the approach strongly suggests that eliminating these less severely injured subjects with a relatively good prognosis in the proposed study will be more likely to demonstrate a beneficial effect of HBO if one exists.

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. Subjects with a GCS score of 7 or 8 with a Marshall CT score of 1 are excluded. Subjects 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 Intensive Care Unit (ICU) compared to adults. Subjects over 65 years old are excluded because they often have increased comorbidities and a higher mortality from severe TBI that would tend to obscure a positive effect from treatment.

Rationale for the Potential Economic Impact if HBO 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 subjects 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 subjects 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 subject over their lifetime). Using the above suppositions, we can therefore calculate that of the approximately 30,000 severe TBI subjects there would be 9,000 left severely disabled or vegetative. Supposing there is a 10% improvement to favorable or functional abilities in 900 subjects, 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 HBO monoplace chamber and installation is approximately $250,000. To modify an existing monoplace chamber to accommodate and monitor severe TBI subjects 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, HBO chambers are not limited to treating only severe TBI subjects.

Two types of HBO delivery systems exist. One is the traditional multiple-occupancy large compartment chamber. It is designed to accommodate several subjects and attendant medical personnel and has long represented the technology standard. Advantages include the fact that multiple subjects can be treated at one time and there is direct subject attendance during each HBO treatment. There are no modifications needed to a multiplace chamber to treat TBI subjects. 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 subject with attendance and support provided from the chamber exterior. The monoplace chamber has been employed across a broad range of subject 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 subjects 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.

The problem of "generalizability" of HBO treatment of severe TBI subjects 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 subjects. A 2-day focus course in the management of severe TBI subjects 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 subjects. 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 subject 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 Principal Investigator (PI)s, Clinical Project Coordinator (CPC), and Study Coordinators (SC)s of all aspects of the process will be critical. If HBO ultimately proves to be an effective treatment for severe TBI subjects, 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 subjects. There are a number of hospital-based emergent/critical care 24/7 HBO facilities being installed in the country at the present time. Undersea and Hyperbaric Medicine is a recognized subspecialty 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 HBO therapy can be delivered to severe TBI subjects 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. 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.

2.2 Background

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 HBO 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 HBO treatment which would be secondary to improved mitochondrial function. In addition, this effect is seen for at least 5 days post injury in TBI subjects treated with HBO (Rockswold 2001, Rockswold 2010). Thus, HBO improves oxidative metabolism during the period of prolonged post trauma hypometabolism. In addition, HBO 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 HBO may promote blood-brain barrier integrity, thus reducing cerebral edema and hyperemia, and therefore reducing the elevated ICP.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

Known potential risks of HBO treatment include:

- Extremely rare risk of fire or explosion due to the oxygen rich environment in a hyperbaric chamber. Fire hazard is a potential risk in HBO 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)

- Rare risk of injury or disconnection of oxygen tubes when the subject is moved from their bed to be placed in the hyperbaric chamber.
- Rare risks of complications from the myringotomy (hole placed in ear drum) include: the hole placed in the eardrum not healing (typically the hole will close within 1 week), ear infection, thickening of the eardrum, and decreased hearing inability to hear, and/or scarring of the eardrum.
- The risk of lung problems that can occur as a result of oxygen treatments.
- The risk of injury to the lung caused by high doses of oxygen.
- Slight risk (less than 1% risk) of developing seizures from hyperbaric oxygen treatments.

In facilities that rigidly follow these standards, there have been no fatalities due to hyperbaric chamber fire in North America.

2.3.2 Known Potential Benefits

Potential benefits of hyperoxia include improved oxidative metabolism and mitochondrial function, and reductions in intracranial hypertension, apoptosis, neuroinflammation, and free radical mediated damage.

2.3.3 Assessment of Potential Risks and Benefits

Safety Record for Hyperoxia Treatment. An exemplary safety record for HBO 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 HBO treatments delivered to 167 subjects with no permanent complications related to the HBO treatment and no subject emergently evacuated from the chamber. In August 2015, the Food and Drug Administration (FDA) gave the HOBIT Trial a “Study May Proceed” notification. All SAEs for our four clinical trials were presented for the FDA review. All of the HBO chambers at our 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 subject during HBO treatment. First is that the inclusion/exclusion criteria for the subject entering the study be strictly enforced. The subject must be hemodynamically stable and the subject’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 subject’s transport to and from the HBO chamber (Weaver 1999). Third, the HBO chamber and its environment must become an extension of the ICU. Expertise of appropriate personnel must be as readily available in the HBO environment as it is in the ICU. Unlike the ICUs where the subjects may be left unattended for brief periods of time, the subject is under the constant observation and supervision by several staff members during the HBO treatment. Fourth, the safe application of HBO requires an additional set of skills, knowledge base, and experience that are unique to hyperbaric medicine and essential to the subject and staff safety. A well trained staff of hyperbaric nurses and technicians working under the supervision of a qualified HBO physician, each of whom have a thorough knowledge of the procedures and physiology of HBO 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.

The subjects receiving NBH (100% FiO_2 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 O_2 toxicity.

3 Objectives and Endpoints

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To definitively determine the most effective *hyperbaric oxygen* therapy paradigm and to predict the probability that this treatment will result in a successful Phase III trial.	Proportion of subjects with favorable outcome at 6-months (Severity adjusted GOS-E)	GOS-E is the most frequently used functional outcome measure for TBI studies.
Secondary		
1. Determine the effect of HBO treatment on the duration of ICP elevation.	The level and duration of intracranial hypertension (ICP>22 mmHg) will be measured.	Intracranial hypertension is the leading cause of death and deterioration in the first week following TBI (Jull, 2000).
2. Determine the effect of HBO treatment on therapeutic intensity level (TIL) scores for controlling intracranial pressure (ICP).	Therapeutic intensity level (TIL) scores. This documents the level of therapies used to control ICP and will be tracked daily during the treatment period.	TIL scores will quantify the intensity of treatment required to control ICP between treatment groups.
3. Determine the effect of HBO treatment on brain tissue partial pressure of oxygen (PO2)monitoring.	The level and duration of brain tissue hypoxia (brain tissue PO2 <20 mmHg).	Brain tissue PO2 levels <20mmHg correlate with poor outcome in severe TBI (VanDen Brink, 2000).
4. Compare the type and incidence of SAEs between hyperoxia treatment arms and control.	SAEs include: Pneumothorax secondary to HBO, pulmonary dysfunction defined as PaO2/FiO2 (PF) ratio<200, pneumonia, and seizures during HBO.	Special scrutiny is required for complications related to hyperoxia treatment.
5. Estimate the effect of peak brain tissue PO2 during hyperbaric oxygen treatment on GOS-E at 6-months.	Dichotomized GOS-E.	Level of O2 achieved in the brain during HBO treatment may correlate with outcome.

