Surgery Department

701 Park Avenue
Minneapolis, Minnesota
55415-1829

Tel: 612-873-2810

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Hennepin County
Medical Center

Mark D. Odland, MD
Chief of Surgery

June 5, 2015

Division of Receipt and Referral
Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Suite 1040
MSC 7710
Bethesda, MD 20892-7710

To Whom It May Concern:

Attached is the grant entitled, "Hyperbaric Oxygen Brain Injury Treatment (HOBIT) Trial – CCC" from the Hennepin County Medical Center (Principal Investigators: Gaylan Rockswold, William Barsan and Byron Gajewski).

This grant is part of a cluster of two grants. Your office has received a linked grant entitled, "Hyperbaric Oxygen Brain Injury Treatment (HOBIT) Trial – SDMC" from the Medical University of South Carolina (Principal Investigator: Renee Martin). This grant is in response to the program announcement, PAR-13-281 (NINDS Exploratory Clinical Trials [RO1]). An IND/IDE application to the FDA has been submitted and is under review.

This cluster of grants has received approval for applications requesting $500,000 or more per year as per Dr. Scott Janis (NINDS Program Office), and the review branch at NINDS is expecting this proposal for review.

Please contact me if you have any questions or concerns.

Sincerely,

Gaylan L. Rockswold

Gaylan L. Rockswold, MD, PhD
Medical Director of the Traumatic Brain Injury Center,
Hennepin County Medical Center
Professor of Neurosurgery,
University of Minnesota

GLR:th

cc: Scott Janis, PhD, NINDS

OMB Number: 4040-0001
Expiration Date: 06/30/2016

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	**State Application Identifier**

1. TYPE OF SUBMISSION*

❍ Pre-application ● Application ❍ Changed/Corrected Application

4.a. Federal Identifier

b. Agency Routing Number

c. Previous Grants.gov Tracking Number

2. DATE SUBMITTED | **Application Identifier**

5. APPLICANT INFORMATION **Organizational DUNS*:** 068195064

Legal Name*: Minneapolis Medical Research Foundation
Department:
Division:
Street1*: 701 Park Ave
Street2:
City*: Minneapolis
County:
State*: MN: Minnesota
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 55415-1623

Person to be contacted on matters involving this application
Prefix: First Name*: Avery Middle Name: Last Name*: Tooley Suffix:
Position/Title: Grant Administrator
Street1*: 701 Park Ave
Street2: Suite PP7.704
City*: Minneapolis
County:
State*: MN: Minnesota
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 55415-1623
Phone Number*: 612-873-2145 Fax Number: 612-339-5601 Email: atooley@mmrf.org

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 411677920

7. TYPE OF APPLICANT* M: Nonprofit with 501C3 IRS Status (Other than Institution of Higher Education)

Other (Specify):
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*

● New ❍ Resubmission
❍ Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).
❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

Is this application being submitted to other agencies?* ❍Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
93.853
TITLE: Extramural Research Programs in the Neurosciences and Neurological Disorders

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Hyberbaric Oxygen Brain Injury Treatment (HOBIT) Trial - CCC

12. PROPOSED PROJECT
Start Date* Ending Date*
04/01/2016 03/31/2021

13. CONGRESSIONAL DISTRICTS OF APPLICANT
MN-005

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Gaylan Middle Name: Last Name*: Rockswold Suffix:
Position/Title: Medical Director, Professor
Organization Name*: Minneapolis Medical Research Foundation
Department: Traumatic Brain Injury Center
Division:
Street1*: 701 Park Ave
Street2:
City*: Minneapolis
County:
State*: MN: Minnesota
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 55415-1623
Phone Number*: 612-873-2825 Fax Number: 612-904-4297 Email*: gaylan.rockswold@hcmed.org

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$8,102,020.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$8,102,020.00
d. Estimated Program Income*	$0.00

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ❍ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR
❍ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: Avery Middle Name: Last Name*: Tooley Suffix:
Position/Title*: Grant Administrator
Organization Name*: Minneapolis Medical Research Foundation
Department:
Division:
Street1*: 701 Park Ave
Street2:
City*: Minneapolis
County:
State*: MN: Minnesota
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 55415-1623
Phone Number*: 612-873-2145 Fax Number: 612-339-5601 Email*: Atooley@mmrf.org

Signature of Authorized Representative*
Avery Tooley

Date Signed*
06/04/2015

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:1249-HOBIT cover letter06022015.pdf

424 R&R and PHS-398 Specific Table Of Contents

OMB Number: 4040-0010
Expiration Date: 06/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	Minneapolis Medical Research Foundation
Duns Number:	0681950640000
Street1*:	701 Park Ave
Street2:	
City*:	Minneapolis
County:	
State*:	MN: Minnesota
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	55415-1623
Project/Performance Site Congressional District*:	MN-005

Project/Performance Site Location 1

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	The Regents of the University of Michigan
DUNS Number:	0731335710000
Street1*:	3003 South State Street
Street2:	
City*:	Ann Arbor
County:	
State*:	MI: Michigan
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	48109-1274
Project/Performance Site Congressional District*:	MI-012

Project/Performance Site Location 2

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	University of Kansas Medical Center Research Institute, Inc
DUNS Number:	0160608600000
Street1*:	3901 Rainbow Boulevard
Street2:	
City*:	Kansas City
County:	
State*:	KS: Kansas
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	66103-2937

Funding Opportunity Number: PAR-13-281. Received Date: 2015-06-04T15:12:25.000-04:00

Project/Performance Site Congressional District*: KS-003

File Name

Additional Location(s)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ● **Yes** ❍ **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ❍ Yes ● No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6

If NO, is the IRB review Pending? ● **Yes** ❍ **No**

IRB Approval Date:

Human Subject Assurance Number

2. Are Vertebrate Animals Used?* ❍ **Yes** ● **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ❍ Yes ❍ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. Is proprietary/privileged information included in the application?* ❍ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ❍ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ❍ Yes ❍ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ❍ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ❍ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	1244-Project Summary.pdf
8. Project Narrative*	1245-Project Narrative.pdf
9. Bibliography & References Cited	1246-References Final.pdf
10.Facilities & Other Resources	1247-Facilities and Resources.pdf
11.Equipment	1248-Equipment.pdf

Funding Opportunity Number: PAR-13-281. Received Date: 2015-06-04T15:12:25.000-04:00

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 (HBO2) has a positive impact on reducing brain injury and improving outcomes in severe TBI. By markedly increasing oxygen (O2) delivery to the traumatized brain, HBO2 can reverse the lack of O2 that precipitates cellular energy failure and subsequent brain cell death. In past clinical investigations, HBO2 in comparison to standard care has significantly improved energy production in the brain and improved clinical outcome. However, prior to a formal phase III definitive efficacy study, important information is required regarding optimizing the HBO2 treatment schedule to be instituted in terms of pressure and frequency and other parameters. The lungs in severe TBI patients 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 HBO2 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.

Primary aims of this trial are to select, in patients with severe TBI, the combination of HBO2 treatment parameters that is most likely to demonstrate improvement in the outcome of severe TBI patients in a subsequent phase III trial. Also the trial will determine, in patients with severe TBI, whether there is a > 50% probability of HBO2 treatment demonstrating improvement in the outcome of severe TBI in a subsequent confirmatory phase III trial.

This trial is supported and sponsored by the Neurological Emergency Treatment Trial (NETT) Network which is funded by the National Institutes of Neurologic Disease and Stroke to conduct clinical trials such as the one described. The NETT helps ensure a well-planned and well-conducted clinical trial.

The human and economic consequences of severe TBI are enormous. Despite approximately 30 clinical trials evaluating various treatments for severe TBI, a specific treatment has been elusive. Hyperbaric oxygen provides one of the best opportunities for demonstrating a specific treatment for severe TBI. If successful, the human and economic benefits to society worldwide would be great.

The Minneapolis Medical Research Foundation (MMRF) will be administrating the financial and compliance processes of the Hyperbaric Oxygen Brain Injury Treatment (HOBIT) Trial. MMRF was founded in 1952. It is the third largest non-profit medical research institution in the state of Minnesota. MMRF consistently ranks nationally in the top 10% of institutions receiving funding from the National Institutes of Health (NIH). MMRF occupies approximately 60,000 square feet on the HCMC campus. This includes clinical research space, basic science laboratories, AAALAC-accredited large and small animal facilities, and space for research administration and accounting services.

In 1989, Hennepin County Medical Center (HCMC) was the first hospital in Minnesota to be verified as a Level I Trauma Center by the American College of Surgeons. This status has been maintained with successful site visits every three years, the most recent in April 2013. In addition, the separate verification as a Level I Pediatric Trauma Center was achieved in October 2010.

The Emergency Department (ED) is the portal of entry for all severe traumatic brain injury (TBI) patients who are potential candidates for this study. HCMC's ED is the largest and busiest in the state of Minnesota with 101,219 patient visits in 2009. The hospital-owned and managed ambulance service provides advanced life support services for approximately 700,000 residents in Hennepin County, covering 266 square miles and 14 communities. In 2009, the ambulance service logged nearly 50,000 runs. HCMC is part owner of Life Link III along with eight other large medical providers in Minnesota and Wisconsin. Life Link III provides critical care transport services via ground ambulances, helicopter, and fixed-wing aircraft.

The HCMC ED has a state-of-the-art stabilization room where critically ill patients are stabilized and the various trauma services converge for the initial triage and management of the patient. The ED is staffed 24/7 by fully trained and board certified emergency medicine physicians. The ED has its own computerized tomography (CT) scanner in its area.

A trauma registry has been maintained by the Trauma Services Department since 1987. Approximately 3,000 patients are entered into the database each year. This registry supports many activities including performance improvement, education, and research. The trauma data is also used for benchmarking through submission to the Minnesota Department of Health and the National Trauma Data Bank. HCMC is one of only two Minnesota hospitals currently participating in the new Trauma Quality Improvement Program through the American College of Surgeons.

Severe TBI patients will be cared for the in the Surgical/Neurotrauma Intensive Care Unit (ICU), which is a 24-bed unit with state-of-the art monitoring equipment. The Neurotrauma ICU is staffed by board certified neurointensivists and surgical critical care specialists. Routine monitoring of severe TBI patients includes intracranial pressure (ICP) monitoring and brain tissue oxygen monitoring with the Licox system. The neurosurgical staff at HCMC are all University of Minnesota faculty. At any given time, there are two University of Minnesota neurosurgery residents rotating at HCMC. The chief neurosurgical resident is in the last year of training and the junior neurosurgical resident is typically a PGY-3. The PI of this grant is the medical director of the TBI Center at HCMC. The TBI Center was established as a comprehensive multidisciplinary Center of Excellence for patient care, education, and research to serve people who have sustained a TBI. The center admits approximately 900 new TBI patients per year with over 100 of them being severe.

The Hyperbaric Medicine Program at HCMC has been in continuous operation since 1964. It has been the only clinical HBO chamber facility in the state of Minnesota until this year and has served the entire state, as well as the bordering regions, of the adjacent five states and parts of Canada. In 2010, the Hyperbaric Medicine Program delivered 3,131 HBO treatments, of which 154 were emergencies. The hyperbaric facility falls within the administrative structure of Emergency Services/Emergency Medicine. Christopher Logue, M.D., board certified in Emergency Medicine and Undersea Hyperbaric Medicine (UHM), is the Medical Director of the Hyperbaric Medicine Program.

The staff for the Hyperbaric Medicine Program provide 24/7 coverage and are always available for emergencies. This staff consists of two full-time, certified hyperbaric technicians with two intermittent technicians to help with call coverage. Three registered nurses with certified hyperbaric nursing and critical care credentials cover the unit. The unit's nurse manager is also a certified hyperbaric nurse. Two emergency

medicine physicians board certified by Emergency Medicine and UHM participate in the program along with Dr. Logue.

The severe TBI patients will be treated in a 34-inch diameter Bara-Med XD monoplace chamber manufactured by Environmental Technonics Corporation installed in a specially adapted room directly across the hallway from the Surgical/Neurotrauma ICU. The 34-inch diameter of this new chamber allows the head of the patients' bed to remain at 20 degrees or more. The chamber door has been customized to include 6 intravenous penetrations, 2 ventilator penetrations, 2 study penetrations for Licox brain tissue oxygen and microdialysis monitoring, and a 55-pin electrical wiring harness that allows monitoring of electrocardiogram, the ventilator, and 2 pressure lines for ICP and blood pressure.

A Magellan ventilator manufactured by Oceanic Medical Products, Inc., is used for ventilating severe TBI patients receiving HBO treatment. The Magellan ventilator gas inlet pressure ranges from 30 to 150 pounds psi. This ventilator has been thoroughly tested under HBO conditions. The Magellan ventilator is equipped with an Ohmeda 5410 volume monitor. This monitor records individual title volumes, respiratory rates, and minute ventilation. It has an adjustable alarm for high and low minute ventilation and an apnea alarm after 20 seconds of no detectable breaths. We have now given 88 HBO treatments to 31 patients with severe TBI without complication while maintaining their baseline ventilation in this monoplace chamber using the Magellan ventilator.

Duke University Medical Center is a full-service tertiary and quaternary care facility, Level I Trauma Center licensed for 924 acute care beds. Duke's Emergency Department provides cutting edge medical care to North Carolina and surrounding area ranging as far as Virginia and South Carolina. The ED is staffed continuously by attending emergency physicians certified by the American Board of Emergency Medicine to treat adult and pediatric patients and is equipped to serve over 90,000 patients per year. Duke Hospital has over 66,000 annual emergency visits, 63,000 inpatient admissions and 81,000 surgical procedures. The Division of Neurosurgery maintains an active clinical service with 11 staff neurosurgeons, a 16-bed intensive care area and an 18-bed stepdown unit. The Division has three dedicated operating rooms, including one for pediatric cases, and up to 6 operating rooms available on any given day. There is also a dedicated neuroendovascular suite for interventional cases. Full diagnostic imaging capabilities are available at all hours, 7 days per week.

The Center for Hyperbaric Medicine and Environmental Physiology is a multidisciplinary organization involved in clinically treating patients with hyperbaric oxygen and researching in the fields of oxygen biology and environmental physiology. The Center contains a seven-chamber 254 cu m complex with a 5,660 cu m compressed air storage field, three 3 cu m/min air compressors, a 2,633 cu m liquid oxygen system, two vacuum pumps, and a complete gas mixing facility. The chambers are outfitted with environmental control units, which regulate temperature, humidity, and CO_2 accumulation. Patient care capabilities while delivering hyperbaric oxygen include mechanical ventilation, invasive monitoring, vasoactive drug administration, general anesthesia and defibrillation. Through-hull EEG and evoked potential monitoring are available. Hyperbaric consultation is available 24 hours per day, 7 days per week by staff physicians who are critical care trained.

Intermountain Medical Center (IMC) opened in October 2007. IMC is made up of five specialty hospitals covering over 1.3 million square feet on a 100-acre campus in Salt Lake Valley. It is the largest medical campus in Utah and one of the largest in the western United States. The central location of this 360-bed Level 1 trauma center enhances response times for trauma care and patient access throughout the Salt Lake Valley. Emergency and critical care patient services are housed in the J.L. Sorenson Patient Tower. This facility participates in training medical students, residents of multiple specialties, and fellowship programs in collaboration with the University of Utah.

The ED is located on Lower Level 1 of the J.L. Sorenson Patient Tower. The Roy W. and Elizabeth S. Simmons Emergency & Trauma Department is the portal of entry for all severe TBI patients who are potential candidates for this study. The unit consists of 42 beds, including 4 trauma bays and 13 rooms dedicated to critically ill patients requiring monitoring and extensive emergent and urgent medical care. As the leading ED in the Intermountain region, the Simmons Emergency & Trauma Department is staffed 24/7 by fully trained and board certified emergency medicine physicians. It is directly adjacent to the medical center's imaging services.