4 Study Design

4.1 Overall 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. Subjects with a GCS score of 7 or 8 and a Marshall CT score of 1 , as well as subjects 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 *Baseline,* Day 30, and Day 90 will be used to predict 6-month data. The trial will explore *seven* different active treatment arms for relative efficacy in comparison to the control arm. *Four* pressures (*1.0,* 1.5, 2.0 and 2.5 ATA) and HBO with or without NBH will be studied. *NBH will also be evaluated without HBO, 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 randomized is 200.

4.2 Scientific Rationale for Study Design

The trial will utilize response adaptive randomization (RAR) to favor the better performing experimental arms. Also, using RAR (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 t*o 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.

4.3 Justification for Dose

Preclinical investigators working with TBI models and hyperoxia have used pressures varying from 1.0 to 3.0 atmospheres absolute (ATA). Clinical investigators have used pressures varying from 1.0 to 2.5 ATA. However, the lungs in severe TBI subjects have frequently been compromised by direct lung injury and/or acquired ventilator associated pneumonia and are very susceptible to oxygen (O2) toxicity. Working within those constraints, it is essential to determine the most effective hyperoxia dose schedule without producing O2 toxicity and clinical complications. This proposed clinical trial is designed to answer these questions and to provide important data to plan a definitive efficacy trial.

4.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Data Collection Schedule, withdraws consent, or dies. Section 1.3.

5 Study Population

5.1 Inclusion Criteria

- Age 16-65 years
- Severe TBI, defined as an index GCS (iGCS) of 3 to 8 (if intubated, motor score<6) in the absence of paralytic medication
- For patients with a GCS of 7 or 8 or motor score = 5, Marshall computerized tomography (CT) score >1
- For patients with an alcohol level >200 mg/dl, Marshall computerized tomography (CT) score >1
- For patients not requiring a craniotomy/craniectomy or any other major surgical procedure, the first hyperbaric oxygen treatment can be initiated within 8 hours of **arrival at** enrolling hospital
- For patients requiring a craniotomy/craniectomy or major surgical procedure, the first hyperbaric oxygen treatment can be initiated within 14 hours of **arrival at** enrolling hospital
- Written, informed consent from LAR

5.2 Exclusion Criteria

Criteria	Metric	Rationale
First hyperbaric oxygen treatment cannot be initiated within 24 hours **of injury**	Time to first hyperbaric oxygen treatment	Subjects treated >24 hours are unlikely to benefit
GCS of 3 with mid-position and non-reactive pupils bilaterally (4mm) in the absence of paralytic medication	GCS	Avoid enrolling futile cases.
Penetrating head injury	Clinician exam	Avoid enrolling subjects with very poor prognosis
Pregnant	For women of childbearing age, pregnancy will be assessed either by urine or serum pregnancy test	The effect of hyperbaric oxygen treatment on unborn fetus is unknown
Prisoner or ward of the state	Documentation of same	Challenges to conducting follow

		up assessments
Acute spinal cord injury with neurologic deficits.	Clinical exam	Contraindication to transporting subject to chamber. Additionally prior spinal cord injury with paralysis is a confounder for outcome assessment
Contraindication to ICP monitor placement	Clinician determination	ICP monitoring is important to delivering effective care
Pulmonary dysfunction	PaO2/FiO2 ratio≤200 using no more than 10 cm of H20 of PEEP	Risk of worsening pulmonary toxicity from hyperbaric oxygen treatment
Coma suspected to be due to primarily non-TBI causes	Clinical exam	TBI may not be the primary explanation for subject's mental status
Non-survivable injury (e.g. withdrawal of care prior to randomization, no intention for aggressive intervention, on hospice or Do Not Resuscitate (DNR) order, etc.)	Clinician determination	Poor prognosis
Concern for inability to follow-up at 6 months	Available history indicative that the subject will be inaccessible at the time of outcome determination.	High likelihood of being lost to follow-up at 6 months resulting in missing data.
Inability to perform activities of daily living (ADL) without assistance prior to injury	Clinician determination	Difficulties with ascertaining outcomes
Implantable device/drug that is incompatible with HBO treatment	Refer to manual of procedures for list of potential devices	Device may malfunction in hyperbaric chamber

Non-English Speaking Subjects

There is no exclusion based on language. We recognize, however, that several issues arise when including non-English speaking subjects. These include challenges with obtaining informed consent, and barriers to family interaction, subject tracking, follow-up, and outcomes assessment. As eligible subjects for this study cannot consent for themselves, informed consent will be sought from an English-speaking LAR or using an IRB-approved informed consent process for non-English speaking LARs. Interactions with the family during the course of the study may require translation services. Tracking and follow up will be more difficult. Translation services will also be needed for phone and in-person follow-up. One of the most important issues will be the outcomes assessment. Fortunately, the primary outcome (GOSE at 6 month), is language-and culture-neutral, and can be assessed with a translator.

5.3 Screen Failures

The purpose of tracking screen failures is to characterize the population of TBI patients that are not enrolled in the study at participating. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics and reason(s) for exclusion.

5.4 Strategies for Recruitment and Retention

Identifying and Recruiting Candidates. Potential subjects for this trial will be recruited from subjects 16-65 years of age, with a severe TBI, presenting within 24 hours of injury to the 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.

Anticipated accrual rate: 1.6 subjects per week

Source of participants: Hospital emergency departments and intensive care units

How potential participants will be identified and approached: Trained research coordinators will monitor all trauma presentations for eligible subjects. They will be asked to inform clinical site PI and his/her team of potentially eligible participants. The subject's legally authorized representative will be approached for informed consent.

See section 10.1.1 for information on informed consent procedures.

5.5 Pre-treatment Evaluation

Index GCS (iGCS)

At the time of randomization in WebDCU™, the enrolling investigator determines the subject's iGCS. The iGCS is post resuscitation, meaning oxygenation and blood pressure have been adequately stabilized. Administered short-acting sedative (propofol etc) and/or paralytics (succinylcholine) would be given time for resolution of drug effect prior to assessing the iGCS. The iGCS does not have to be performed by the study investigator. Since potential subjects will be intubated, motor score can be used for assessment and corresponds to the iGCS listed in the table below for the purpose of this study. The GCS should always be explicitly measured and should never be estimated from casual observation.

iGCS	Corresponding Motor Score
3 - 5	1 - 3
6 - 8	4 - 5

Age

Age is necessary for randomization. Age should ideally be obtained from objective documentation, such as a driver's license, other formal identification, or official records. Subject, family or acquaintances can provide age in circumstances where objective documentation is not available.

6 Study Intervention

6.1 Study Intervention(s) Administration

6.1.1 Study Intervention Description

The study interventions will be hyperbaric oxygen with or without additional normobaric hyperoxia or normobaric hyperoxia alone (NBH), or routine care (no hyperoxia). Hyperbaric oxygen therapy consists of breathing 100% oxygen (hyperoxia) while under increased atmospheric pressure.

6.1.2 Dosing and Administration

HBO Treatments

If the subject meets inclusion criteria, has no exclusions and informed consent is obtained, they will be randomized to either one of six HBO treatment paradigms, one NBH treatment paradigm, or the control group. Oxygen toxicity unit (OTU) is a means of quantifying the amount of O2 exposure to the subject based on duration and pressure. Despite its name, OTU is not actually a measure of oxygen toxicity. For the purposes of this study, OTUs will be used as a measure of oxygen dose. The OTUs for the different treatment groups are listed in the table below.

Treatment	Oxygen toxicity Unit (OTU)
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 3 hours of NBH twice a day	310 x 2 = 620
6. 2.0 ATA 60 minutes with 3 hours of NBH twice a day	388 x 2 = 776
7. 2.5 ATA 60 minutes with 3 hours of NBH twice a day	476 x 2 = 952
8. Control (no hyperoxia treatment)	

For subjects receiving HBO treatment, bilateral myringotomies will be performed prior to the first treatment. For all randomized subjects, ICP will be monitored during HBO treatments and ICP will be recorded every 15 minutes. Brain tissue PO2is optional. Brain tissue PO2 values should be recorded every 15 minutes during HBO treatment HBO 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 is 33 minutes, and for 1.5 ATA is 16.5 minutes. Each treatment will be for 60 minutes at the specified pressure. NBH will consist of the subject breathing 100% O2 for 3 hours following HBO decompression which will be continued in the ICU. The NBH without HBO treatment arm will likewise be ventilated with 100% O2 for 4.5 hours at 1.0 ATA in the ICU. The second dive will be administered at least 8 hours following the first dive. Subsequent dives will be administered at 12 hour intervals (+/- 2 hours) for a maximum of 10 dives or until the subject is following commands or determined to be brain dead. The time intervals are defined as from the start of the one dive to the start of the next dive. The first dive of the study should be started within 8 hours of presenting to the enrolling hospital.

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". 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 subjects, particularly those with direct lung injuries or acquired ventilator associated 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.

Transport of the Severe TBI Subject. Transport of critically ill subjects 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 subject transport (Weaver 1999). During the transport of the HOBIT subject to and from the HBO chamber and while the subject is in the HBO chamber, there will be at least one appropriately trained clinician with the subject at all times who is able to manage a ventilator and one critical care nurse present and available to address subject's clinical needs. Monitoring the ventilatory status of severe TBI subjects during transport is critical. If the subject requires mechanical ventilation with positive end expiratory pressure (PEEP) in the ICU, then a transport ventilator with PEEP or a manually-operated resuscitation bag with a PEEP valve will be used. Pulse oximetry to monitor O2 saturations and portable end tidal carbon dioxide (EtCO2) monitor are used routinely. Ideally, the HBO 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.

6.2 Preparation For Study Intervention

6.2.1 Preparation

Assessing Subject's Ability to Tolerate Transport and HBO Treatment
It is critical that any hemodynamic, pulmonary or intracranial instability occurring in a subject prior to HBO treatment be thoroughly assessed and stabilized prior to consideration of transport to the HBO 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 subject has sustained both to the brain as well as to other regions of the body. The Clinical Standardization Guidelines presented in the manual of procedures are state-of-the-art and will be adhered to and monitored closely. 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 subjects will have an external ventricular drain/intraparenchymal ICP monitor placed for both ICP monitoring as well as treatment of intracranial hypertension by removal of Cerebrospinal fluid (CSF). Routine systemic monitoring of the subject includes continuous heart rate, blood pressure, electrocardiogram, and central venous or wedge pressures as needed.

Prior to transporting HOBIT subjects to the HBO chamber, subject's ability to tolerate transport and HBO treatment should be assessed. Assessment of subject's stability for transport to to the HBO chamber should be performed within 2 hours of each scheduled HBO treatment. These assessments may be performed by any physician member of the clinical team including the neurointensivist, neurosurgeon, trauma surgeon, emergency physician in collaboration with the hyperbaric staff physician. If the physician member of the clinical team feels for any reason the subject is not stable to be transported to the hyperbaric chamber or to undergo a hyperbaric treatment, the scheduled treatment will be canceled. There will be no "make-up" HBO treatments. If a subject misses a scheduled HBO treatment(s) due to physiologic instability or other reasons, that treatment(s) will be considered missed and will not be re-scheduled. If subject's clinical condition improves, they may be considered for the next scheduled HBO treatment.

Management of subjects randomized to HBO treatment who cannot tolerate HBO treatments
Subjects randomized to one of the six HBO treatment groups but are not clinically stable enough to receive HBO treatment will receive "usual care" (no hyperoxia treatment). Usual care will be dictated by the clinical standardization guidelines.

Preparing the severe TBI subject for HBO treatment.
Cerebral O2 toxicity can potentially manifest itself as seizures. Severe TBI subjects are susceptible to seizures and all subjects will be loaded with prophylactic anticonvulsants and started on maintenance doses to achieve and maintain therapeutic levels for 7 days.

There are many details requiring special attention prior to the placement of the subject in the HBO 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 procedures include ensuring that: chest tubes are connected to a Heimlich type 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 subjects are connected to the hyperbaric ventilator at least 15 minutes prior to being pressurized in the HBO chamber. Ventilatory parameters are set and stabilized, and arterial blood gases are checked to verify that the ventilator parameters are appropriate. If secretions are present, the subject is suctioned thoroughly prior to the HBO treatment. Bilateral myringotomy is performed prior to the first HBO treatment. The myringotomy can be accomplished with an 18-gauge 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 pre-treatment checklist is maintained and all items performed and checked off prior to the subject entering the HBO chamber.

Monitoring of the Severe TBI Subject During HBO Treatment.