Patients will be treated in the Intermountain Shock-Trauma ICU or the Neurological ICU at IMC. Both ICUs are staffed 24 hours per day, 7 days per week, by critical care attending level physicians (at least 2 critical care attending physicians are in-house 24/7). The Shock-Trauma ICU cares for patients with higher acuity than that of the Neurological ICU, and most patients enrolled in this trial will be cared for in the Shock-Trauma ICU. However, some patients with isolated head injury might be transferred to the Neurological ICU after care in the Shock-Trauma ICU. These two units are separated by one floor.

Both ICUs use ICP monitoring and the Shock Trauma ICU uses the Licox PO2 monitor. Both ICUs follow standard approaches to the management of TBI. The Shock-Trauma ICU is well-recognized in conducting clinical trials, which include steroids for septic shock and being an active participant in the ARDS Net Consortium clinical trials. In addition, our facility uses a highly sophisticated computerized program for data gathering, which improves patient care and streamlines efficiency of patient care management.

At IMC, the hyperbaric service is equipped with both a multiplace (multi-person) chamber and monoplace (single-person) chambers. The state-of-the-art 8-person multiplace chamber, manufactured by Fink Engineering, Australia, is one of only a handful of hyperbaric rectangular chambers in the world, and the first in the United States. A rectangular chamber offers many advantages over the traditional cylindrical design, including more usable floor space, easier patient transport in and out of the chamber, and increased patient comfort (it looks just like another hospital room inside). This chamber also has hypobaric (reduced pressure) capabilities to simulate increased altitude, which is used for research and evaluating patients who live or travel to altitude.

Operating monoplace chambers in tandem with a multiplace chamber is the optimal configuration for a hyperbaric service. The multiplace chamber ensures sufficient capacity that patients are not waiting to begin a course of therapy, but monoplace chambers offer flexibility in treatment timing and oxygen dose. Uniquely, at IMC, monoplace chambers are also located in the ICUs to provide hyperbaric oxygen therapy in the critical care environment. For patients enrolled in this study, we plan to use the monoplace chambers located within the ICUs. This permits the same staff to care for the patients and to minimize transport risk.

Hyperbaric treatments will be administered in a 32-inch diameter monoplace chamber manufactured by Sechrist Industries inside the Shock-Trauma ICU or the Neurological ICU. Both ICUs have patient rooms that have been modified to accommodate the hyperbaric chamber. The chamber hatch has been customized to accommodate 10 or more intravenous penetrations, ventilator penetrations, suction, and a variety of monitoring devices.

Subjects will be mechanically ventilated with a Magellan ventilator (Oceanic Medical Products, Inc.) or a Sechrist ventilator (Sechrist Industries, Inc.), depending on patient respiratory requirements. Both ventilators have been extensively tested for ventilating patients receiving hyperbaric oxygen therapy in the monoplace environment.

The Hyperbaric Medicine Program at IMC is staffed by the same clinicians who have operated the world-renowned hyperbaric medicine program at Intermountain LDS Hospital for over 20 years. Medical Director Lindell Weaver, MD, is well-known for his extensive research contributions to the field of hyperbaric medicine. The physicians are joined by a full complement of nurse practitioners, nurses, respiratory therapists, and technicians with an average tenure of 10 years in hyperbaric medicine. The staff provides hyperbaric medicine at IMC and Intermountain LDS Hospital as a single service. We have considerable experience with the application of hyperbaric oxygen to critically ill patients, including a publication track record and training courses. The service is staffed 24-hours per day, 7-days per week to accommodate patients who need hyperbaric oxygen therapy on an emergency basis.

Erlanger Health System (EHS) is an 818-bed regional tertiary care facility and is a major teaching hospital of the University of Tennessee College of Medicine (UTCOM). EHS currently has UTCOM residencies in surgery, orthopedics, medicine, obstetrics-gynecology, pediatrics, family medicine, plastic surgery, and emergency medicine. It has fellowships in surgical critical care, vascular surgery, and trauma orthopedics. The ED serves patients from southeastern Tennessee, Alabama, Georgia and North Carolina.

The adult ED sees approximately 50,000 patients each year and the pediatric ED at the EHS T.C. Thompson Children's Hospital sees 40,000 patients a year. An EHS community ED and small rural access hospital see close to 30,000 patients annually.

Erlanger also houses the Regional Medical Control Communications Center which directs approximately 36,000 ground units and 3,000 helicopter flights each year. The EHS ED physicians function as a major regional resource as part of the unified Med Com OnLine Physicians Group.

As the region's Level I Trauma Center, and one of the busiest in the Southeast, EHS is the portal of entry for severe trauma, and TBI patients. The ED is staffed 24/7 by Emergency Medicine trained and American Board of Emergency Medicine certified physicians.

Life Force is Med Trans owned and operated aero medical flight service utilizing five helicopter airships strategically positioned throughout the catchment area. The flight crews are credentialed in rapid sequence intubations, advanced airway techniques and routinely carry mannitol and O-negative packed red blood cells for initiating resuscitation of closed head injury and hemorrhagic shock in flight. EHS has numerous evidenced-based protocols that dictate the management of these patients prior to arrival at the Trauma Center.

EHS receives approximately 3,000 trauma and 100 burn admissions annually. Eighty five percent of the admissions are the result of blunt and fifteen percent penetrating trauma. Approximately 700 of these patients require admission to an ICU. Of this total in 2008, there were 404 trauma patients admitted with intracranial hemorrhage identified on head computed tomography scan. Head injury patients are primarily admitted to an eight bed Neurosurgical ICU, 12-bed Trauma ICU and 10-bed Surgical ICU. Dr. Robert A. Maxwell is medical director of both Surgical and Trauma ICUs and chairman of the Critical Care Committee.

The Trauma Service is staffed by five fellowship-trained physicians who are board certified in General Surgery and Surgical Critical Care. These individuals are faculty members of the University of Tennessee College of Medicine and are an integral part of the Accreditation Counsel for Graduate Medical Education accredited general surgery and surgical critical residencies housed at EHS. Dr. Robert A. Maxwell is also the Program Director of t he Surgical Critical Care Fellowship. These two training programs form the backbone of the Trauma Service and the collaboration between Resident and faculty enhance the academic mission of the institution. The Trauma Faculty take in house calls 24/7 and are immediately available for any patient care concern.

The Neurosurgery Service is comprised of six board certified neurosurgeons who serve as faculty members at the University of Tennessee College of Medicine; this group is led by Dr. Lee Kern. They provide 24/7 consultant coverage for the Trauma Service and collaborate extensively with the Trauma Service regarding patient care and evidence based protocol development.

The Hyperbaric Medicine Program began at EHS in 1997 and has operated continuously since opening. Recently the facility successfully completed a UHMS recertification and was awarded accreditation as a Level I hyperbaric facility. The EHS Program is one of thirty six accredited hyperbaric facilities in the nation and is operational 24/7. Approximately 1700 patients are treated each year, many of whom are critically ill with conditions such as gas gangrene, carbon monoxide toxicity, crush injury, and Fournier's.

The hyperbaric facility is located on the main campus of EHS and its lead physician Dr. James H. Creel is board certified in emergency medicine and UHM. In addition, Dr. Creel serves as Vice Chair of Emergency Medicine and is past Chief of Staff.

The facility has four Register Hyperbaric Nurses certification prepared and one hyperbaric paramedic. Four American Board of Emergency Medicine Certified physicians, who are HBO trained, provide coverage and support to the program. In addition, two of the physicians are board certified in Undersea and Hyperbaric Medicine. The University is going to pursue a fellowship in Hyperbaric Medicine in the next several years.

The HBO facility has three Seachrist 3200 mono chambers. All chambers have six penetrations and two chambers have ventilator penetrations. The ventilator is a Seachrist 500A model. ECG/Respiration monitoring is conducted on all patients. Arterial line monitoring can also be conducted and pressure lines are available for ICP.

The R. Adams Shock Trauma Center (STC) is a multidisciplinary clinical, research, and educational institution devoted to the care of complex, multisystem trauma patients. The STC is designated by Maryland State law to be the "core element" of the state's emergency medical system and serves as the state's Primary Adult Resource Center for adult trauma. The STC is also Maryland's designated statewide referral center for adult patients with severe brain and/or spinal cord injuries, severe multisystem injuries, and acute complex musculoskeletal injuries. Last year more than 8,000 trauma patients were admitted to the STC, 88% directly

from the scene of injury and the remainder as transfers from other facilities. Over three hundred of these patients suffered TBI resulting in GCS score ≤ 8 at the time of presentation.

The STC includes two helipads, an admitting area (Trauma Resuscitation Unit) with 13 resuscitation bays; 10 operating rooms; 2 CT scanners, an angiography suite; and a total of 127 patient care bed, including 72 ICU beds (separated into multi-trauma and neurotrauma). STC physicians also staff the neuro ICU, Surgical ICU, and cardiac surgery ICU. The program in trauma acts as a multispecialty group of over 40 physicians, including trauma surgeons, orthopedic surgeons, neurosurgeons, vascular surgeons, anesthesiologists, critical care practitioners, infectious disease physicians, hyperbaric specialists and a highly skilled nursing staff, all with a practice specialized to the care of injured patients. Ongoing collaboration with the Department of Defense has led to residency training opportunities for surgical, orthopedic, anesthesia, and critical care residents, the Air Force "CSTARS" military medicine training program, and research collaborations in the areas of pre-hospital shock resuscitation the effects of air transport on TBI, and others. Subspecialty faculty and trauma operating room personnel are in-house and on call 7 days a week, 24 hours a day.

The Section of Hyperbaric Medicine of the STC is one of the oldest hyperbaric medicine programs in the country to be intimately associated with a major neurotrauma center. The hyperbaric chamber at STC is designated by Maryland State law to be the primary receiving center for all patients suffering from carbon monoxide poisoning in the state. The Divers' Alert Network has additionally designated this program as a regional referral center for diving emergencies. The chamber routinely receives a wide variety of emergency/critical transfers from all parts of Maryland as well as from numerous surrounding states.

The state-of-the art multiplace hyperbaric chamber measures 53 feet x 10 feet and has three separate linterconnecting locks. The chamber has 23 oxygen breathing stations with space for up to 23 seated patients or 10 patients on stretchers or beds. All cardiac monitors and IV pumps at the STC are "chamber compatible," i.e., capable of functioning at a wide range of pressures. Additionally, dedicated patient ventilators have been modified to work at high pressures, allowing the staff to treat up to three patients simultaneously requiring mechanical ventilation.

The hyperbaric chamber is open daily for routine treatments and available 24/7 for emergencies. The chamber is staffed by five critical care nurses, three hyperbaric technicians, as well as four physicians who cumulatively encompass board certified expertise in internal medicine, emergency medicine, critical care, as well as certification in medical examination of divers. Direct physician supervision is provided for all clinical treatments.

The University of Iowa is the only hospital in Eastern Iowa certified by the American College of Surgeons as a Level I trauma center. The Emergency Treatment Center at the University of Iowa Hospitals provides care for the most critically ill patients. In its present facilities, newly built in 2007, the Emergency Treatment Center handles trauma cases from throughout Iowa and surrounding states. The multidisciplinary services work closely with the medical and surgical departments at the University of Iowa Hospitals to optimize the care and outcomes of patients.

The trauma and critical surgery service consists of faculty members with a special interest in the care of the severely injured. The interdisciplinary team uses rapid surgical assessment in the management of patients with acute general surgical problems. The hospital admits more than 1,400 patients for traumatic injuries each year. Resources include a trauma registry, multidisciplinary trauma teaching conferences, and collaborative research within the University of Iowa Injury Prevention Center. In the 36-bed surgical intensive care unit, surgeons and anesthesiologists cooperate to provide optimal care for severely injured patients.

From the University of Iowa prospectively collected trauma registry, there were 165 trauma patients with a Glasgow Coma Scale score between 3 to 8 in the year 2009. The Department of Neurosurgery is responsible for all operative and nonoperative head injury patients. The neurosurgery research team has vast experience in surgical human trials. There is a close relationship between the neurosurgery service and the trauma and critical surgery services working in the surgical intensive care unit.

The University of Iowa Hyperbaric Medicine Service operates the only chamber in the state of Iowa. This chamber was installed in 1995 and is capable of holding up to six patients plus one inside attendant. The chamber was custom ordered from Perry Baromedical and is 23 feet long, seven feet in diameter, and weighs approximately 24,000 pounds. In addition to the main treatment area, this chamber is also equipped with a med lock and an entry chamber. The med lock is large enough to allow medicines, blankets, equipment, etc. to

be sent into the chamber when it is at depth. Similarly, the entry chamber allows attendants and physicians can get into and out of the chamber as needed during a treatment without having to de-pressurize the main treatment chamber.

Because its size and proximity to operating room and the surgical intensive care unit (all located on the same floor and adjacent to each other), and because the chamber is staffed with trained anesthesiologists and respiratory therapists, critically ill patients requiring multiple medicine infusions and mechanical ventilation are easily treated in this chamber.

The Hyperbaric Medicine Service is a division of the Department of Anesthesia at the University of Iowa. Thus, all the physicians on this service are board-certified Anesthesiologists who have undergone additional training in Hyperbaric Medicine. A physician is in constant attendance during a treatment to supervise the dive, asses the patients' progress, and to deal with any medical issues that may arise.

The non-physician staff of the Hyperbaric Medicine Service are all registered respiratory therapists who have had additional training in hyperbarics. In fact, most of the therapists are Certified Hyperbaric Technologists. These therapists perform multiple duties including operating the chamber, diving with patients, administering medications and regulating drips, and managing ventilators at depth.

Froedtert Hospital is the primary adult hospital affiliate of The Medical College of Wisconsin and is staffed by College physicians providing care in all medical specialties and subspecialties, with particular strengths in cancer, heart and vascular diseases, brain injury and disorders, spinal cord injury, transplant, communication disorders, digestive diseases, diabetes, orthopedics, urology, and women’s health. A 451-bed hospital, Froedtert has the only adult Level 1 Trauma Center in eastern Wisconsin. Nearly every physician practicing at Froedtert is a Medical College of Wisconsin faculty member, and the two institutions share the academic mission.

The Froedtert & The Medical College of Wisconsin Neuro Intensive Care Unit (NICU), Acute Care units and Rehabilitation units are available to serve patients with different types of neurological injuries, including brain injuries. The NICU is equipped with state-of-the-science monitoring equipment and is staffed by a skilled and experienced team of physicians and nurses. Experts from other disciplines, such as Urology and Plastic Surgery, are readily available for consultation, further enhancing the recovery process and promoting a faster return to the community.

When an adult suffers a traumatic injury, the Trauma Center at Froedtert & The Medical College of Wisconsin is ready to respond 24 hours a day. The Trauma Center combines the latest technology with exceptional staff to provide the highest level of care to trauma patients in the region. Severely injured patients from as far away as Marinette and Clark counties in Wisconsin to McHenry and Cook counties in Illinois are brought to the Trauma Center for life-saving care. In the last year, 2,277 people received care in the Trauma Center, and 73 patients with brain injuries (GCS 3-8) were admitted. The Brain Injury Program at Froedtert & The Medical College of Wisconsin provides comprehensive, continuous care to patients with brain injuries. We provide treatment for all types of traumatic brain injuries. The brain injury rehabilitation program is accredited by the Commission on Accreditation of Rehabilitation Facilities (CARF), a designation that recognizes its adherence to strict requirements for hospital programs providing comprehensive rehabilitation services.

Research--The Medical College of Wisconsin operates 27 academic departments and diverse federal and institutional research centers. In FY 2008-09, faculty received approximately $157 million in external support for research, teaching, training and related purposes, of which approximately $142 million is for research, including about $110.0 million from the National Institutes of Health (NIH). Sixty-five percent of the AHW endowment spending noted above is used for research and education projects proposed by MCW faculty. The College is the largest research institution in the Milwaukee metro area and the second-largest in Wisconsin.

The Hyperbaric Medicine Department at Froedtert & The Medical College of Wisconsin performs 500 – 1,000 hyperbaric oxygen treatments each year to aid healing for many types of conditions. The Hyperbaric Unit has two Seachrist Monoplace Chambers, with 24/7 capability, able to accommodate iv lines and ventilator equipment.