Subject monitoring and safety within the HBO 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 monitoring of the subject includes continuous heart rate, blood pressure, electrocardiogram, and central venous pressures as needed. Intracranial monitoring, including ICP will continue throughout the HBO treatment. Brain tissue PO2 and brain temperature monitoring will be optional. ICP will be monitored using an intraventricular catheter or parenchymal monitor . If the subject has an intraventricular catheter and in a monoplace chamber, a pressure transducer is connected to the ventriculostomy line inside the HBO chamber. 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.

Management of the Severe TBI Subject in the HBO Chamber

Monoplace Chamber

Adequate mechanical ventilation throughout the hyperbaric treatment is essential for TBI subjects 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 subject. 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. There will be an appropriately trained clinician responsible for ventilatory management present at all times during the hyperbaric treatment.

There are special requirements for delivering IV fluids and medications to a subject in the monoplace chamber. In a monoplace chamber, IV fluids which are delivered to the subject 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 subject in the monoplace chamber. Most severe TBI subjects are sedated as a routine part of their ICP management. Elevated ICP or a decrease in cerebral perfusion pressure (CPP) is treated during HBO 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 gases prior to initiating treatment and rechecked as needed during treatment. There will be an appropriately trained clinician responsible for ventilatory management present at all times during the hyperbaric 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.

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 subjects in the multiplace chamber must undergo medical clearance according to the standards of the Undersea and Hyperbaric Medical Society (UHMS).

The various HBO treatment paradigms to be evaluated in the HOBIT trial are well within the normal limits of HBO treatments utilized for standard indications.

6.3 Measures to Minimize Bias: Randomization and Blinding

Randomization Procedures

A web-based central randomization system will be developed by the DCC 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 fixed allocation balanced across pre-specified covariates during a burn-in period (first 56 randomizations; 11 in control and 6 in each active arm except arm 2.5 ATA+NBH which is 9 subjects). Imbalances in the following baseline covariates between the treatment groups will be controlled: age, Baseline GCS score, and enrolling site. Once 56 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 after every 20 subjects enrolled (note: the last interim analysis will be at 176 subjects before the final analysis at 200 subjects) . 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 subject. 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 SIREN CCC and DCC 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.

Blinding

Following serious consideration of sham HBO 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 HBO treatment (Weaver 2002, Clarke 2009). The HBO technician administering the HBO 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 subject is under pressure. 2) Evaluation of any potential harm from HBO treatment should include the potential increased morbidity associated with transporting subjects to an HBO chamber (see adverse event section). Any outcome difference resulting from transportation of critically ill subjects should be accounted for in the HBO group only. 3) Primary outcome assessments will be done by blinded evaluators who were not involved in the treatment portion of the subject's course.

6.4 Study Intervention Compliance

Adherence to the study protocol will be assessed and verified based on a review of hyperbaric oxygen treatment logs. These logs will document key data points including: start time for HBO treatment, end time for HBO treatment, start time for NBH treatment, end time for NBH treatment, compression time, and decompression time. Completion of these logs will be mandatory.

7 Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

1. Cardiac arrest or serious arrhythmias
2. Spontaneous pneumothorax
3. Seizure
4. Unstable vital signs, BP, arrhythmias
5. Refractory intracranial hypertension
6. Refractory low CPP
7. Increasingly high peak inspiratory airway pressures
8. Uncontrolled bleeding
9. Inability to ventilate

7.2 Participant Discontinuation/Withdrawal from the Study

1. Participants and their LARs are free to withdraw from participation in the study at any time upon request.
2. The reason for participant discontinuation from the study will be recorded on the Case Report Form (CRF). Subjects who are randomized and subsequently withdraw informed consent, will not be replaced.

7.3 Subject tracking and Lost to Follow-Up

To attain a high rate of follow up (>90%), the study team will request multiple phone numbers (home, cell phones, pagers, etc) and addresses from the subject and his/her relatives, friends, primary doctor (if available), clergy and clinics. At the time of consent and enrollment, proxy respondents will be asked to provide the address and telephone number of the place where the subject will likely reside following discharge. At the time of hospital discharge, each subject’s disposition will be noted (nursing home, rehabilitation facility, another acute care hospital, subject’s home, relative’s home) so plans can be made for the Day 180 follow-up visit.

During the post discharge interval, a research coordinator will telephone subjects monthly for a health status inquiry and to maintain and update tracking information. During follow-up phone call, if medical concerns are raised, subjects will be referred to their usual care provider if non-TBI related and to the trauma/TBI clinic if TBI related.

Subjects cannot be deemed “Lost to Follow” without the HOBIT Operations Committee approval. The site PI must present a case to the Operations committee that includes the efforts exerted to locate the study subject. The Site PI may be asked to continue their efforts prior to approval.

8 Study Assessments and Procedures

8.1 Efficacy Assessments

Primary Outcome: The GOS-E will be performed at Day 30 (± 7 days), Day 90 (± 14 days), and Day 180 (± 21 days). The Day 30 and Day 90 assessments may be done by telephone interview, although in person interviews are preferred. Barring unusual circumstances, the subject should be interviewed in person rather than by telephone for the Day 180 GOS-E assessment. The GOS-E will be done by a trained and certified investigator who is either a nurse, physician, or neuropsychologist. The Day 30, 90 and 180 GOS-E must be done by a blinded assessor(s).

Secondary Outcomes: Intracranial pressure will be monitored and recorded during the treatment period. Brain tissue oxygen will be recorded at sites that utilize brain tissue PO2 monitoring.

8.2 Clinical Data

Baseline Data

a. Baseline data: 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, labs, vital signs, medical history, and information related to the accident (e.g., mechanism of injury) are collected. If a subject is meets study inclusion/exclusion criteria but is not randomized, the reason is captured on the Screen Failure Log.

b. Injury severity: The Abbreviated Injury Score (AIS), from which the Injury Severity Score (ISS) can be derived, will be collected to allow quantitative and consistent characterization of associated injuries.

c. Baseline Head CT scans: Sites will read the baseline Head CT scans to ensure that a traumatic intracranial abnormality exists. Head CTs will be evaluated for monitor placement. Baseline CT scans will be sent to the HCMC (Central Reader) for review at a later time

d. Data for International Mission for the Prognosis and Analysis of Clinical Trials in TBI (IMPACT) prognostic model: Specific data to predict 6-month outcome will be collected on admission. These include: age, motor score, pupil reactivity.

Treatment (Randomization/Day 1 through Day 6/Hospital Discharge)

a. Treatment: Data are collected to document all study treatments and monitoring of ICP, CPP, FiO2, brain tissue PO2, and Mean Arterial Pressure (MAP).

b. Therapeutic intensity levels and GCS will be documented daily during the treatment period.

c. Surgical Procedures: All surgical procedures performed until Day6 or Discharge (whichever occurs first) will be documented in the database.

d. First follow up Head CT scan: The first follow up head CT scan will be sent to the HCMC (Central Reader) for review at a later time.

e. Hospital discharge information will be collected including discharge location.

Follow-up assessments

The GOSE will be assessed at all follow-up visits (see primary efficacy outcome above)

8.3 Safety and Other Assessments

All adverse events (AEs) will be recorded through Day 6 or Discharge, whichever comes first. All serious adverse events (SAEs) will be recorded through the end of study.

- Blood pressure will be monitored via an arterial line during the treatment period and mean arterial pressure will be recorded (MAP) by the clinical team. Hypotension will be defined as MAP<70. The extent and duration of hypotension will be recorded.
- ICP will be monitored by the clinical team and the duration and extent of intracranial hypertension (ICP>22 mmHg) will be recorded.
- Cerebral perfusion pressure will be monitored by the clinical team. The extent and duration of cerebral hypoperfusion (CPP <60 mmHg) will be recorded.
- FiO2 levels will be monitored daily.
- Chest x-rays will be obtained as clinically indicated to assess for subcutaneous emphysema, pneumothorax, pneumonia, infiltrates suggestive of pulmonary oxygen toxicity/ARDS.

8.4 Adverse Events and Serious Adverse Events

8.4.1 Definition of Adverse Events (AE)

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses.

8.4.2 Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions. Important medical events may also be considered serious when they require medical or surgical intervention to prevent death, risk of permanent injury or disability, or prolonged hospitalization.

The population being studied has a high rate of clinically expected adverse events related to their underlying condition and standard treatment, independent of any research intervention. Subjects with severe TBI have an average of 3 critical complications per subject. This subpopulation of the most severely injured subjects has a mortality rate of 40%. Examples of common medical events in this population include (but are not limited to): ventilator associated pneumonia, venous thromboembolic disease, or progressive cerebral edema. Examples of common medical or surgical interventions include: evacuation of an intracerebral hematoma secondary to ventriculostomy insertion, or inferior caval filter placement to prevent pulmonary embolism.

Subjects may also incur AE that could be expected to occur at higher rates because of the study intervention with hyperbaric exposure. These include medical events such as exacerbated lung injury, oxygen related seizures, or interventions such as placement of a chest tube for a pneumothorax associated with an HBO treatment. Particular attention will be paid to potential complications from HBO treatment listed in section 9.4.

Pre-existing medical conditions or unchanged, chronic medical conditions. Pre-existing medical conditions or unchanged, chronic medical conditions are NOT considered AEs and should not be recorded on the AE case report form (CRF). These medical conditions should be adequately documented on the medical history and/or other source documents. In the HOBIT Trial, any medical condition not present prior to randomization but that emerge after randomization are considered AEs.

Exacerbation of Pre-existing medical conditions. A pre-existing medical condition judged by the investigator to have worsened in severity or frequency or changed in character is considered an adverse event.

8.4.3 Classification of an Adverse Event

8.4.3.1 Severity of Event

For adverse events (AEs) not included in the protocol defined grading system, the severity of adverse events will be determined referencing the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE). The CTCAE provides a grading (severity) scale for AEs with unique clinical descriptions of severity based on this general guidance:
Grade 1: Mild AE
Grade 2: Moderate AE
Grade 3: Severe AE
Grade 4: Life-Threatening or Disabling AE
Grade 5: Death related to AE

8.4.3.2 Relationship to Study Intervention

Adverse reaction is different than an adverse event. Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the study intervention caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the study intervention and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event is definitely caused by the study intervention.

Per FDA guidance a suspected adverse reaction is one that is known to be strongly associated with the study intervention, or one that is very uncommon in study population, or one shown in aggregate analysis to occur more frequently in the treatment group. Generally anticipated adverse events are not suspected adverse reactions.

Because 'reasonable possibility' can be difficult to determine, this trial uses an algorithmic approach to describing relatedness.

Algorithm to Determine Relatedness of Adverse Event to Study Agent	
Not Related	The temporal relationship between treatment exposure and the adverse event is unreasonable or incompatible and/or adverse event is clearly due to extraneous causes (e.g., underlying disease, environment)
Unlikely	Must have both of the following 2 conditions, but may have reasonable or only tenuous temporal relationship to intervention.
	• Could readily have been produced by the subject's clinical state, or environmental or other interventions. • Does not follow known pattern of response to intervention.

Reasonable Possibility	Must have at least 2 of the following 3 conditions	
	• Has a reasonable temporal relationship to intervention. • Could not readily have been produced by the subject's clinical state or environmental or other interventions. • Follows a known pattern of response to intervention.	
Definitely	Must have all 3 of the following conditions	
	• Has a reasonable temporal relationship to intervention. • Could not possibly have been produced by the subject's clinical state or have been due to environmental or other interventions. • Follows a known pattern of response to intervention.	

8.4.4 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

Certain adverse events will be captured and reported in WebDCU™. Information to be collected includes time of onset, clinician's assessment of severity, relatedness to study intervention, and time of resolution/stabilization of the event. All AEs occurring through Day 6 or Discharge, whichever comes first must be reported in WebDCU™. After Day 6 or Discharge, whichever comes first, only serious adverse events will be reported in WebDCU™.All AEs will be followed to adequate resolution/stabilization or subject end of study.

8.4.5 Adverse Event Reporting

Refer to the HOBIT safety monitoring plan for detailed information on adverse event reporting.

9 Statistical Considerations

9.1 Statistical Hypotheses

In this phase II clinical trial we hypothesize that there is at least one treatment arm that will demonstrate neurological improvement that warrants further exploration in a confirmatory Phase III trial. The HOBIT trial uses an 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).