Because the department is directed by neurologists who focus on the neurological applications of hyperbaric oxygen therapy, the department is unique in the world of hyperbaric medicine.

Since 1997 The Ohio State University Medical Center has been verified by the American College of Surgeons as a Level 1 adult trauma center. This status has been continuously maintained since that time. A performance improvement trauma registry is maintained and available to query. Last year (2013), the trauma center treated 2,722 injured patients. The University Medical Center is one of two Level 1 trauma centers located in Central Ohio. It is served by a helicopter aero-medical transport service which provides on-scene as well as inter-hospital transfer of trauma patients.

The Emergency Department is in the process of opening a new expanded Emergency Department as part of the opening of the new Cancer Hospital. When fully opened in March 2015, the ED will consist of > 100 beds, which includes 3 large trauma suites for care of trauma patients, 4 resuscitation rooms, a 20 bed observation unit, 2 new state of the art CT scanners, point of care laboratory, 2 hyperbaric oxygen chambers, and a portion of the new ED devoted to emergent care of cancer patients and geriatric patients. The ED is staffed 24/7 by fully trained and board certified emergency medicine physicians.

Severe TBI patients will be cared for in a state of the art 23 beds Neurocritical Care unit. The unit is staffed by board certified Neurointensivists. Routine monitoring of severe TBI patients includes intracranial pressure (ICP) monitoring, brain tissue oxygen monitoring and microdialysis.

The Hyperbaric Medicine Program at OSUWMC has been in continuous operation since the 1980s. There are three sites within the Medical Center in which Hyperbaric therapy is provided; one at an outpatient clinic facility, one at the OSU East hospital, a smaller community hospital, and one at the Main Medical Center. While the first two sites offer services only during weekday hours, the facility at the Main Medical Center offers emergency services 24-7. The Main Medical Center Hyperbaric Facility is the only clinical HBO chamber facility in central Ohio to provide emergency after hours service. In the past 3 years, the Main Medical Center Hyperbaric Medicine Program delivered following number of treatments; 1,045 (FY 2012), 1,788 (FY 2013), 1,101 (FY 2014), of which approximately 5% were hyperbaric emergencies. This hyperbaric facility falls within the administrative structure of the Emergency Department and is physically located in the Emergency Department. Sorabh Khandelwal, M.D., board certified in Emergency Medicine and Hyperbaric and Undersea Medicine, is the Medical Director of the Hyperbaric Medicine Program. A core group of four physicians staff the hyperbaric center with support from 15 additional Emergency physicians when they are working in the Emergency Department. Three of the core physician group, including the Director, are board certified in Emergency Medicine and Hyperbaric and Undersea Medicine (Sorabh Khandelwal, MD, Mark Angelos, MD and Colin Kaide, MD).

The staff and physicians for the Hyperbaric Medicine Program provide 24/7 coverage and are for on call for emergencies. This staff consists of 2 part-time, respiratory therapists and 4 registered nurses with certified hyperbaric nursing and critical care credentials. Two chambers are utilized for treatments and would be available for TBI patients, a Sechrist Model 3300H/HR monoplace hyperbaric oxygen chamber and a Sechrist 3200P/3200PR monoplace hyperbaric oxygen chamber. Both chambers are located within the Emergency Department. The 32-33-inch diameter of these chambers allows the head of the patients' bed to remain at 20 degrees or more. Each chamber door has been customized to include 3 intravenous penetrations, 1 ventilator penetration, and monitoring capability for an electrocardiogram, the ventilator, and 2 pressure lines for ICP and blood pressure. A Sechrist (model 500 A) pressure cycled ventilator is used for ventilating intubated and critically ill patients, (including severe TBI patients) receiving HBO treatments. The staff and physicians are experienced in the use of this ventilator under HBO conditions critically ill ventilated patients.

Chandler Medical Center is one of only two Level I Trauma Centers in KY verified by the American College of Surgeons. This status was achieved in 1990 has been maintained with successful site visits every three years. We completed a reverification visit in Dec 2014 and our status is currently pending. In addition, the separate verification as a Level I Pediatric Trauma Center was achieved in 1996 and reverified in October 2012.

The Emergency Department (ED) is the portal of entry for all severe traumatic brain injury (TBI) patients who are potential candidates for this study. Chandler ED is the largest and busiest in the state of Kentucky with 72,000 patient visits in 2014. The state of Kentucky has more air medical helicopters per capita than any other state. Multiple services bring patients from all regions of the state to our medical center in central KY.

The UK Chandler ED has 7 state-of-the-art stabilization rooms where critically ill trauma patients are stabilized and the various trauma services converge for the initial triage and management of the patient. The ED is staffed 24/7 by fully trained and board certified emergency medicine physicians. The ED has two computerized tomography (CT) scanners immediately adjacent to the Trauma Unit with in the center of our ED.

A trauma registry has been maintained by the Trauma Services Department since 1990. Approximately 3,500 patients are entered into the database each year. This registry supports many activities including performance improvement, education, and research. The UK Chandler Trauma Center admits 2850 patients per year.

Severe TBI patients will be cared for the in the Neurosurgical Intensive Care Unit (ICU), which is a 24-bed unit with state-of-the art monitoring equipment. The Neurotrauma ICU is staffed by board certified neurointensivists and surgical critical care specialists. Routine monitoring of severe TBI patients includes intracranial pressure (ICP) monitoring and brain tissue oxygen monitoring with the Licox system. The neurosurgical staff at Chandler Medical Center are all University of Kentucky faculty. The PI of this grant is the medical director of Neurotrauma at the University of Kentucky. The center admits approximately 991 new TBI patients per year with over 200 of them being severe (GCS 8 or less on arrival).

The Hyperbaric Medicine Program at the University of Kentucky has been in continuous operation since 1992. It is the only clinical HBO chamber facility in the state available for emergent treatments. In 2013, the Hyperbaric Medicine Program delivered 400 HBO treatments, of which 20 were emergencies. The hyperbaric facility falls within the administrative structure of the Department of Emergency Medicine. Charles Eckerline, M.D., board certified in Emergency Medicine and trained in Hyperbaric Medicine has been the Medical Director of the Hyperbaric Medicine Program for the last 12 years. Dr. Humphries is also trained in Hyperbaric Medicine.

The staff for the Hyperbaric Medicine Program provide 24/7 coverage and are always available for emergencies. This staff consists of one full-time, certified hyperbaric technicians with four part-time technicians to help with call coverage. Four emergency medicine physicians board certified by Emergency Medicine with special training in Hyperbaric Medicine participate in the program along with Dr. Eckerline.

We will replace our current HBO chamber and will be moving in 2015 into a state of the art HBO facility located in the same building as our Neurocritical Care ICU. While we have not purchased the HBO chamber yet, we when the facility opens we will have a chamber that has the capacity to treat critically ill neurotrauma patients with intracranial pressure monitors and mechanical ventilation.

Memorial Hermann Hyperbaric Center is the first and only multiplace hyperbaric facility at the University of Texas Medical Center in Houston. We treated our first patient on August 23, 1989. We are located on the second floor of the Robertson Pavilion at the Memorial Hermann Hospital Texas Medical Center, one of only two certified Level I trauma centers in the Greater Houston area. Our Memorial Hermann Life Flight® provides emergency rescue within a 150-mile radius.

Our chamber is six feet in diameter and thirty four feet long. It was manufactured in 1989 by Pacific Coast Welding & Machine INC. The chamber has three compartments. The tri-lock configuration allows routine hyperbaric treatments to continue when emergency treatments are performed. The largest, the main lock, is nineteen feet long and accommodates 12 patients seated or 4 patients supine. This lock has the capability of suction and mechanical ventilation.

The second largest compartment is the critical care or trauma lock of eleven feet in length. It accommodates 6 patients seated or 2 patients supine. It is equipped with a mechanical ventilator and suction.

The third compartment is the crossover lock. It is four feet in length and is used to transfer medical personal in and out of compartments while they are above the sea level pressure.

The chamber is equipped with overboard dump for built in breathing system (BIBS). We have two cardiac monitors (Dash 3000 GE) and IV pumps (Alaris) completely compatible with the hyperbaric treatment. Our chamber has multiple penetrators that can be adapted for pass-through of leads and electrodes for additional monitoring equipment. It allows keeping the monitor outside of the chamber while the patients can be connected to the electrodes (transcutaneous oximetry, etc).

Two Univent Eagle mechanical ventilators (Model 754, Impact Instrumentation, Inc.) are available with one remaining ready continuously in the “trauma lock” at all times. This ventilator Eagle offers PEEP with Controlled Assist, SIMV, CPAP, and CMV ventilation modes.

Compressed air is supplied by two Bauer 30hp rotary screw compressors. Oxygen is supplied from a liquid source, although banked oxygen is available as well.

The staff for our Hyperbaric Medicine Program provides 24/7 coverage and are always available for emergencies. The staff consists of three full-time, certified hyperbaric technicians with one intermittent technician to help with call coverage. In addition, two registered nurses with hyperbaric training and critical care credentials cover the unit. The unit’s nurse manager is a certified hyperbaric nurse. Three hyperbaric physicians participate in the program: two internists and one anesthesiologist.

In 2013, our center delivered 1,529 HBO treatments.

The UPMC Trauma Center serves as the primary trauma center for 29 counties in Western Pennsylvania and 19 surrounding counties in Ohio and West Virginia. The current 2007 population of this catchment area is estimated at 5,699,665. Allegheny County is the most represented county in this catchment area (21.4%), with constituents from this county comprising almost 40% of the population hospitalized with TBI at UPMC Trauma Center. Adult trauma admissions to UPMC Presbyterian Hospital have increased from 1200 in 1988 to 5000 in the year 2009.

Emergency Medical Services for UPMC are provided through the Center for Emergency Medicine. The mean transport time from the estimated time of injury to arrival in our trauma center is 35 minutes. Patients arrive at our trauma center via both ground (68%) and helicopter transport (32%). UPMC Presbyterian Hospital, a Level I Trauma Center, has protocols currently in place that include the preferential transfer of all severely head injured patients to UPMC by our regional helicopter system. All pre-hospital providers adhere to head injury protocols which recommend the use of short acting neuromuscular paralytic agents when needed for pre-hospital intubation of patients, and the conservative use of hyperventilation. These protocols allow clinicians to obtain an accurate GCS score in the Emergency Department for almost all of our TBI patients. The guidelines described in the American College of Surgeons Advanced Trauma Life Support (ATLS) Manual are followed during initial resuscitation and treatment of our trauma patients.

Patients with acute traumatic brain injuries are assessed and treated at UPMC Presbyterian Hospital, a 670-bed, Level-1 regional trauma center fully accredited by the Pennsylvania Trauma Systems Foundation.

The ED has fully equipped trauma resuscitation areas, with full monitoring and overhead radiographic capabilities. Two of the ten computed tomography (CT) units in the hospital are housed within the trauma resuscitation area to facilitate care of the trauma patients requiring urgent CT imaging, including CT perfusion and CT angiography. The system has an all-digital radiology system that allows for rapid transfer and collection of radiological data.

Following stabilization in the Emergency Department and emergency surgery if needed, TBI patients are transferred to a dedicated 10-bed Neurotrauma ICU. The Neurotrauma ICU is staffed by board-certified neuro-intensivists and surgical critical care specialists as well as experienced neurotrauma nurses, 50% of whom have worked there for more than five years. Patients with severe TBI are routinely monitored with an external ventricular drain, a parenchymal ICP monitor, brain tissue oxygen and temperature monitoring, and cerebral blood flow probes.

The University of Pittsburgh Brain Trauma Research Center (Clinical Director: David O. Okonkwo, MD, PhD) is a premier clinical TBI research program that annually treats over 500 patients with traumatic brain injury. The program has a full time staff of six experienced research nurses with a 19-yr track record of successful design and execution of clinical trials in neurotrauma. Research coordinators are on-call twenty-four hours a day, seven days a week to screen and enroll patients into clinical research protocols.

In the Neurotrauma ICU, all real-time physiological data from each ICU bed is downloaded every minute to the Brain Trauma Research Center Database within the BTRC Clinical Laboratory. The BTRC Database accommodates 24,480 points of physiologic data collected each day per patient for a total of approximately 122,400 total datapoints during the first five days after admission to the hospital with severe TBI. Electronic and manual entry of additional physiological, clinical and radiological information to the database occurs throughout the initial critical care phase. Blood and CSF samples from every patient consented into the database is collected every six hours during the first five days postinjury, processed, and stored in the BTRC Clinical Laboratory freezers. If patients require emergent craniotomy with lobectomy, brain tissue samples are

collected, processed, and likewise stored within the BTRC Laboratory. Functional, neuropsychological and psychosocial assessments are collected at 3, 6, 12 and 24 months after injury for all severe TBI patients.

The UPMC Department of Hyperbaric Medicine is located at UPMC Presbyterian Hospital, and is one of the tri-state area's major resources for life threatening emergencies and outpatient treatments in the Pittsburgh and Western Pennsylvania region for over 20 years. The department maintains two monoplace chambers, and is in the progress of replacing/updating one of its monoplace chamber. The new chamber will allow for treatment of virtually any sized patient up to 700lbs, and allows for up to 4 continuously running IV drips (if 4 hyperbaric IV pumps are present). The department has one Sechrist Hyperbaric Ventilator and two Abbott Hyperbaric IV pumps, as well as equipment that allows for monitoring of critical care parameters such as ECG and arterial line waveform while the patient is inside the chamber. The department is staffed with one full time hyperbaric nurse and 5 casual hyperbaric nurses, all of whom have emergency and critical care credentials, and whom provide 24/7 emergency coverage for the department. Specially trained respiratory therapists are also available to the department to help manage intubated patients who require hyperbaric therapy. Department functions are supervised by its medical director, Dr. Kevin S. O'Toole, and treatments are considered to be physician supervised using the resources of the Presbyterian University Hospital Emergency Department. The department can manage critically ill and/or intubated patients whom are dependent on up to two continuous IV infusions. In 2010, the department delivered 1,168 treatments (198 urgent or emergent and 970 routine).

Loma Linda University Medical Center is a 900-bed tertiary care facility, and the only Level I trauma center serving San Bernardino, Riverside, Inyo and Mono counties. Each year, the institution admits more than 33,000 patients, which includes 150-200 adult patients with severe traumatic brain injuries. The emergency department at Loma Linda consists of separate adult and pediatric areas, and 55,000 patients are seen each year. There is a CT scanner in the emergency department. The medical center has two helipads to accommodate the most critically ill patients.

The neuroscience department consists of a multidisciplinary team of six attending neurosurgeons, nine resident neurosurgeons, physician assistants, nurse practitioners and support staff, all dedicated to providing excellent patient care. A neurosurgery resident is on-site 24 hours a day to ensure immediate care to patients with neurological emergencies.

The Zhang Neuroscience Research Laboratories involve training in neuroscience research; in particular, in the area of hyperbaric oxygenation in experimental protocols. The Laboratories currently host researchers from America, Canada, Jamaica, Puerto Rico, Iraq, Japan, China, Poland, Russia, Ireland, Turkey, and India. Dr. Zhang's research efforts have been and are supported by grants from American Heart Association, National Institute of Health, and several other foundations.

The surgical/trauma intensive care unit is a 24-bed intensive care unit with an all registered nurse staff, who work closely with the medical staff and other departments to provide nursing care for the critically ill adult patients. The unit staff are supported by the trauma support service to provide optimal care for trauma and neurosurgical patients. The ICU is run by board certified/eligible surgical critical care specialists and anesthesiologists. A full array of state-of –the-art monitoring is available to care for the patient with severe head injury, such as ICP monitoring, ventriculostomies, Licox O_2 equipment, etc.