Treatment arms.
There are eight treatment arms defined in the trial:

	Arm	Dose (OTU)
1	Control (1.0 ATA)	N/A*
2	1.5 ATA	260
3	2 ATA	417
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

**NOTE : In the control arm, subjects will be at 1.0 ATA, however the percent of FiO2 will not be regulated. Thus, it is theoretically possible that these subjects are accumulating OTUs. For the purposes of this study they will consider the “dose” to be zero and this arm will be modeled separately. The FiO2 will be recorded throughout the study. Subjects will receive at least 21% O2 outside of the chamber, but the level of oxygen supplementation may be higher though not typically exceeding 50%.*

Primary Endpoint. The primary analysis will use the intention to treat (ITT) sample to compare the proportion of favorable outcomes in the 6-month dichotomized, severity adjusted, GOS-E (section 11.1

of the SAP) in each treatment arm to control dose regimen (1.0 ATA). Favorable outcome for an individual subject is defined according to a sliding dichotomy (Murray, 2005), where the definition of favorable outcome varies according to baseline prognosis. Prognosis will be defined according to the probability of poor outcome predicted by the IMPACT Core Model (Steyerberg EW, 2008); see section 11.1.2.1 of the SAP). The favorable outcome definition is more stringent for subjects predicted to do well (i.e. a low probability of poor outcome), as outlined in the Table below. The IMPACT core score will be based on the covariate as known at randomization. The primary endpoint will analyze the GOS-E at 26 weeks; intermediate measurements will be taken at 4, 13 weeks.

Severity Adjusted GOS-E

Probability of poor Outcome on IMPACT	Glasgow Outcome Scale-Extended						
	Upper Good Recovery	Lower Good Recovery	Upper Moderate Disability	Lower Moderate Disability	Upper Severe Disability	Lower Severe Disability	Vegetative or Death
GOS -E	8	7	6	5	4	3	2/1
0 to <0.21							
0.21 to <0.41					Poor Outcome		
0.41 to <0.56		Favorable Outcome					
0.56 to ≤1.0							

That is, the primary outcome of favorable GOS-E outcome is derived as follows:

$$Y = \begin{cases} 1 \quad if \quad 0 \leq Impact < 0.21 \; and \; GOS-E \; is \geq 7 \\ 1 \quad if \quad 0.21 \leq Impact < 0.41 \; and \; GOS-E \; is \geq 6 \\ 1 \quad if \quad 0.41 \leq Impact < 0.56 \; and \; GOS-E \; is \geq 5 \\ 1 \quad if \quad 0.56 \leq Impact \leq 1 \; and \; GOS-E \; is \geq 4 \\ 0 \quad otherwise \end{cases}$$

Primary Analysis. The primary analysis is of the GOS-E response at 6 months will use the sliding dichotomy methodology. To assess efficacy, the treatment groups will be compared with respect to the proportion with favorable outcome. The primary analysis will be that a treatment arm is superior to the control arm, meaning that the posterior probability 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 0.975 posterior probability of being better than control. Minimum subjects enrolled before the study can stop for early success is 116.

2. End of Enrollment Success: If at the conclusion of accrual, the most likely arm has at least a 0.85 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.

3. Early Futility: If at any interim analysis the maximum probability of active dose being better than control by more than 0.10 across all doses is less than 0.10. Minimum subjects enrolled before the study can stop for early futility is 116.

Specific details of the models and assumptions are found in the HOBIT Statistical Analysis Plan.

9.2 Sample Size Determination

With a maximum sample size of N=200, this design provides at least 77% power when there is improvement (effect) in favorable GOS-E outcomes for active arms over control (Table X). If the treatment arms have a medium or large effect over control, the power is respectively 92% and 98%. If the active arms have no improvement (e.g. 'none') or are worse than control (e.g. harmful) then the early futility rates are respectively 29% and 53% (Table X). Results for other assumptions including other scenarios, longitudinal assumptions, and accrual rates are presented in the HOBIT Statistical Analysis Plan.

Although the maximum sample size is N=200, the simulations conducted indicate the average sample size under the complete null scenario (effect is 'none') is 183 and under the scenarios with small, medium, and large effect of active arms relative to control is respectively 184, 172, and 155. For the harmful scenario the sample size is 169. The type I error probability (incorrectly identifying treatment(s) to success that are truly no better than control) for the complete null scenario ('none') is 0.21.

Table X- Power, Futility, Sample Size, and Trial Duration for Varying Effects for Various Scenarios (Accrual is 1.6 subjects/week)					
	Proportion of TBI Subjects with Favorable GOS-E Outcomes (6 months)				
Arm	Scenario 1 None	Scenario 2 Small	Scenario 3 Medium	Scenario 4 Large	Scenario 5 Harmful
Control	0.40	0.40	0.40	0.40	0.40
1.5 ATA	0.40	0.49	0.54	0.59	0.35
2.0 ATA	0.40	0.50	0.55	0.60	0.35
1.0 ATA+NBH	0.40	0.51	0.56	0.61	0.35
2.5 ATA	0.40	0.52	0.57	0.62	0.35
1.5 ATA+NBH	0.40	0.53	0.58	0.63	0.35
2.0 ATA+NBH	0.40	0.54	0.59	0.64	0.35
2.5 ATA+NBH	0.40	0.55	0.60	0.65	0.35
Pr{Success}	0.21	0.77	0.92	0.98	0.08
Pr{Futility}	0.29	0.03	0.01	0.00	0.53
Sample Size	183	184	172	155	169
Trial Duration (wks)	133	140	133	123	118

9.3 Populations for Analyses

We will use the Intent-to-treat sample (ITT). The ITT sample will include all subjects randomized, where subjects will be classified by the OTU dose in which they are randomized, regardless of the dose received. For each interim analysis (e.g. RAR, interim assessment for efficacy and futility) the analysis population will be defined as all subjects who have been randomized ≥ 4 weeks from the time of the data freeze; the final analysis will occur once all subjects have the opportunity to complete the final study visit (i.e. randomized ≥ 26 weeks previously).

Secondary Aims Analysis. 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 subjects will be compared to controls; and (2) in centers utilizing 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. Full details of the models and assumptions associated with each may be found in the HOBIT Statistical Analysis Plan.

Secondary Efficacy Analysis. Secondary Analyses:
A series of secondary analysis models have been defined in the statistical analysis plan to evaluate the relationship of HBO treatment to the observed brain tissue PO2, ICP elevation, and amount of corrective treatment received as measured by therapeutic intensity level (TIL) scores. Broadly, the models will seek to answer whether treatment with hyperbaric oxygen prevents brain tissue hypoxia, better controls the level of ICP elevation, leads to less ancillary intervention during care, and whether peak brain tissue oxygen during HBO treatment is associated with improved outcomes at 6 months.

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%.

Handling of Missing Data
Under the ITT principle, all subjects 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-E 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 multiple imputation from a Bayesian hierarchical model. The specific imputation model and secondary sensitivity analyses are defined in HOBIT Statistical Analysis Plan.

9.4 Safety Analyses

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.

Safety Monitoring

The review of safety data will focus on the following adverse events potentially caused by HBO treatment. This subject population presents with significant morbidity with respect to all of the below adverse events; as such it is important to evaluate the presence of events with respect to temporal relationship to treatment (i.e. novel onset or worsening) as well as its relationship across doses. The below table provides the most common adverse events, as well as the expected temporal and dose relationship:

Adverse Event	Clinical Relevance
Pneumothorax Induced by HBO therapy	Abnormal collection of air in the pleural space between the lung and the chest wall, can result in steadily worsening oxygen supply. This is a pressure related phenomena that can also be caused by major trauma or medical procedure. As an AE it is expected to increase as a function of dose atmospheres, but not duration of exposure or number of days treatment (i.e. treatment specific or cumulative OTUs). This is expected to occur during the dive and result in aborting the treatment.
Signs of Pulmonary Dysfunction	Signs of pulmonary dysfunction, including PaO2/FiO2 $\leq$ 200 or requiring PEEP > 10 cm of water to maintain a PaO2/FiO2 ratio of > 200. This is an adverse event which is related to total oxygen toxicity exposure and as such should increase with dose and number of treatments. Symptoms are expected to progressively worsen over subsequent dives.

Pneumonia	This is an adverse event which is related to total oxygen toxicity exposure and as such should increase with dose and number of treatments. Symptoms are expected to progressively worsen over subsequent dives.
Critical decreased CPP (<60 mmHg)	This AE is not specific to HBO therapy, but related to poor outcome (reperfusion). It is expected to be the same in all groups but could demonstrate differences if the process of transferring to the dive chamber causes increased AEs. This should be analyzed as active vs. control.
Critical hypotension (MAP<70 mmHg)	This AE is not specific to HBO therapy, but related to transfer from critical care unit (e.g. disconnecting and reconnecting of lines). It is expected to be the same in all groups but could demonstrate differences if the process of transferring to the dive chamber causes increased AEs. This should be analyzed as active vs. control.
Seizures during HBO treatment	These are expected to occur immediately proximal to treatment as a function of dose oxygen toxicity (rather than cumulative exposure). It is possible to have multiple episodes of AE. Subjects with a baseline propensity to seize may elevate the numerator for this AE.
Hypercarbia during transportation (PaCO2>45 mmHg)	This AE is not specific to HBO therapy, but related to transfer from critical care unit (e.g. disconnecting and reconnecting of lines). It is expected to be the same in all groups but could demonstrate differences if the process of transferring to the dive chamber causes increased AEs. This should be analyzed as active vs. control.

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. Cumulative incidences of the specific SAEs related to HBO, as well as all SAEs, will be compared across arms. Additional evaluation of safety events will be conducted adjusting for relative baseline co-variants, such as age at baseline and GCS score.

10 Supporting Documentation and Operational Considerations

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Informed Consent Process

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the Central IRB. 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.

10.1.1.1 Consent/assent and Other Informational Documents Provided to participants

A copy of the consent form will be given to the LAR, and this fact will be documented in the subject's record.

10.1.1.2 Consent Procedures and Documentation

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 is documented and maintained in WebDCU™. 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 subject's legally authorized representative (LAR) has been given an adequate explanation of the purpose, methods, risks, potential benefits and subject responsibilities of the study. The consent form must be an up-to-date document that has been approved by the Central institutional review board (CIRB). A signed and dated informed consent is required prior to randomization.

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

10.1.2 Study Discontinuation and Closure

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

10.1.3 Confidentiality and Privacy

The subject's identity will be kept as confidential as possible as required by law. Upon enrollment, WebDCU™ assigns a unique subject ID to each subject. The link between the subject ID and the subject's name will be confidentially maintained at the enrolling sites. In compliance with Health Information Portability and Accountability Act (HIPAA), collection, storage, display, and transfer of study subject personal identifiers in the WebDCU™ are carefully controlled. Prior to creating the Public Use Dataset any personal identifiers, such as date of enrollment, will be de-identified.

10.1.4 Key Roles and Study Governance

The HOBIT trial will be conducted in the SIREN network funded by the National Institutes of Neurological Disorders and Stroke (NINDS) and the National Heart, Lung, and Blood Institute (NHLBI). The Clinical Coordinating Center (CCC) for the HOBIT trial will be the SIREN CCC at the University of Michigan and the Data Coordinating Center (DCC) will be the SIREN DCC 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 (CCC). 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 SIREN CCC has a Financial Specialist who will provide management and reconciliation of the HOBIT financial activities within the SIREN CCC, including review and processing of invoices for HOBIT funded activity and enrollment at the clinical sites.

Data Coordinating Center (DCC). The main responsibilities of the DCC are to provide the database, data management, and statistical support for the HOBIT trial. The DCC will 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). The DCC will also implement the adaptive design procedure provided by the Analytic Center for interim analyses and provide statistical support throughout the trial.

Analytic Center (AC). The AC is responsible for the Bayesian adaptive portion of the project. The AC will write and validate 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 (SCC). The SCC consists of the contact PI, the clinical project coordinator (CPC), the internal quality reviewer (IQR), 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 (HBO) administration. The

CPC assists the PI in day-to-day implementation in various trial activities. The IQR will be responsible for reviewing adverse events (AE) prior to being forwarded to the independent medical safety monitor (IMSM). The IQR will also assist the PI, the CPC, CCC and DCC in monitoring protocol compliance. The FM, together with the PI, is responsible for subcontracts to the CCC, the DCC, and the AC.

Executive Committee (EC). The EC consists of the leadership of the SCC, the CCC, the DCC 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 SAEs (occurrences and other important events pertinent to the study), and communication among all components of the study participants (e.g., CCC, DCC, 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 ESC serves in an advisory capacity to the study scientific leadership.

***Independent Medical Safety Monitor (IMSM)*.** The IMSM is a neurointensivist experienced in severe TBI management. The IMSM is not affiliated with any of the institutions participating in the HOBIT trial. The IMSM responsibilities are to review all SAEs and determine whether they are serious, possibly related to HBO administration, and unexpected. If all three criteria are met, expedited reporting the the FDA and cIRB will be initiated. The IMSM 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 (DSMB). 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 HBO treatment. Upon review of the periodic data, they advise the NINDS regarding continuation of the trial.

10.1.5 Safety Oversight

Data Safety Monitoring Board. The DCC will generate safety and other reports as requested by the DSMB.