The Hyperbaric Medicine Service at Loma Linda University Medical Center was started in 1981 with one Sechrist 2500 monoplace chamber. The service now operates with 4 Sechrist monoplace chambers; two 32-inch diameter chamber, one 36-inch diameter chamber, and a new 41-inch diameter chamber. All chambers are equipped to receive and treat ICU patients. The chambers can accommodate the patient that requires ventilator support, administration of IV fluids and drugs, ECG, transcutaneous, non-invasive and invasive blood pressures monitoring and intracranial pressure monitoring. The unit is open 24 hours a day with afterhours covered by on-call staff. The unit is staffed with 6 licensed respiratory care practitioners. All personnel have received training at approved Undersea Hyperbaric Medicine Society (UHMS) programs, 5 are CHT's. The safety director is on the nationally accrediting committee for the UHS.

The Hamilton General Hospital (HGH) (237 Barton Street East, Hamilton, Ontario, L8L 2X2, Canada) is a major teaching hospital operated by the Hamilton Health Sciences Corporation, and is formally affiliated with

the McMaster University DeGroote School of Medicine. HGH is a tertiary care centre for Southwestern Ontario and a regional centre in cardiovascular care, neurosciences, trauma and burn treatment, rehabilitation, acquired brain injury and hyperbaric medicine.

The Trauma Program at HGH currently functions as Canada's second largest trauma centre, and sees approximately 27 cases of traumatic brain injured patients each year with GCS < 7 and with injury severity score > 15. Please see aggregate data compiled in January 2015.

The portals of entry for severe TBI patients as potential candidates for this study will be through the HGH Emergency Department, as the Regional Trauma Hospital and through the CritiCall Network which arranges emergent transfer of critical TBI patients within the province of Ontario, from those centres without such expertise. This transport encompasses land, fixed wing and rotary wing services.

The HGH Emergency Department has been recently renovated to encompass state of the art monitoring, stabilisation and imaging. The Emergency Department is staffed around the clock with certified Emergency Physicians, with a 24 hour specialized Trauma Team on stand-by.

Severe TBI patients will be cared for in the Medical/Surgical Intensive Care Unit. This 30 bed unit is staffed with a multidisciplinary team lead by certified intensivists with training in neuro-trauma care. Routine monitoring of severe TBI patients includes intracranial pressure monitoring and transcranial doppler.

Neurosurgical and neurological expertise is consistently available to the unit at any time.

The Hyperbaric Medicine Unit (HMU) at HGH has been in continuous operation since 1993, and is only one of three hospital based hyperbaric facilities in the province of Ontario. This HMU is responsible of more than 50% of all critical / emergent hyperbaric treatments for the province of Ontario. In 2013 the HMU provided 1800 treatments, and included 104 emergent / urgent treatments.

The HGH HMU staff is on-call 24/7 to deal with emergent / urgent patients. Physician staffing of the HMU is provided by three Royal College certified physicians with expertise in hyperbaric medicine, and specialty interests in Intensive Care, Surgery, Internal and Emergency Medicine. Ten respiratory therapist support the unit on a rotational basis, and have specialized training in hyperbaric treatment and ventilators.

The HGH HMU will treat severe TBI patients in one of three Sechrist 32-33 inch diameter monoplace chambers, allowing for elevated head-of-bed. The chambers are adapted for critical care treatments with multiple door penetrators for ventilation, IV infusions and critical care monitoring capabilities. Ventilated patients will be cared for using a Sechrist Model 500A ventilator, specifically designed for monoplace hyperbaric treatments. It has been modified to provide a range of FiO2 concentrations while in the hyperbaric oxygen enriched environment. The HMU has direct access to the Neurotrauma ICU.

Massachusetts General Hospital (MGH) is the third oldest general hospital in the United States. It is a 1,057 bed tertiary care hospital. It is a Level I adult trauma, pediatric trauma, and burn center, with approximately 47,000 inpatient admissions per year. The MGH Emergency Department comprises 64 beds with 16 critical care beds. The ED sees approximately 100,000 visits per year. It is staffed by a faculty of approximately 40 Emergency Medicine attendings, 60 residents, and 4 fellows. There are two CT scanners, one MRI machine, and 7 portable ultrasound machines in the department. Dedicated radiologists (including neuroradiologists) staff the ED 24/7. The recently expanded MGH Neurosciences Intensive Care Unit (NeuroICU) is 14,747 square feet, contains 22 beds, and is staffed by 80 Neurointensive Nurses, a Clinical Nurse Specialist, and a nursing director. Physician coverage is provided by two teams of fellows and residents and board-certified Neurointensive Care attending physicians. A full range of neurosurgical and neurointerventional services are available 24/7 at MGH.

The Norman Knight Hyperbaric Medicine Center at the Massachusetts Eye and Ear Infirmary in Boston has been in continuous operation since April 1st, 2001. It has been the only clinical center in the New England area to open on a 24/7 basis since that time, and is the only facility in the area to accept intubated patients in need of critical care and HBO Therapy. In 2013, the Hyperbaric Medicine Program delivered 1441 HBO treatments, of which 84 were emergencies. The hyperbaric facility falls within the administrative structure of the Department of Head and Neck Surgery and Hyperbaric Medicine. Dr. Daniel Deschler, M.D., F.A.C.S., is the medical director of the program and Dr. Jean Bruch, D.D.S., M.D., is the assistant medical director. The staff for the Hyperbaric Medicine program provide 24/7 coverage and are always available for emergencies. This staff consists of two full-time and three per-diem nurses, who are certified in primary hyperbaric nursing from Palmetto Richland Memorial Hospital in Columbia, South Carolina. All nurses are also ACLS certified. The

clinical resource nurse is a VHMS certified hyperbaric nurse. Seven doctors, all certified in Hyperbaric Medicine from Palmetto Richland Memorial Hospital in South Carolina, and one doctor, certified in Undersea and Hyperbaric Medicine, staff the unit and participate in the on-call program. Respiratory therapists and critical care nurses from Massachusetts General Hospital are part of the team for patients requiring mechanical ventilation. The unit has three Sechrist monoplace chambers, two of which are equipped with Sechrist ventilators. Four pass-through pins are available to administer IV's in-chamber. In-chamber blood pressure monitoring is available using Medical Systems Oscillomate 1630. A-line and EKG monitoring is available using Nihon Khoden America monitors and the necessary pass-throughs.

Nebraska Medical Center in Omaha, NE is ranked nationally in 6 adult specialties. It was also high-performing in 6 additional adult specialties. It scored high in patient safety, demonstrating commitment to reducing accidents and medical mistakes. Nebraska Medical Center is a 495-bed general medical and surgical facility with 23,848 admissions in the most recent year reported. It performed 7,877 annual inpatient and 8,179 outpatient surgeries.

Hyperbaric Medicine Center

Nebraska Medicine is the only hospital in the state of Nebraska that offers 24/7 hyperbaric oxygen therapy as well as the only critical care capable hyperbaric oxygen center. We have four (4) Sechrist monoplace chambers ranging from 2800 to 3600 cubic inches capacity. The Hyperbaric Medicine Program at UNMC has been in continuous operation since 1986. It has been the only clinical HBO chamber facility in the state of Nebraska until a few years ago and has served the entire state, as well as the bordering regions Iowa, Kansas and South Dakota. In 2014, the Hyperbaric Medicine Program delivered 2237 HBO treatments, of which 11% were emergencies. The hyperbaric facility falls within the administrative structure of Adult Acute Care Services. Jeff Cooper, M.D., board certified in Emergency Medicine, is the Medical Director of the Hyperbaric Medicine Program.

The staff for the Hyperbaric Medicine Program provide 24/7 coverage and are always available for emergencies. This staff consists of two full-time, certified hyperbaric nurses with one certified hyperbaric LPN/ technician. Several other nurses help with call coverage. The unit's nurse manager is also a certified hyperbaric nurse. Three physicians (two board certified by Emergency Medicine, one in Pulmonology/Critical Care, two in UHM) participate in the program and supervise all treatments.

The severe TBI patients will be treated in the larger monoplace chambers installed in a specially adapted room directly across the hallway from the Burn ICU. The diameter of these chambers allows the head of the patients' bed to remain at 20 degrees or more. The chambers have 3-4 IV penetrations as well as ventilator penetrations. Additional penetrations are present to add additions for the study's needs. There is a Sechrist "New Pin" system for electrical wiring harness that allows monitoring of electrocardiogram, arterial line, etc.

Two Sechrist Ventilators are used for ventilating severe TBI patients receiving HBO treatment. This ventilator is fairly limited but has been used successfully by our staff on numerous hyperbaric treatment patients. Exhaled Tidal volume, peak inspiratory pressure and PEEP are the only variables which can be monitored with this ventilator.

Emergency Department

Nebraska Medicine's Emergency Department is one of the largest emergency departments in the Midwest, with an annual Census of 50,244 and an admission rate of 25%. It serves a 23 county region of approximately 1,000,000 people as well as being a referral center for other regions in Nebraska and Western Iowa. The ED has 46 rooms including 4 trauma bays and sees Level I traumas 24 hours a day. The ED is staffed 24/7 by fully trained and board certified emergency medicine physicians. The UNMC ED has a state-of-the-art stabilization room where critically ill patients are stabilized and the various trauma services converge for the initial triage and management of the patient. The ED has adjacent computerized tomography (CT) and Magnetic Resonance Imaging (MRI). The Nebraska Medicine Med Center Campus has been heralded as one of the finest academic medical centers in the country. At the present time, the Department's main focus is on patient-oriented research. Basic/Clinical research in Heart Failure and Heart and Lung Injury/Resuscitation is conducted in collaboration with the Division of Cardiology, Division of Pulmonary Medicine and Critical Care, Department of Cellular and Integrative Physiology, and Department of Surgery.

Comprehensive Trauma Center

Nebraska Medicine is the only state designated Comprehensive Trauma Center in Nebraska serving both pediatric and adult patients. It is pending verification as a Level I Trauma Center by the American College of Surgeons. A trauma registry has been maintained by the Trauma Services Department since 1994. Approximately 1,800 patients are entered into the database each year. In 2014 there were 62 patients with GCS≤8 which would have been possible candidates for this study.

Surgical specialties include:

- Trauma surgery
  - All the trauma surgeons at Nebraska Medicine are specialty trained and board certified in critical care surgery in order to provide additional expertise when caring for the injured patient. A board certified trauma surgeon is in the hospital twenty-four hours each day, seven days each week, to oversee the care of patients.
- Neurosurgery
  - Nebraska Medicine's Neurosurgery Department offers a full range of treatment options for all traumatic neurosurgical problems including traumatic brain injuries and spinal cord injuries.
- Vascular surgery
- Thoracic (chest) surgery
- Plastic surgery
- Orthopedic surgery
- Hand surgery
- Pediatric surgery
- Otolaryngology (ear, nose and throat)
- Ophthalmology

Major equipment available in all clinical centers include: Hyperbaric Oxygen chambers, ventilation systems, monitoring equipment. Upgrades will be made as necessary to current chambers. Specific equipment available at each site is outlined in the Facilities and Resources section.

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

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	File Name
Attach Biographical Sketch*:	1237-Rockswold biosketch May 2015.pdf
Attach Current & Pending Support:	

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Phone Number*: 734-232-2142 Fax Number: 734-232-2122 E-Mail*: wbarsan@med.umich.edu

Credential, e.g., agency login: wbarsan

Project Role*: PD/PI Other Project Role Category:

Degree Type: MD Degree Year: 1975

File Name

Attach Biographical Sketch*: 1238-Barsan Biosketch for HOBIT.pdf

Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Byron Middle Name Last Name*: Gajewski Suffix:

Position/Title*: Professor of Biostatistics
Organization Name*: University of Kansas Medical Center
Department:
Division:
Street1*: 3901 Rainbow Blvd
Street2: MSN 1039
City*: Kansas City
County:
State*: KS: Kansas
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 66103-2937

Phone Number*: 913-588-1603 Fax Number: 913-588-0252 E-Mail*: bgajewski@kumc.edu

Credential, e.g., agency login: bgajewski

Project Role*: PD/PI Other Project Role Category:

Degree Type: PhD Degree Year: 2000

File Name

Attach Biographical Sketch*: 1239-Gajewski NIH biosketchNIHhobitNewFormat.pdf

Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Sarah Middle Name Last Name*: Rockswold Suffix:

Position/Title*: Assistant Professor
Organization Name*: Minneapolis Medical Research Foundation
Department: Physical Medicine
Division:
Street1*: 701 Park Ave
Street2:
City*: Minneapolis
County:
State*: MN: Minnesota
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 55415-1623

Phone Number*: 612-873-8700 Fax Number: E-Mail*: sarah.rockswold@hcmed.org

Credential, e.g., agency login:

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: MD Degree Year: 1995

File Name

Attach Biographical Sketch*: 1240-rockswold_Sarah_NIHbiosketch_HBO_2015.pdf

Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Uzma Middle Name Last Name*: Samadani Suffix:

Position/Title*: Assistant Professor
Organization Name*: Minneapolis Medical Research Foundation
Department: Neurosurgery
Division:
Street1*: 701 Park Ave
Street2:
City*: Minneapolis
County:
State*: MN: Minnesota
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 55415-1623

Phone Number*: 212-686-7500 Fax Number: E-Mail*: uzma@samadani.com

Credential, e.g., agency login:

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: MD Degree Year: 1990

File Name

Attach Biographical Sketch*: 1241-Samandani biosketch.pdf

Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Robert Middle Name Last Name*: Silbergleit Suffix:

Position/Title*: Professor
Organization Name*: Regents of the University of Michigan
Department:
Division:
Street1*: 3003 South State Street
Street2:
City*: Ann Arbor
County:
State*: MI: Michigan
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 48109-1274

Phone Number*: 734-232-2142 Fax Number: E-Mail*: robie@med.umich.edu

Credential, e.g., agency login: silbergleit

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: MD Degree Year: 1992

File Name

Attach Biographical Sketch*: 1242-Silbergleit Biosketch for HOBIT.pdf

Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Scott Middle Name Last Name*: Berry Suffix:

Position/Title*: President and Senior Statistical Scientist
Organization Name*: Berry Consultants
Department:
Division:
Street1*: 4301 Westbank Drive
Street2: Bldg B, Suite 140
City*: Austin
County:
State*: TX: Texas
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 78746-0008

Phone Number*: 512-213-6428 Fax Number: E-Mail*: scott@berryconsultants.net

Credential, e.g., agency login: STATBERRY

Project Role*: Other (Specify) Other Project Role Category: Other Significant Contributor

Degree Type: PhD Degree Year: 1994

File Name

Attach Biographical Sketch*: 1243-SMB_Biosketch_NewVersion.pdf

Attach Current & Pending Support:

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person.

NAME	POSITION TITLE
Gaylan L. Rockswold, MD, PhD	Professor of Neurosurgery Medical Director, Traumatic Brain Injury Center
eRA COMMONS USER NAME (credential, e.g., agency login) GAYLAN_ROCKSWOLD	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
St. Olaf College, Northfield, MN	BA	1962	Chemistry
University of MN Med School, Minneapolis, MN	MD, BS	1966	Medicine
University of Edinburgh School of Med, Scotland		1965	Medicine
University of Minnesota, Minneapolis, MN	Residency	1974	Neurosurgery
University of Minnesota, Minneapolis, MN	PhD	1976	Neurosurgery

Please refer to the application instructions in order to complete sections A, B, C, and D of the Biographical Sketch.