10.1.6 Quality Assurance and Quality Control

See monitoring plan for details

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, with applicable FDA regulations (21 CFR 312), and with the FDA's "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring." Monitoring for this study will be performed by the DCC/CCC centrally, on site, and remotely. Per the study's monitoring plan, monitoring will include a combination of on-site monitoring (to verify data entered into the WebDCU™ database against source documents and query inaccuracies between the source documents and WebDCU™ database), remote monitoring (source document verification, including verification of written consent, may be performed remotely by reviewing source documents that have been uploaded into WebDCU™ or via remote access to electronic medical records), and central monitoring (using web-based data validation rules, data manager review of entered data, statistical analysis, and on-going review of site metrics). Further details of clinical site monitoring are documented in the study's Monitoring Plan.

The EC, on a regular basis, will review a summary of the data entered in the HOBIT WebDCU™ 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 DCC Data Manager (DM) and IMSM of data entered by all participating clinical sites.

10.1.7 Study Records Retention

Refer to the manual of procedures for additional details on retention of study records.

10.1.8 Protocol 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 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.

10.1.9 Publication and Data Sharing Policy

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).

10.2 Abbreviations

10.3 Protocol Amendment History

Page of Change	Section	Version 4	Version 5	Rationale
Page 1	Title Page	Version Number: 4 - January 21st 2019	Version Number: 5 – April 5th 2019	
Page 1	Title Page	Principal Investigators: Gaylan Rockswold, M.D., Ph.D.; William Barsan, M.D., Byron Gajewski, Ph.D.,	Principal Investigators: Gaylan Rockswold, M.D., Ph.D.; William Barsan, M.D., Byron Gajewski, Ph.D., Frederick Korley, M.D., Ph.D.	
Header	Header	HOBIT Protocol Version 4	HOBIT Protocol Version 5	
Page 5	Signature Page	4, dated January 21st 2019	5, dated April 5th, 2019	
Page 8	Section 1.1	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 upper	The primary analysis will use the intention to treat (ITT) sample to compare the proportion of favorable outcomes in the 6-month dichotomized, severity adjusted, GOS-E (section 11.1 of the SAP) in each treatment arm to control dose regimen. Favorable outcome for an individual subject is defined according to a sliding dichotomy (Murray, 2005), where the definition of favorable outcome varies according to baseline prognosis. Prognosis will be defined according to the probability of poor outcome predicted by the IMPACT Core Model (Steyerberg EW, 2008); see section 11.1.2.1 of the SAP). The favorable outcome definition is	This is change was made to ensure that the protocol summary is consistent with the rest of the protocol and with the statistical analysis plan.

		good recovery to upper 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 upper good recovery to lower moderate disability	more stringent for subjects predicted to do well (i.e. a low probability of poor outcome), as outlined in the Table in Section 9.1. The IMPACT core score will be based on the covariate as known at randomization. The primary endpoint will analyze the GOS-E at 26 weeks; intermediate measurements will be taken at 4, 13 weeks.	
Page 10	Section 1.3	Day 180 +/- 30 days	Day 180 +/- 21 days	+/- 30 days is incorrect
Page 22	Section 5.4	Potential subjects for this trial will be recruited from all subjects with a severe TBI	Potential subjects for this trial will be recruited from subjects 16-65 years of age, with a severe TBI	For clarificatio n.
Page 29	Section 6.3	The randomization scheme will be equal allocation balanced across pre-specified covariates during a burn-in period (first 53 randomizations; 11 in control and 6 per active arm per arm).	The randomization scheme will be fixed allocation balanced across pre-specified covariates during a burn-in period (first 56 randomizations; 11 in control and 6 in each active arm except arm 2.5 ATA+NBH which is 9 subjects).	Randomiza tion scheme has been modified due to account for an error identified.
Page 29	Section 6.3	Once 53 subjects are randomized	Once 56 subjects are randomized	See above
Page 29	Section 6.3	The target allocation ratio will be updated after every 20 subjects enrolled	The target allocation ratio will be updated after every 20 subjects enrolled (note: the last interim analysis will be at 176 subjects	See above

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<tr><td></td><td></td><td></td><td>before the final analysis at 200 subjects)</td><td></td></tr>
<tr><td>Page 38</td><td>Section 9.1</td><td>section 11.1</td><td>section 11.1 of the SAP</td><td>For clarification</td></tr>
<tr><td>Page 38</td><td>Section 9.1</td><td>section 11.1.2.1</td><td>section 11.1.2.1 of the SAP</td><td>For clarification</td></tr>
<tr><td>Page 38</td><td>Section 9.1</td><td></td><td>$$Y = \begin{cases} 1 \quad if \quad 0 \le Impact < 0.21 \text{ and } GOS-E \text{ is} \ge 7 \\ 1 \quad if \quad 0.21 \le Impact < 0.41 \text{ and } GOS-E \text{ is} \ge 6 \\ 1 \quad if \quad 0.41 \le Impact < 0.56 \text{ and } GOS-E \text{ is} \ge 5 \\ 1 \quad if \quad 0.56 \le Impact \le 1 \text{ and } GOS-E \text{ is} \ge 4 \\ 0 \quad otherwise \end{cases}$$</td><td>For clarification</td></tr>
<tr><td>Page 39</td><td>Section 9.2</td><td>early futility rates are respectively 29% and 52%</td><td>early futility rates are respectively 29% and 53%</td><td>Randomization scheme has been modified</td></tr>
<tr><td>Page 39</td><td>Section 9.2</td><td>Although the maximum sample size is N=200, the simulations conducted indicate the average sample size under the complete null scenario (effect is ‘none’) is 186 and under the scenarios with small, medium, and large effect of active arms relative to control is respectively 187, 176, and 163. For the harmful scenario the sample size is 174.</td><td>Although the maximum sample size is N=200, the simulations conducted indicate the average sample size under the complete null scenario (effect is ‘none’) is 183 and under the scenarios with small, medium, and large effect of active arms relative to control is respectively 184, 172, and 155. For the harmful scenario the sample size is 169.</td><td>See above</td></tr>
<tr><td>Page 40</td><td>Table X</td><td><table>
<tr><td>2.0 ATA+ NBH</td><td>0.40</td><td>0.55</td><td>0.60</td><td>0.65</td><td>0.35</td></tr>
<tr><td></td><td>0.21</td><td>0.77</td><td>0.92</td><td>0.98</td><td>0.08</td></tr>
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<tr><td>2.5 ATA+ NBH</td><td>0.40</td><td>0.55</td><td>0.60</td><td>0.65</td><td>0.35</td></tr>
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<tr><td></td><td>133</td><td>140</td><td>133</td><td>123</td><td>118</td></tr>
</table></td><td>Randomization scheme modified</td></tr>
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11 References

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