Gaylan L. Rockswold, M.D., Ph.D., is Professor of Neurosurgery at the University of Minnesota and Medical Director of the Traumatic Brain Injury Center at the Hennepin County Medical Center. He has a longstanding interest and expertise in neurotrauma, particularly in traumatic brain injury (TBI). He has been acknowledged by the Brain Injury Association of Minnesota on three occasions for extraordinary contributions to the welfare of TBI victims. Dr. Rockswold is the leading authority and investigator in the clinical application of hyperbaric oxygen (HBO2) to patients with severe TBI. He has been the PI for three NINDS grants investigating HBO2 therapy in TBI. He has had extensive administrative experience in directing a busy neurosurgical service at a level I trauma center, a large multidisciplinary TBI Center of Excellence, and as an executive in the Minneapolis Medical Research Foundation and as Chairman of the Board of the Hennepin Health Foundation. With his background and expertise in both management of severe TBI, as well as in critical care hyperbaric medicine and its application in severe TBI, he is well qualified to serve as PI on the HOBIT trial.

a. Diaz FG, Yock DH, Larson DA and Rockswold GL: Early diagnosis of delayed post-traumatic intracerebral hematomas. J Neurosurg 50:217-223, 1979
b. Rockswold GL, Leonard PR, Nagib MG: Analysis of management in thirty-three closed head injury patients who talked and deteriorated. Neurosurg 21(1):51-55, 1987
c. Rockswold SB, Rockswold GL, Vargo JM, Erickson CA, Sutton RL, Bergman TA, Biros MH: Effects of hyperbaric oxygen therapy on cerebral metabolism and intracranial pressure in severely brain-injured patients. J Neurosurgery 94(3):403-411, 2001
d. Gossett WA, Rockswold GL, Rockswold SB, Adkinson CD, Bergman TA, Quickel RR: The safe treatment, monitoring and management of severe traumatic brain injury patients in a monoplace chamber. Undersea Hyperbaric Medicine 37(1):35-48, 2010

1966-1967	Intern, Hennepin County General Hospital, Minneapolis, MN
1967-1968	Resident, General Surgery, U.S. Public Health Service Hospital, Baltimore, MD
1967-1969	Surgeon, U.S. Public Health Service (military service)
1968-1969	Medical Associate, National Cancer Institute, Section of Neurosurgery
1969-1974	Resident, Department of Neurosurgery, University of Minnesota, Minneapolis, MN
1974-1976	Assistant Chief, Division of Neurosurgery, Department of Surgery, Hennepin County Medical Center, Minneapolis, MN
1974-1976	Instructor in Neurosurgery, University of Minnesota, Minneapolis, MN
1976-1981	Assistant Professor of Neurosurgery, University of Minnesota, Minneapolis, MN

1977-2011	Chief, Division of Neurosurgery, Department of Surgery, Hennepin County Medical Center, Minneapolis, MN
1981-1992	Associate Professor of Neurosurgery, University of Minnesota, Minneapolis, MN
1992-present	Professor of Neurosurgery, University of Minnesota, Minneapolis, MN
2206-present	Medical Director, Traumatic Brain Injury Center, Hennepin County Medical Center, Minneapolis, MN

1976-present	Congress of Neurological Surgeons
1977-present	American Association of Neurological Surgeons
1985-1990	American College of Surgeons, Minnesota State Committee on Trauma
1989-present	Neurosurgical Society of America
1989-1991	Secretary-Treasurer, Minnesota Neurosurgical Society
1989-1993	Vice President/President Elect, Minnesota Neurosurgical Society
1990-1995	Advisor, THINK FIRST, Head and Spinal Cord Injury Prevention Program, Minnesota
1994-1995	President, Minnesota Neurosurgical Society
1999-present	Invited Reviewer: Surgical Neurology, Pediatrics, Journal of Trauma, Journal of Neurotrauma, and Annals of Medicine
2004	Invited Member, Special Emphasis Panel of the National Institute on Deafness and Other Communication Disorders
2008-2009	Temporary Member, Acute Neural Injury and Epilepsy Study Sections (ANIE), National Institutes of Health
2009	Temporary Member, Central Nervous System Injury and Neurodegeneration Study Section, National Institutes of Health
2013-2014	Lead Unaffiliated Neurotrauma Consultant, National Football League, Minnesota Vikings, Minneapolis, MN

1962	Phi Beta Kappa, St. Olaf College
1965	Alpha Omega Alpha, Honor Medical Society
1965	Smith-Kline-French Foreign Fellowship, Malawi, East Africa
1966	Mosby Book Award
1986	Honorary Member, Colombian College of Surgeons (South America)
1993	Annual Recognition Award, Minnesota Head Injury Association
2000	Special Recognition Award, Brain Injury Association of Minnesota
2005	Distinguished Alumni Award, St. Olaf College
2006	Robert L. Karol Care Beyond Expectations Award, Brain Injury Association of Minnesota

1. . My basic and clinical research efforts have been primarily in the area of the use of hyperbaric oxygen in the treatment of TBI. This has resulted in 11 peer-reviewed basic and clinical research publications on the subject. This body of work has demonstrated mechanisms in animal models which have included improvement in mitochondrial function and adenosine triphosphate production following HBO2 treatment for TBI. The mechanisms have been then demonstrated in clinical research using surrogate markers such as the cerebral metabolic rate of oxygen to demonstrate improvement in oxidative metabolism. In addition, clinical outcome, both in terms of improvement in favorable clinical outcome and reduced mortality rates has been demonstrated. Reduction in intracranial hypertension and the therapeutic intensity required for the treatment of intracranial pressure has also been demonstrated. The next logical step is this proposed phase II trial to determine the optimal treatment paradigm for HBO2 in severe TBI as well as demonstrate the probability that a subsequent confirmatory phase III trial would be successful.
    a. Rockswold SB, Rockswold GL, Zaun DA, Liu J: A prospective, randomized clinical trial to evaluate the effect of combined hyperbaric and normobaric hyperoxia on cerebral metabolism, intracranial pressure, oxygen toxicity and clinical outcome in severe traumatic brain injury. J Neurosurg 118(6):1317-1328, 2013

b. Rockswold SB, Rockswold GL, Zaun DA, Zhang X, Cerra CE, Bergman TA, Liu J: A prospective, randomized clinical trial to compare the effect of combined hyperbaric and normobaric hyperoxia on cerebral metabolism, intracranial pressure, and oxygen toxicity in severe traumatic brain injury. J Neurosurg 112(5):1080-94, 2010; response 113:1134-1335, 2010.
c. Rockswold GL, Ford SE, Anderson DC, Bergman TA, Sherman RE: The results of a prospective, randomized trial for treatment of severely brain-injured patients with hyperbaric oxygen. J Neurosurg 76:929-934, 1992.
d. Zhou Z, Daugherty WP, Sun D, Levasseur JE, Altememi N, Hamm RJ, Rockswold GL, Bullock R: Protection of mitochondrial function and improvement in cognitive recovery in rats treated with hyperbaric oxygen following lateral fluid-percussion injury. J Neurosurg 106:687-694, 2007.

2. . I have participated and supervised the care of thousands of patients experiencing neurotrauma to both the brain and spine and peripheral nerves. This has been direct hands-on care as well as teaching and supervising neurosurgical, emergency medicine, general surgery and other resident trainees. Intracranial hypertension is the leading cause of death and deterioration following severe TBI. Our clinical investigations have demonstrated the value of hypertonic saline in reducing intracranial pressure and its apparent superiority to mannitol. I've had particular interest in the management of cervical spine fractures with immobilization and Halo vest which frequently renders surgical procedures unnecessary. I have published 20 peer-reviewed articles on neurotrauma in leading trauma journals. I have been either the lead author or senior managing author for most of these publications. Examples of that are listed below.
   a. Rockswold GL, Solid CA, Paredes-Andrade E, Rockswold SB, Jancik JT, Quickel RR: Hypertonic saline and its effect on intracranial pressure, cerebral perfusion pressure, and brain tissue oxygen. Neurosurgery 65(6):1035-41; discussion 1041-2, 2009.
   b. Rockswold GL, Bergman TA, Ford SE: Halo immobilization and surgical fusion: Relative indications and effectiveness in the treatment of 140 cervical spine injuries. J Trauma 30(7):893-898, 1990.
   c. Nagib MG, Rockswold GL, Sherman RE, Lagaard MW: Civilian gunshot wounds to the brain: Prognosis and management. Neurosurg 18:533-537, 1986.
   d. Paredes-Andrade E, Solid CA, Rockswold SB, Odland RM, Rockswold GL: Hypertonic saline reduces intracranial hypertension in the presence of high serum and cerebrospinal fluid osmolalities. Neurocrit Care. Published online Jul 2011; 17(2):204-201; 2012.

3. . Early in my career I performed basic research on the innervation of the urinary bladder and urinary sphincters in higher primates. In addition, I participated and led investigations in the surgical treatment of spastic bladders caused primarily by multiple sclerosis. This resulted in 10 publications in peer-reviewed journals. This work contributed significantly to an understanding of the innervation of the urinary bladder and sphincters as well as better treatment of patients with uninhibited bladder reflexes.
   a. Rockswold GL, Bradley WE, Chou SN: Effect of sacral nerve blocks on the function of the urinary bladder in humans. J Neurosurg 40:83-89, 1974.
   b. Rockswold GL, Bradley WE, Timm GW, Chou SN: Electrophysiological technique for evaluating lesions of the conus medullaris and cauda equine. J Neurosurg 45:321-326, 1976.
   c. Rockswold GL, Chou WN, Bradley WE: Reevaluation of differential sacral rhizotomy for neurological bladder disease. J Neurosurg 48:773-778, 1978.
   d. Rockswold GL, Bradley WE, Chou SN: Innervation of the urinary bladder in higher primates. J Comp Neurol 193:509-520, 1980.

"Hyperbaric and Normobaric Oxygen in Severe Brain Injury"
Principal Investigator: Gaylan L. Rockswold, M.D., PhD.
Funding Source: National Institutes of Neurologic Disease and Stroke
Period: 12/01/2002 to 11/30/2005

"Low Molecular Weight Heparin in Acute Head Injury"
Principal Investigators: John K. Cumming, M.D., Gaylan L. Rockswold, M.D., Ph.D.
Funding Source: Minneapolis Medical Research Foundation
Period: 12/01/2002 to 11/30/2005

"Hyperbaric and Normobaric Oxygen in Severe Brain Injury" – Supplemental Grant
Principal Investigator: Gaylan L. Rockswold, M.D., Ph.D.
Funding Source: National Institutes of Neurologic Disease and Stroke
Period: 12/01/2005 to 11/30/2008

"Progesterone for Traumatic Brain Injury: Experimental Clinical Treatment (ProTect)"
University of Minnesota Hub Site
Principal Investigator: Gaylan L. Rockswold, M.D., Ph.D., Hennepin County Medical Center
Neurological Emergencies Treatment Trial (NETT) Network
Funding Source: National Institutes of Neurologic Disease and Stroke
Period: 2009-2014

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person.

NAME: William G. Barsan, MD

eRA COMMONS USER NAME (credential, e.g., agency login): wbarsan

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Cincinnati, Cincinnati, Ohio	BS	1972	Biology
Ohio State University, Columbus, Ohio	MD	1975	Medicine
University of Virginia Hospital, Charlottesville, VA		1975-77	Surgery & Radiology

I am an emergency physician with over 30 years of experience in neurological clinical trials. I was an investigator on the NINDS tPA pilot study from 1986 to 1988. I helped to design and was co-principal investigator for the University of Cincinnati team in the pivotal NINDS tPA study. Since 2006, I have been the principal investigator for the Neurologic Emergency Treatment Trials (NETT) network Clinical Coordinating Center funded by the NINDS. In this role I am responsible for all aspects of the development, design and conduct of clinical trials in the NETT. Since 2006, the NETT has conducted seven large randomized clinical trials of which four are still ongoing. In 2010, I was the co-principal investigator on a grant funded by the NIH Common Fund and FDA titled “Accelerating Drug and Device Evaluation through Innovative Clinical Trial Design” (ADAPT-IT). As part of this grant, we developed Bayesian adaptive clinical trials for the NETT and have been performing a mixed methods analysis to evaluate the barriers to adoption and acceptance of these novel clinical trial designs from FDA, NIH, study sections, statisticians and clinical trialists. As part of the ADAPT-IT project, we designed five novel Bayesian adaptive clinical trials, one of which has been recently funded and will begin enrollment in 2015. The adaptive design for HOBIT was built on our experiences through the ADAPT-IT project. I was also the director of the hyperbaric program (HBO) at the University of Cincinnati in the late 1980’s and have personal experience managing patients receiving hyperbaric oxygen treatment. My experiences is in the design, conduct, management of clinical trials and my experience with HBO makes me well suited for my responsibilities to the current application.

1. Silbergleit, R., Durkalski, V., Lowenstein, D., Conwit, R., Pancioli, A., Palesch, W., Barsan, W., NETT Investigators “Intramuscular versus intravenous therapy for prehospital stats epilepticus. N Engl J Med, Feb. 2012. PMCID: PMC3307101
2. Meurer, W.J., Lewis, R.J., Tagle, D., Fetters, M.D., Legocki, L., Berry, S., Connor, J., Durkalski, V., Elm, J., Zhao, W., Frederiksen, S., Silbergleit, R., Palesch, Y., Berry, D.A., Barsan, W.G. “An overview of the adaptive designs accelerating promising trials into treatments (ADAPT-IT) project. Ann Emerg Med, Oct. 2012. PMCID: PMC3557826
3. Ginsberg, MD, Palesch Y, Hill MD, Martin, RH, Moy, CS, Barsan, WG, Waldman, BD, Tamariz, D, Ryckborst, KJ, NETT Investigators “High-dose albumin treatment for acute ischaemic stroke (ALIAS) part 2: a randomized, double-blind, phase 3, placebo-controlled trial” The Lancet Neurology, Nov. 2013. PMCID: PMC3929943
4. Wright DW, Yeatts SD, Silbergleit R, Palesch YY, Hertzberg VS, Frankel M, Goldstein FC, Caveney AF, Howlett-Smith H, Bengelink EM, Manley GT, Merck LH, Janis LS, Barsan WG. Very early administration of progesterone for acute traumatic brain injury. N Engl J Med. 2014 Dec 25;371(26):2457-66. PubMed PMID: 25493974; NIHMSID: NIHMS653108; PubMed Central PMCID:PMC4303469.

1979-1985 Assistant Professor, Dept of Emergency Medicine, Univ of Cincinnati College of Medicine
1981-1984 Residency Coordinator, Dept of Emerg Medicine, Univ of Cincinnati College of Medicine

1985-1991	Associate Professor, Dept of Emergency Medicine, Univ of Cincinnati College of Medicine
1991-1992	Professor, Dept of Emergency Medicine, Univ of Cincinnati College of Medicine
1992-1999	Professor and Section Head, Dept of Emergency Medicine, Univ of Michigan
1999-2012	Professor and Chair, Dept of Emergency Medicine, Univ of Michigan
2012-Present	Professor, Dept of Emergency Medicine, Univ of Michigan

1985-1993	Society for Academic Emergency Medicine, Board of Directors
1991-1992	Society for Academic Emergency Medicine, President
1993-2001	American Board of Emergency Medicine, Board of Directors
1999-2001	American Board of Emergency Medicine, President
2002-2004	Chair, Board of Trustees, Huron Valley Ambulance
2002-2006	Deputy Editor, Annals of Emergency Medicine

1986	Founding Member, Greater Cincinnati/Northern Kentucky Stroke Team
1992	Golden Apple Teaching Award, Univ of Cincinnati, Dept of Emergency Medicine
1995	Hal Jayne Academic Excellence Award, presented by SAEM
2003	Elected to the Institute of Medicine, National Academy of Sciences
2004	Peter Rosen Award for Academic Leadership, American Academy of Emergency Physicians
2004	Outstanding Contributions in Research Award, American College of Emergency Physicians
2005	SAEM Leadership Award

1. Neurotrauma: As principal investigator of the NETT Clinical Coordinating Center, I was intimately involved in the planning, design and conduct of the ProTECT study evaluating the use of early administration of Progesterone in patients with moderate to severe traumatic brain injury. This was a hyperacute interventional study in traumatic brain injury that utilized exception from informed consent and randomized all patients within four hours of the time of injury. The ProTECT trial has been cited as a well-designed trial that has advanced the field of TBI research. As part of the ADAPT-IT project, I was also responsible for helping to design the ARCTIC study, which is a dose finding and efficacy trial of induced hypothermia in acute cervical and spinal cord injury. I am also currently involved in helping design the BOOST 3 study which will evaluate the use of brain tissue oxygen monitoring and its effect on outcome in patients with severe traumatic brain injury. I will be co-PI on an upcoming grant submission for this project.
   a. Meurer WJ, Barsan WG, “Spinal cord injury neuroprotection and promise of flexible adaptive clinical trials” World Neurosurgery PMCID:PMC4050030
   b. Tosetti P, Hicks RR, Theriault E, Phillips A, Koroshetz W, Draghia-Akli R; Workshop Participants. Toward an international initiative for traumatic brain injury research J Neurotrauma. 2013 Jul 15;30(14):1211-22. doi: 10.1089/neu.2013.2896. PMCID:PMC3713440
   c. Wright DW, Yeatts SD, Silbergleit R, Palesch YY, Hertzberg VS, Frankel M, Goldstein FC, Caveney AF, Howlett-Smith H, Bengelink EM, Manley GT, Merck LH, Janis LS, Barsan WG. Very early administration of progesterone for acute traumatic brain injury. N Engl J Med. 2014 Dec 25;371(26):2457-66. PubMed PMID: 25493974; NIHMSID: NIHMS653108; PubMed Central PMCID: PMC4303469.
   d. Stocchetti N, Taccone FS, Citerio G, Pepe PE, Le Roux PD, Oddo M, Polderman KH, Stevens RD, Barsan W, Maas AIR, Meyfroidt G, Bell MJ, Silbergleit R, Vespa PM, Faden AI, Helbok R, Tisherman S,Zanier ER, Valenzuela T, Wendon J, Menon DK and Vincent JL. Neuroprotection in acute brain injury: an up-to-date review. *Crit Care* 2015. PMCID: PMC4404577

2. Adaptive Clinical Trial Designs: In response to a RFA from the NIH Common Fund and FDA for advances in regulatory science, I was Principal Investigator along with Donald Berry, PhD and Roger Lewis, MD, PhD in the ADAPT-IT project. Adaptive clinical trial designs represent a broad category of innovations intended to address a variety of long standing challenges faced by investigators such as sensitivity to previous assumptions and delayed identification of an effective treatment. In the ADAPT-IT project we built a multi-disciplinary team to study how adaptive clinical trial methods could be implemented in planning actual confirmatory phase trials in an established NIH funded clinical trials network (NETT). We identified and quantitatively characterized the adaptive clinical trial methods of greatest potential value in confirmatory

phase clinical trials and performed a mixed methods analysis to understand the enthusiasm and concerns of key stakeholders that influence their willingness to try these innovative strategies. I have lectured widely on the use of adaptive clinical trial designs and have helped design six confirmatory phase adaptive clinical trials.

a. Meurer, W.J., Lewis, R.J., Tagle, D., Fetters, M.D., Legocki, L., Berry, S., Connor, J., Durkalski, V., Elm, J., Zhao, W., Frederiksen, S., Silbergleit, R., Palesch, Y., Berry, D.A., Barsan, W.G. “An overview of the adaptive designs accelerating promising trials into treatments (ADAPT-IT) project. Ann Emerg Med, Oct. 2012 PMCID:PMC3557826. PMCID: PMC3557826
b. Meurer WJ, Barsan WG, “Spinal cord injury neuroprotection and promise of flexible adaptive clinical trials” World Neurosurgery July 9, 2013 PMCID: PMC4050030

3. Acute Stroke: I have been involved in multiple acute stroke trials since the early 1980’s and treated the first stroke patient with intravenous tPA in the NINDS tPA pilot study in 1987. I was subsequently involved in designing the NINDS randomized tPA trial and the NIH stroke scale, which is the instrument for measuring the severity of stroke and has become the standard of care throughout the world. I was co-chair for the NINDS workshop that developed the standards for prehospital and emergency department care for acute stroke patients after the approval of tPA. I also helped design and was co-investigator on the ultra-early evaluation of intracerebral hemorrhage in the early 1990’s, which was the first study to demonstrate acute growth of intracerebral hemorrhage and its impact on neurological outcome. Within the NETT, we have conducted or are currently conducting four clinical stroke trials including ALIAS 2, ATACH 2, POINT and SHINE.
   a. The National Institute of Neurological Disorders and Stroke t-PA Stroke Study Group (W.G. Barsan), "Tissue Plasminogen Activator for Acute Ischemic Stroke". New England Journal of Medicine, 333:1581-87, December, 1995.
   b. Brott, T., Broderick, J., Kothari, R, Barsan, W., Tomsick, T., "Early Hemorrhage Growth in Patients with Intracerebral Hemorrhage." Stroke, 28(1):1-5. January, 1997
   c. Broderick, Barsan,W.G., et al, "Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Statement for Healthcare Professionals From a Special Writing Group of the Stroke Council, American Heart Association." Stroke, 1999;30:905-915.
   d. Ginsberg, MD, Palesch Y, Hill MD, Martin, RH, Moy, CS, Barsan, WG, Waldman, BD, Tamariz, D, Ryckborst, KJ, NETT Investigators “High-dose albumin treatment for acute ischaemic stroke (ALIAS) part 2: a randomized, double-blind, phase 3, placebo-controlled trial” The Lancet Neurology, Nov. 2013 PMCID:PMC3929943

4. Emergency Care Research: I have been involved in various aspects of emergency care research and the organization of clinical trials for 30 years. I was a leading participant in the NIH roundtables evaluating emergency care research and was part of the Emergency Neurological Clinical Trials Network Conference held by NINDS in 2003. I have advocated for the involvement of emergency medicine leadership in emergency care research at NIH and within the field of emergency medicine.
   a. Papa Linda, Kuppermann Nathan, Lamond Katherine, Barsan William G, et al, “Structure and Function of Emergency Care Research Networks: Strengths, Weaknesses, and Challenges.” Academic Emergency Medicine 16(10): 995-1004, 2009.
   b. Cofield Stacey, Conwit Robin, Barsan William, Quinn James, “Recruitment and Retention of Patients into Emergency Medicine Clinical Trials.” Academic Emergency Medicine 17(10):1104-1112, October 2010. PMCID:PMC3058592
   c. Cairns Charles B, Maier Ronald V, Adeoye Opeolu, Baptiste Darryl, Barsan William G, et al., “NIH Roundtable on Emergency Trauma Research.” Annals of Emergency Medicine 2010;56:538-550.
   d. D’Onofrio G, Jauch E, Jagoda A, Allen MH, Anglin D, Barsan WG, et al. “NIH Roundtable on Opportunities to Advance Research on Neurologic and Psychiatric Emergencies.” Annals of Emergency Medicine 2010;56:551-564.

1 U01 NS056975 Barsan (PI) 08/2006-07/2016
Neurological Emergencies Treatment Trials Network Clinical Coordinating Center
The goal of the Neurologic Emergencies Treatment Trials (NETT) Network is to improve outcomes of patients with acute neurologic problems through innovative research focused on the emergent phase of patient care.
Role: Principal Investigator

1U01NS062835 Johnston (PI) 09/2009-08/2015
POINT: Platelet-Oriented Inhibition in New TIA
The Primary Specific Aim of this randomized, double-blind, multicenter clinical trial is to determine whether clopidogrel (Plavix) 75 mg/day by mouth after a loading dose of 600 mg is effective in reducing the 90-day risk of major ischemic vascular events (ischemic stroke, myocardial infarction, and ischemic vascular death) when initiated within 12 hours of TIA onset in patients receiving aspirin 50-325 mg/day.
Role: Co-Investigator

1U01NS062778 Wright (PI) 07/2009-06/2015
Progesterone for Traumatic Brain Injury: Experimental Clinical Treatment
Progesterone is a steroid found to have neuroprotective properties in multiple different animal models of brain injury. The ProTECT trial will determine the efficacy and confirm safety of this treatment in adults with moderate to severe TBI.
Role: Co-Investigator

1U01NS073476-01
Accelerating Drug and Device Evaluation through Innovative Clinical Trial Design 09/2010-08/2015
The use of adaptive trial designs for confirmatory phase clinical trials has the prospect for accelerating the process of drug and device acceptance and regulatory approval. Four adaptive clinical trials will be designed for potential use in the NETT. The project will evaluate the process and potential barriers to use of adaptive designs for confirmatory phase clinical trials.
Role: Principal Investigator

1-U01-NS-069498-01 Johnston (PI) 08/2011-07/2016
Stroke Hyperglycemia Insulin Network Effort (SHINE)
Serve as the Clinical Coordinating Center for a multicenter, prospective, randomized, controlled trial, with blinded outcomes aims to determine the efficacy and provide further safety data on the use of insulin infusion therapy for glucose control in hyperglycemic acute ischemic stroke patients. The primary outcome to be assessed at 90 days will be the difference in favorable outcome measured by the modified Rankin Scale score in the insulin infusion group compared to the control group.
Role: Co-Investigator

U01 NS 079077 Gentile (PI) 02/2013-01/2015
Serve as the PI for the Clinical Coordinating Center for the multicenter Insights on Selected Procoagulation Markers and Outcomes in Stroke Trial (I-SPOT) trial. Compare the effects of strict hyperglycemia control with standard treatment of hyperglycemia on membrane-bound TF-PCA and markers of blood coagulation in T2DM patients after AIS.
Role: Co-Investigator

1R24TW00889901 (Barsan/Donkor) 11/2010-08/2015
Ghana Emergency Medicine Collaborative Training Program
The 5 year project will generate a cadre of well-trained EM personnel who will sustain training of EM providers in Ghana. Approximately 100 nurses, 100 residents and 40 EMS providers will undergo training over the 5 year period. 900 medical students will be educated about EM. Exposure to research methodology will produce residency graduates fluent in research methods and capable conducting locally-based research. Ultimately, the in-country program will improve retention of EM providers and decrease preventable acute injury and illness related deaths in Ghana.

Role: Principal Investigator

1U01NS062091 (Qureshi) 10/2013-07/2015
Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH)-II: A Phase III Randomized Multicenter Clinical Trial of Blood Pressure Reduction for Hypertension in Acute Intracerebral Hemorrhage.
ATACH-II is a multicenter, randomized, concurrently-controlled, parallel arms design to determine the therapeutic benefit of intensive SBP treatment (SBP<140 mmHg) compared with standard SBP treatment (SBP<180 mmHg) in reducing the proportion of patients with death and disability (mRS of 4-6) at Day 90 among subjects with ICH treated within 4.5 hours of symptom onset. Dr. Barsan, in collaboration with Dr. Quresh, will oversee the Clinical Coordination for the US sites participating in this trial.
Role: Co-Investigator

(past 3 years)

1 U01 NS056975 08/2006-07/2011
Sponsor: NIH/NINDS
Title:
Role: Co-Investigator
The goal of RAMPART is to study will determine if the anti-seizure drug midazolam given via IM stops seizures as well as the anti-seizure medicine lorazepam given IV, and if there is a difference in the rapidity and safety of these two medicines given in these different ways.

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person.

NAME	POSITION TITLE
Gajewski, Byron J.	Professor of Biostatistics
eRA COMMONS USER NAME bgajewski	

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Marquette University, Milwaukee, WI	BS	1993	Civil Engineering, Mathematics
Marquette University, Milwaukee, WI	MS	1995	Mathematics
Texas A&M University, College Station, TX	PhD	2000	Statistics

For almost 14 years, I have obtained specific education and expertise in Bayesian biostatistics and clinical trials, key research areas for this proposed work. Human development, outcomes, health disparities, and clinical trials are included in my translational applications expertise. I have spent the past year working with the team of this proposal on finding an optimal Bayesian adaptive design for this proposed DHA confirmatory clinical trial. I have strong experience working with co-PI Carlson on a current DHA clinical trial, as evidenced by the publication in *The American Journal of Clinical Nutrition* showing DHA supplementation improves pregnancy outcomes. I have expertise in the design and implementation of Bayesian designs. I have published new Bayesian clinical trials methodology in a top tier biostatistics journal (*Statistics in Medicine*), of which one was quoted in NHLBI's RFA-HL-08-013. I have also published two papers showcasing novel Bayesian predictors of clinical trials accrual with co-PI Carlson (one of which is shown below). I was also successful in gaining PCORI funding for a novel Bayesian adaptive design which is a comparative effectiveness trial aimed at finding best treatment for pain in patients with painful neuropathy. The work on this current proposal is a blend of both design and methods. As PI, co-Investigator, and statistician of a number of funded grants over the course of my career, I believe that I am well qualified as co-PI (leading the Bayesian Adaptive Design and methods) for this proposal.

1. , Mayo, M.S. (2006), "Bayesian Sample Size Calculations in Phase II Clinical Trials using a Mixture of Informative Priors," *Statistics in Medicine,* 25(15), 2554-2566.
2. Carlson, SE, Colombo, J, Gustafson, KM, Mundy, D, Yeast,J, Georgieff, MK, Markley, LA, Kerling, EH, & Shaddy, DJ (2013), "Docosahexaenoic Acid Supplementation and Pregnancy Outcomes," *The American Journal of Clinical Nutrition*, 97(4), 808-815 (PMCID: PMC3607655).
3. Berry, SM, Quintana, M, Pasnoor, M, Dimachkie, M, Herbelin, L, and Barohn, R (2015), "Building Efficient Comparative Effectiveness Trials through Adaptive Designs, Utility Functions, and Accrual Rate Optimization: Finding the Sweet Spot," *Statistics in Medicine,* 34(7), 1134-1149 (PMCID: PMC4355191).

2000−2002	Statistical Consultant to University of Florida School of Medicine
2000−2002	Assistant Professor of Statistics, St. Cloud State University
2002−2008	Assistant Professor, University of Kansas Schools Nursing and Allied Health
2008-2012	Associate Professor of Biostatistics, University of Kansas School of Medicine
2012-pres	Professor of Biostatistics, University of Kansas School of Medicine

1996-Pres	American Statistical Association
2004-2008	Council, American Statistical Association, Kansas – Western Missouri Chapter
2002-Pres	Eastern North American Region, International Biometrics Society
2006-Pres	Reviewer *Statistics in Medicine*
2004-2009	Protocol Review and Monitoring Committee (PRMC) of the University of Kansas Cancer Center
2009-2011	Reviewer, American Cancer Society IRG Grant Program
2007-Pres	Full Member, University of Kansas Cancer Center (2009-present, "Cancer Control & Population Health")
2009-2010	NIH Peer Review Committee, Clinical Hematology Special Emphasis Panel, reviewer
2014-Pre	Patient Centered Outcomes Research Institute (PCORI) Scientific Reviewer
2013-Pre	PStat® Accredited Professional Statistician, American Statistical Association

1997	Kosciusko Foundation Fellowship
2008	Gajewski & Mayo (2006) study quoted in NHLBI's RFA-HL-08-013
2013	Director's Award: Faculty from the American Indian Health Research and Education Alliance

My statistical methodological research focuses on Bayesian data analysis specifically in the design and modeling of clinical trials, health care services, and latent variable modeling. My collaborative work spans medicine, nursing, health professions, and other related fields.

1. Clinical Trials
    a. Mayo, M.S., and (2004), "Bayesian sample size calculations in phase II clinical trials using informative conjugate priors," *Controlled Clinical Trials*, 25, 157-167.
    b. Simon, S, and Carlson, S (2008). Predicting accrual in clinical trials with Bayesian posterior predictive distributions. *Statistics in Medicine*, 27(13), 2328-2340. (accepted before April 7, 2008, no PMCID needed)
    c. Jiang, Y, Simon, S, Mayo, MS, & (in press), "Modeling and Validating Bayesian Accrual Models on Clinical Data and Simulations Using Adaptive priors," *Statistics in Medicine* (PMCID: PMC4314351).
    d. Wick, J, Berry, SM, Yeh, H, Choi, W, Pacheco, CM, Daley, C, (in press), "A Novel Evaluation of Optimality for Randomized Controlled Trials," Conditionally accepted *Journal of Biopharmaceutical Statistics* (PMCID: in process).

2. Health care services
    a. ., Lee, R, Thompson, S, Dunton, N, Becker, A, Wells, V (2006), "Non-Normal Path Analysis in the Presence of Measurement Error and Missing Data: A Bayesian Analysis of Nursing Homes' Structure and Outcomes," *Statistics in Medicine*, 25(21), 3632-3647.
    b. Nicholson, N. and Widen, J.E. (2009), "Predicting Hearing Threshold in Non-Responsive Subjects Using a Log-Normal Bayesian Linear Model in the Presence of Left Censored Covariates," *Statistics in Biopharmaceutical Research*, 1(2), 137–148 (not NIH funded).
    c. Lee, R, Dunton, N (2012), "Data Envelopment Analysis in the Presence of Measurement Error: Case Study from the National Database of Nursing Quality Indicators® (NDNQI®)," *Journal of Applied Statistics*, 39 (12), 2639-2653 PMCID: PMC3544524 .
    d. & Dunton, N (2013), "Identifying Individual Changes in Performance with Composite Quality Indicators while Accounting for Regression-to-the Mean," *Medical Decision Making, 33(3), 396-406 (*PMCID: PMC3538092*).*

3. Latent variable modeling (Psychometrics/Patient Reported Outcomes)

a. Thompson, S., Dunton, N., Becker, A. and Wrona, M. (2006), “Inter-rater Reliability of Nursing Home Surveys: A Bayesian Latent Class Approach,” *Statistics in Medicine*, 25(2), 325-344.
b. Hart, S, Bergquist, S, & Dunton, N (2007), “Inter-rater Reliability of Pressure Ulcer Staging: Ordinal Probit Bayesian Hierarchical Model that allows for Uncertain Rater Response,” *Statistics in Medicine*, 26(25), 4602-4618.
c. Jiang, Y, Boyle, DK, Bott, MJ, Wick, JA, Yu, Q, (2014), "Expediting Clinical and Translational Research via Bayesian Instrument Development," *Applied Psychological Measurement*, 38(4), 296-310 (PMCID: PMC4034393).

http://www.ncbi.nlm.nih.gov/pubmed/?term=gajewski+byron

CER-1306-02496 Barohn (PI) 04/01/2014-3/31/2017
Patient Centered Outcomes Research Institute (PCORI)
PAIN-CONTOLS
Determine which drug is most effective in producing pain relief and improving quality of life in patients with CSPN. We will perform a prospective randomized comparative effectiveness Bayesian adaptive design study with those who do not have diabetes and for whom no other cause has been found. The four drugs we will use are nortriptyline, duloxetine, pregabalin and mexiletine.

R01 HD047315 Carlson (PI) 04/04/2006-01/31/2016 (renewal)
National Institutes of Health
DHA Supplementation and Pregnancy Outcomes
To determine whether maternal RBC PL DHA can be significantly increased by supplementation, assess the effect of DHA supplementation on duration of gestation, evaluate adverse events in women and infants in the treated and placebo groups, evaluate the effect of maternal DHA supplementation on visual evoked potential acuity in infancy, and evaluate the effect of DHA supplementation on the development of fundamental measures of cognitive function in infancy.

R03 NR013236 Gajewski (PI) 05/21/2014 - 05/20/2016
National Institutes of Health
A Novel Method for Expediting the Development of Patient Reported Outcome Measures
Major Goals: The specific aims for this proposed study are to: 1) Test Ordinal Bayesian Instrument Development (OBID) by comparing its performance (i.e., stability and development time differences) to classical instrument development using simulation date 2) Beta test OBID across settings of patient and family caregiver populations 3) Disseminate OBID software for evaluation by investigators in varied research communication.

CDRN-1306-04631 Waitman (PI) 03/06/2014-09/05/2015
Patient Centered Outcomes Research Institute (PCORI)
Greater Plains Collaborative Clinical Data Research Network
Establishment of Greater Plains Collaborative (GPC) Clinical Data Research Network with 10 institutions for standardizing data across i2b2 platforms and creating common infrastructure/methodologies to conduct comparative effectiveness research in future phases. Focus is on three patient cohorts: ALS, breast cancer, obesity.

1 P30 CA168524-01 Jensen (PI) 07/11/2012 – 6/30/2017

NIH/NCI

The University of Kansas Cancer Center is a growing matrix organization that aims to leverage unique scientific assets to build a nationally significant cancer research and treatment center that will become the leading academic institution in the world for transforming discoveries in the laboratory into new therapeutic approaches.

Gajewski (PI) 06/01/2013-6/01/2014
NCI (The KUCC)
The KUCC Pilot of Bayesian Prediction for Interim Review of Studies with Slow Accrual
The aims of this research study are to develop and test a software program for accrual (Aim #1) and develop a hierarchical extension to the accrual model (Aim #2). In Aim #1, we will develop a web-based applet that will provide a simple and easy to use interface that will encourage use of Bayesian models by a broader range of researchers. In Aim #2, the research team will develop a hierarchical accrual model. These extensions would provide modeling of individual strata in a stratified randomized study.

1UL1RR033179-01 Barohn & Aaronson (PI) 04/01/2011-3/31/2014
National Institutes of Health
Frontiers: Heartland Institute for Clinical and Translational Research
The University of Kansas Heartland Institute for Clinical and Translational Research is an academic home for clinical and translational research, providing support to scientists and involving the community, so that discoveries and research findings wi|l be brought more rapidly to the point of care, thus improving the health of all Kansans.

P20 MD004805-01 Daley & Greiner (PI) 04/01/2010-3/31/2015
National Institutes of Health
Center for American Indian Community Health (CAICH)
The CAICH addresses health disparities among American Indians, who face some of the greatest health disparities of any racial/ethnic group in the US and who have not historically been well represented in medical research or education in the health professions. The center addresses a variety of health issues and focuses on two major health issues among American Indians, smoking and mammography. American Indians have the highest rates of smoking and rising incidence and disproportionate mortality for breast cancer.

Dunton (PI) 01/01/2003-6/31/2014
American Nurses Association
National Database of Nursing Quality Indicators (NDNQI)
The National Database of Nursing Quality Indicators is established and maintained to: (1) provide benchmarking information on nursing-sensitive indicators to acute care hospitals for use in their quality improvement initiatives; and (2) monitor local and national trends in hospital nurse staffing to facilitate the American Nurses Association's *Patient Safety, Nursing Quality* initiative.

Pilot Grant Daley & Befort (PI) 6/01/2011- 5/30/2013
The University of Kansas Cancer Center
Testing a Culturally-Tailored Weight Loss Program for American Indians
The aims of this study are 1) to develop and pilot test a culturally-tailored weight control intervention for a heterogeneous adult AI community; 2) to estimate the effectiveness of the culturally-tailored weight control intervention in a heterogeneous AI community; and 3) to examine the impact of the intervention on weight, diet (daily energy, % kcal from fat, fruit and vegetable servings), and physical activity (min/week and energy expenditure/week). Results from the process evaluation will inform further development of the intervention.

Pilot Grant Befort (PI) 3/01/2013- 2/28/2014
CTSA Frontiers
Reducing sedentary behavior to prevent weight regain among breast cancer survivors The major aim of this study was to investigate the feasibility of decreasing sedentary behavior within a weight loss maintenance intervention. We will conduct a mid- and post-treatment process evaluation to assess acceptability and barriers to adherence and to refine the sedentary behavior component intervention. We expect that maintenance intervention + sedentary behavior component will result in greater reductions in sedentary behavior as objectively measured by accelerometry compared to MAINT alone.

Gajewski (PI) 09/01/2011-8/31/2012
National Institutes of Health ( )

The aims of this current proposal are to: (1) Test Bayesian Instrument Development (BID) by comparing its performance (i.e., stability and development time differences) to classical instrument development with exact estimation procedures, using simulation data. (2) Demonstrate BID with existing clinical data. The Frontiers pilot project will allow our team to increase our team's programming experience on the continuous version of BID and allow us to .

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person.

NAME	POSITION TITLE
Sarah B. Rockswold, M.D.	Assistant Professor of Physical Medicine and Rehabilitation Medical Director, Outpatient Traumatic Brain Injury Program, Hennepin County Medical Center
eRA COMMONS USER NAME (credential, e.g., agency login)	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
St. Olaf College, Northfield, MN	BA	05/1990	Chemistry, Religion
University of Minnesota, Minneapolis, MN	MD	06/1995	Medicine
Hennepin County Medical Center, Minneapolis, MN	Internship	1996-1997	General Surgery
University of Minnesota, Minneapolis, MN	Residency	1996-1998	Orthopedic Surgery
University of Minnesota, Minneapolis, MN	Residency	2000-2003	Physical Medicine & Rehabilitation

I am an Assistant Professor of Physical Medicine and Rehabilitation at the University of Minnesota and the Medical Director of the Outpatient Traumatic Brain Injury (TBI) Program at Hennepin County Medical Center (HCMC), a Level 1 trauma center. For the past 16 years, I have been involved with hyperbaric oxygen (HBO_2) research beginning when I was a graduate research associate in 1999. I was responsible for the analysis and interpretation of the data from the clinical study on HBO_2 funded by the NINDS grant P20NS30322 that was published in the Journal of Neurosurgery in 2001. I was a co-investigator and the study director for the recent prospective randomized clinical studies comparing HBO_2 and normobaric oxygen funded by the NINDS grants RO1-NS042126 and RO1-NS042126-03Sl, both of which were also published in the Journal of Neurosurgery. During both studies, I was directly responsible for the monitoring and quality of the data, adherence to the study protocol, and reporting of adverse events to the IRB at HCMC. I also was responsible for the analysis of the study data. Under my leadership, the HCMC outpatient TBI program has grown from 240 patient visits in 2004 to over 1700 patient visits last year. This growth has resulted in increased referrals to the interdisciplinary TBI team comprised of speech pathology, occupational therapy, neuropsychology, clinical psychology, therapeutic recreation, physical therapy, and social work. Total visits for these therapies increased from 306 in 2005 to 6,700 visits last year. Because of my great experience with both TBI and HBO_2, I am qualified to serve as co-investigator and internal medical monitor for the proposed project.

a. Rockswold SB, Rockswold GL, Vargo JM, Erickson CA, Sutton RL, Bergman TA, Biros MH: The effects of hyperbaric oxygen on cerebral metabolism and intracranial pressure in severely brain-injured patients. Journal of Neurosurgery 94:403-411, 2001.

b. Rockswold SB, Rockswold GL: Hyperbaric oxygen for traumatic brain injury. Hyperbaric Oxygen for Neurological Disorders. Ed: Zhang JH. Best Publishing, Flagstaff, 2008, pp 173-195.

c. Rockswold SB, Rockswold GL, Zaun DA, Zhang X, Cerra CE, Bergman TA, Liu J A prospective, randomized clinical trial to compare the effect of hyperbaric to normobaric hyperoxia on cerebral metabolism, intracranial pressure, and oxygen toxicity in severe traumatic brain injury. Journal of Neurosurgery 112:1080-1094, 2010.

d. Rockswold SB, Rockswold GL, Zaun DA, Liu J: A prospective, randomized clinical trial to evaluate the effect of combined hyperbaric and normobaric hyperoxia on cerebral metabolism, intracranial pressure, oxygen toxicity, and clinical outcome in severe traumatic brain injury. Journal of Neurosurgery 118(6): 1317- 1328, 2013

1989-1990	Undergraduate tutor, St. Olaf College, Department of Chemistry, Northfield, MN
1996-1997	Internship in General Surgery, Hennepin County Medical Center, Minneapolis, MN
1996-1998	Residency in Orthopedic Surgery, University of Minnesota, Minneapolis, MN
1999-2000	Graduate Research Associate, Minneapolis Medical Research Foundation, Minneapolis, MN
2000-2004	Residency in Physical Medicine and Rehabilitation, University of Minnesota, Minneapolis, MN
2004-present	Medical Director, Outpatient Traumatic Brain Injury Program, Hennepin County Medical Center, Minneapolis, MN
2004-present	Assistant Professor, Department of Physical Medicine and Rehabilitation, University of Minnesota, Minneapolis, MN
2004-present	Faculty, Department of Physical Medicine and Rehabilitation, Hennepin County Medical Center, Minneapolis, MN
2004-present	Faculty, Division of Neurosurgery, Department of Surgery, Hennepin County Medical Center, Minneapolis, MN
2011-2012	Site director, Hennepin County Medical Center, Minneapolis, University of Minnesota Physical Medicine and Rehabilitation residency program

2000-2004	Biomedical Studies Advisory Council, St. Olaf College, Minneapolis, MN
2001-2002	Residency Representative, Association of Academic Physiatrists
2001-2003	Member, Association of Academic Physiatrists National Membership Committee
2000-present	Member, Association of Academic Physiatrists
2000-present	Member, American Academy of Physical Medicine and Rehabilitation
2006-present	Board Certification by the American Board of Physical Medicine and Rehabilitation
2006-present	Executive Committee, Traumatic Brain Injury Center, Hennepin County Medical Center, Minneapolis, MN
2011	Guest Examiner for the National Oral Board Examination, American Board of Physical Medicine and Rehabilitation
2013-2014	Unaffiliated Neurotrauma Consultant, National Football League, Minnesota Vikings, Minneapolis, MN

1991	Phi Beta Kappa, St. Olaf College
1991-1995	Vines Medical School Scholarship for Academic Achievement, University of Minnesota
1995	Outstanding Medical School Graduate

1. . My clinical research efforts have been primarily in the area of the use of hyperbaric oxygen in the treatment of severe TBI for the past 16 years. I was responsible for the analysis and interpretation of the data from the clinical study on HBO_2 funded by the NINDS grant P20NS30322 that was published in the Journal of Neurosurgery in 2001. I was a co-investigator and the study director for the RO1 NINDS funded prospective randomized clinical studies comparing HBO_2 and normobaric oxygen, both of which were also published in the Journal of Neurosurgery. During both studies, I was directly responsible for the monitoring and quality of the data, adherence to the study protocol, and reporting of adverse events to the IRB at HCMC. I also was responsible for the analysis of the study data. These efforts have resulted in 7 peer-reviewed clinical research publications on the subject. These clinical investigations in HBO_2 have demonstrated that HBO_2 in comparison with standard care significantly improves markers of oxidative metabolism in relatively uninjured brain as well as pericontusional tissue, reduces intracranial hypertension, and

demonstrates improvements in markers of cerebral toxicity. In addition, clinical outcome, both in terms of improvement in favorable clinical outcome and reduced mortality rates has been shown.

a. Rockswold SB, Rockswold GL, Vargo JM, Erickson CA, Sutton RL, Bergman TA, Biros MH: The effects of hyperbaric oxygen on cerebral metabolism and intracranial pressure in severely brain-injured patients. Journal of Neurosurgery 94:403-411, 2001.
b. Rockswold SB, Rockswold GL: Hyperbaric oxygen for traumatic brain injury. Hyperbaric Oxygen for Neurological Disorders. Ed: Zhang JH. Best Publishing, Flagstaff, 2008, pp 173-195.
c. Rockswold SB, Rockswold GL, Zaun DA, Zhang X, Cerra CE, Bergman TA, Liu J A prospective, randomized clinical trial to compare the effect of hyperbaric to normobaric hyperoxia on cerebral metabolism, intracranial pressure, and oxygen toxicity in severe traumatic brain injury. Journal of Neurosurgery 112:1080-1094, 2010.
d. Rockswold SB, Rockswold GL, Zaun DA, Liu J: A prospective, randomized clinical trial to evaluate the effect of combined hyperbaric and normobaric hyperoxia on cerebral metabolism, intracranial pressure, oxygen toxicity, and clinical outcome in severe traumatic brain injury. Journal of Neurosurgery 118(6): 1317- 1328, 2013

2. The effectiveness and superiority of hypertonic saline in comparison over mannitol in the treatment of intracranial hypertension in severe traumatic brain injury was able to be documented in the below journal articles. Within a team of collaborators, I was able to contribute to the analysis and interpretation of the data. In addition to the treatment of intracranial pressure, it was shown that hypertonic saline improved cerebral perfusion pressure and brain tissue oxygen.

a. Rockswold GL, Solid CA, Paredes-Andrade E, Rockswold SB, Jancik JT, Quickel RR: Hypertonic saline and its effect on intracranial pressure, cerebral perfusion pressure, and brain tissue oxygen. Neurosurgery 65(6):1035-41; discussion 1041-2, 2009.
b. Paredes-Andrade E, Solid CA, Rockswold SB, Odland RM, Rockswold GL: Hypertonic saline reduces intracranial hypertension in the presence of high serum and cerebrospinal fluid osmolalities. Neurocrit Care 17:204-210, 2012.

3. I have specialized in the rehabilitation of patients with TBI for the past 11 years. I am an Assistant Professor at the University of Minnesota as well as the Medical Director of the Outpatient TBI Program at HCMC. I have been responsible for the care of hundreds of patients suffering from mild traumatic brain injury (mTBI). Although mTBI comprises 80% of the 3.5 million brain injuries, they have been underdiagnosed as well as underserved by the medical community. In the past several years, researchers have found that a somewhat silent majority of mTBI patients who develop lasting post-concussive syndrome have concurrent visual dysfunctions. I am currently the principal investigator of the research project, “Magnetic Resonance Imaging and Oculomotor Dysfunction in Mild Traumatic Brain Injury”, at the Center of Magnetic Resonance Research (CMRR) at the University of Minnesota. This research study will contribute greatly to a better understanding of the cerebral structural and metabolic changes associated with post traumatic visual dysfunctions, by using functional and diffusion MRI, as well as MR spectroscopy. Resting state fMRI signal fluctuations have been shown to be of significant clinical value as connectivity changes have indicated disease states such as Alzheimer’s, autism, depression, epilepsy, schizophrenia, multiple sclerosis, attention deficit hyperactivity disorder, and TBI. Correlation of such functional deficits, which have thus far been largely non-disease specific, with anatomical markers of white matter integrity, such as diffusion MRI along with a robust clinical model which suggests oculomotor dysfunction, and subsequent successful interventions, will provide the basis for establishing biomarkers in mTBI. Funded, IRB approved, prospective trial is in progress.

a. Access research database housed at HCMC
b. MRI database housed at CMRR

RO1-NS042126
"Hyperbaric and Normobaric Oxygen in Severe Brain Injury"
Co-Investigator: Sarah B. Rockswold, M.D.
Funding Source: National Institutes of Neurologic Disease and Stroke
Period: 12/01/2002 to 11/30/2005

RO1-NS042126-03S1
"Hyperbaric and Normobaric Oxygen in Severe Brain Injury"
Co- Investigator: Sarah B. Rockswold, M.D.
Funding Source: National Institutes of Neurologic Disease and Stroke
Period: 12/01/2005 to 11/30/2008

"Magnetic Resonance Imaging and Oculomotor Dysfunction in Mild Traumatic Brain Injury"
Principal Investigator: Sarah B. Rockswold, M.D.
Funding Source: Minneapolis Medical Research Foundation
Period: 7/1/14 to 6/30/16

NAME: Uzma Samadani, MD PhD

eRA COMMONS USER NAME: SAMADANI (VA) and samadu01 (New York University School of Medicine)

POSITION TITLE: Chief Neurosurgeon New York Harbor HealthCare System, Co-Director of the Steven and Alexandra Cohen Veterans Center for Post Traumatic Stress and Traumatic Brain Injury, Assistant Professor of Neurosurgery, Psychiatry, Physiology & Neuroscience, New York University School of Medicine

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Wisconsin - Madison	BA	05/1991	Molecular Biology and English Literature
University of Illinois - Chicago	PhD	05/1997	Molecular Biology and Biochemistry
University of Illinois - Chicago	MD	05/1999	
Hospital of the University of Pennsylvania		06/2006	Neurosurgical Residency
Klinikum Goettingen –Georg August Universitaet		07/2007	Van Wagenen Fellowship

I am delighted that Dr. Gaylan Rockswold's team has recruited me to Hennepin County Medical Center as the Rockswold Kaplan Endowed Chair for TBI Research to continue the legacy of brain injury research at HCMC. In this proposed project we will determine the most effective hyperbaric oxygen dose schedule that does not lead to oxygenation toxicity and clinical complications in a multicenter randomized clinical trial. The goal of the work is to identify a dosage and schedule worthy of a phase III clinical trial. Although I will be new to HCMC, I have demonstrated ability to perform clinical trials at a level one trauma center and a track record for effective collaboration. I have discussed the work with Dr. Rockswold and his collaborators and am confident that we will be able to achieve the goals of this project together. I understand that my role will be to assist with organization, recruitment and other procedural objectives. I have 7 years of funded smaller scale collaborative TBI research experience and am active on several national committees focused on TBI. Recently I completed a study assessing an eye tracking biomarker and outcome measure of TBI in which more than 200 trauma patients were recruited and made 545 total visits for research. I look forward to being at HCMC and am pleased to dedicate 20% of my total time specifically for this study investigating hyperbaric oxygen as a potential therapeutic for TBI.

Shi, C, Flanagan, S.R., Vagus Nerve Stimulation to Augment Recovery from Severe Traumatic Brain Injury Impeding Consciousness: A Prospective Pilot Clinical Trial. *Neurological Research* Apr 2013 35(3):263-76.

Farooq, S., Ritlop,R., Warren, F., Reyes, M., Lamm, E., Alex, A., Nehrbass, E., Kolecki., R., Jureller, M., Schneider, J., Chen, A., Shi, C., Mendhiratta, N., Huang, J.H., Qian, M., Kwak, R., Mikheev, A., Rusinek, H., George, A., Fergus, R., Kondziolka, D., Huang, P., Smith, T., Detection of Third and Sixth Cranial Nerve Palsies With A Novel Method for Eye Tracking While Watching a Short Film Clip. *Journal of Neurosurgery* Mar;122(3):707-20. doi: 10.3171/2014.10.JNS14762 2015.

Balser, D.S., Farooq, S., Mehmood, T., , Actual and Projected Incidences of Chronic Subdural Hemorrhage in United States Veterans Administration and Civilian Populations. *Journal of Neurosurgery* (in press) 2015.

Ritlop, R., Reyes, M., Nehrbass, E., Li, M., Lamm, E., Schneider, J.,Shimunov, D., Sava, M., Kolecki, R., Burris, P., Altomare, L., Mehmood, T., Smith, T., Huang, J.H., McStay, R.C., Todd, S.R., Qian, M., Kondziolka, D., Wall, S., Huang, P., Eye Tracking Detects Disconjugate Eye Movements Associated with Structural Traumatic Brain Injury and Concussion. *Journal of Neurotrauma* Apr 15;32(8):548-56. doi: 10.1089/neu.2014.3687 2015. PMCID: PMC4394159

1999-2000	Intern Physician, Surgery, Hospital of the University of Pennsylvania,
2000-2005	Resident Physician, Neurosurgery, Hospital of the University of Pennsylvania
2005-2006	Chief Resident, Neurosurgery, Hospital of the University of Pennsylvania
2006-2007	William P.Van Wagenen Fellow, Department of Neurosurgery. University Hospital of the University of Göttingen. Germany
2007-2015	Assistant Professor, Neurosurgery, New York University
2007-2015	Attending Physician, Department of Surgery, Division of Neurosurgery, New York Harbor Health Care System, Manhattan Veterans Hospital
2010-2015	Chief Neurosurgeon, New York Harbor Health Care System, Manhattan Veterans Hospital
2013-2015	Assistant Professor, Psychiatry and Physiology & Neuroscience Departments, New York University School of Medicine
2013-present	CoDirector Steven and Alexandra Cohen Veterans Center for PTSD and TBI
2015-	Associate Professor, Neurosurgery, University of Minnesota (as of Aug 3, 2015)
2015-	Rockswold Kaplan Endowed Chair for TBI Research, Hennepin County Medical Center (as of Aug 3, 2015)
2015-	Attending Physician, Department of Surgery, Division of Neurosurgery, Minneapolis VA

2010-present	Fellow American Association of Neurological Surgeons
2011-present	Fellow American College of Surgeons
2007-present	Lifetime Member Women in Neurosurgery
2011-present	New York Harbor Health Care Research and Development Committee Member
2009-present	National Neurosurgery Surgical Advisory Board Northeast Representative for the Veterans Administration
2010	Barrow Neurologic Institute Extramural Grant Review Committee
2010	CSP 583 Xstop vs Laminectomy Clinical Trial Organization Committee
2011	VASQIP External Site Peer Review Committee, Richmond, VA
2012-present	Congress of Neurological Surgeons
2013-present	Executive Committee Neurotrauma and Critical Care Joint Section of the AANS-CNS
2013-present	Association for Research in Vision and Ophthalmology
2013-present	National Neurotrauma Society

2015-present Scientific Program Chair AANS/CNS Joint Section of Neurotrauma and Critical Care Meeting at the National Neurotrauma Society
2015-present American Board of Neurological Surgery Written Examination Question Committee
2015-present Congress of Neurological Surgeons Scientific Program Committee
Reviewer: Central European Neurosurgery, American Journal of Neurology, Spine, BMC Neurology, Epilepsy Research and Treatment, Journal of Neurological Surgery

1989 University of Wisconsin Medical Scholars Program Research Grant
1990 University of Wisconsin Academic Excellence Award for Outstanding Research
1990 Center for Biology Education Research Fellowship
1991 *Phi Beta Kappa*
1994 University of Illinois Molecular Biology Retreat First Place Poster Award
1994 Barnes Research Fellowship in Molecular Medicine
1996 University of Illinois Medical Student Research Forum First Place Award
1999 Bertram S. Richardson Fellowship
2006 William P. VanWagenen Fellowship
2013 NYU MBAWorld Stern School Champion
2013 NYU Venture Technology Competition Grand Prize
2013 Innovate HealthTech NYC 15K Prize
2013 MidAtlantic Bioangels First Pitch Life Sciences Event “Best in Show”
2014 TedMed Plenary Speaker

Developed a novel eye tracking algorithm that may serve as a potential classifier and outcome measure for traumatic brain injury and concussion. The algorithm was originally developed as an outcome measure for a clinical trial of an intervention to improve outcomes after severe brain injury. We are currently validating it as a biomarker for concussion. Successful validation could lead to improved ability to detect concussion and classify TBI as well as enable development of therapeutics and diagnostics for brain injury by serving as an objective and sensitive outcome measure. Currently clinical trials for TBI frequently fail due to a lack of objective outcome measures. My role was development of the algorithm and recognition of its significance. I have 8 patents submitted, 2 peer reviewed papers published, 2 papers in press, more than 20 talks nationally and some recognition by popular media, including a TedMed talk.

Samadani, U., Farooq, S., Ritlop,R., Warren, F., Reyes, M., Lamm, E., Alex, A., Nehrbass, E., Kolecki., R., Jureller, M., Schneider, J., Chen, A., Shi, C., Mendhiratta, N., Huang, J.H., Qian, M., Kwak, R., Mikheev, A., Rusinek, H., George, A., Fergus, R., Kondziolka, D., Huang, P., Smith, T., Detection of Third and Sixth Cranial Nerve Palsies With A Novel Method for Eye Tracking While Watching a Short Film Clip. *Journal of Neurosurgery* Mar;122(3):707-20. doi: 10.3171/2014.10.JNS14762 2015.

Samadani, U., Ritlop, R., Reyes, M., Nehrbass, E., Li, M., Lamm, E., Schneider, J.,Shimunov, D., Sava, M., Kolecki, R., Burris, P., Altomare, L., Mehmood, T., Smith, T., Huang, J.H., McStay, R.C., Todd, S.R., Qian, M., Kondziolka, D., Wall, S., Huang, P., Eye Tracking Detects Disconjugate Eye Movements Associated with Structural Traumatic Brain Injury and Concussion. *Journal of Neurotrauma* Apr 15;32(8):548-56. doi: 10.1089/neu.2014.3687 2015. PMCID: PMC4394159

Samadani, U., Li, M., Qian, M., Laska, E., Ritlop, R., Kolecki, R., Reyes, M., Altomare, L., Sone, J., Adem, A., Huang, P., Kondziolka, D., Wall, S., Frangos, S., Marmar, C. Sensitivity and Specificity of an Eye Movement Tracking Biomarker for Concussion, *Concussion,* (in press)

TEDMED Plenary “Will Eye Tracking Change the Way We Diagnose (And Define) Brain Injury?” Washington, DC, Sept 10, 2014

Determined that eye tracking may serve as a useful assessor of the physiologic impact of elevated intracranial pressure. In research funded by the Thrasher Research Fund and National Space and Biomedical Research Institute, we show that eye movement tracking while watching a short film clip can detect the cranial nerve VI and III palsies that have long been associated with hydrocephalus. Validation of this concept will establish eye tracking as a new non-invasive means for assessing central nervous system physiologic function. Clinical applications range from detection of shunt malfunction in children to assessment of astronauts during prolonged space travel. The cranial nerve palsy paper has been published (see above); the ICP and hydrocephalus papers are currently under submission in two different manuscripts.

Kolecki, R., Ritlop, R. Reyes, M. and .: Eye Tracking Detects Ocular Dysmotility Due to Elevated Intracranial Pressure, National Space and Biomedical Research Group, Galveston, TX, January 2015

Han, B., Mehmood, T., Li, M., Tran, R., Schneider, J., Kolecki, R., Reyes, M., Ritlop, R.,Lamm, E., Qian, M., Rodgers, S., Weiner, H., Harter, D., Wisoff, J., Huang, P., and Eye Movement Tracking in Shunted Hydrocephalus and Suspected Shunt Malfunction, American Association of Neurological Surgeons, Washington, DC, April 2015.

Established that chronic subdural hemorrhage in older adults is a sequela of degenerative disease even more so than of trauma by studying patterns of atrophy among veterans subsequently diagnosed with SDH, and also demonstrated that SDH will become the most common cause for adult cranial neurosurgery by 2040. This work has been funded by a VA Merit Award for which I am PI with responsibility for conduct and oversight of all study aspects.

Yang, I., Balser, D.S., Mikheev, A., Offen, S., Huang, J.H., Babb, J., Rusinek, H., Samadani, U., Cerebral Atrophy is Associated with Development of Chronic Subdural Hematoma. *Brain Injury* 2012; 26(13-14):1731-6

Balser, D.S., Farooq, S., Mehmood, T., Samadani, U., Actual and Projected Incidences of Chronic Subdural Hemorrhage in United States Veterans Administration and Civilian Populations. *Journal of Neurosurgery* (in press) 2015.

Successfully submitted an IDE and set up a clinical trial for vagus nerve stimulation to improve outcomes after serious traumatic brain injury resulting in minimally conscious or persistently vegetative states. Currently there are very few effective treatments for severe TBI. Vagus nerve stimulation has shown benefits in reducing elevated intracranial pressure, diminishing cortical spreading depression and seizures and improving sleep, depression and cognition in animal and human studies. We plan to conduct a clinical trial of VNS for TBI using clinical scales, eye tracking and ICP as outcome measures. The trial is IDE approved and could lead to development of a new brain injury therapeutic.

Shi, C, Flanagan, S.R., Samadani, U., Vagus Nerve Stimulation to Augment Recovery from Severe Traumatic Brain Injury Impeding Consciousness: A Prospective Pilot Clinical Trial. *Neurological Research* Apr 2013 35(3):263-76.

http://www.ncbi.nlm.nih.gov/pubmed/?term=samadani%20u

VA Merit Award; Jan 2014 –Dec 2018; Cerebral Atrophy, Anticoagulation and the Risk for Chronic Subdural Hematoma; The goal of this study is to assess the relationship between atrophy, anticoagulation and chronic subdural hematoma development in a cohort of 10,351 veterans followed for seven years. As Principal Investigator I am collaborating with a physicist in radiology and statistician. My role is overseeing all aspects of this study, organizing, and supervising the ongoing conduct of this research as well as generating manuscripts for publication.

Steven and Alexandra Cohen Foundation; Nov 2013-Nov 2018; Biomarkers for Post Traumatic Stress and Traumatic Brain Injury in Veterans; As coinvestigator for this study I am investigating whether eye tracking while watching a short film clip serves as a reliable marker for traumatic brain injury as part of a prospective observational multicenter collaborative study. We have already recruited more than 1500 patients at multiple sites. The study is a collaboration of more than 30 investigators at four study sites including the Ft. Campbell military base.

SMARTCAP Grant – National Space and Biomedical Research Institute; July 2014-July 2015; Eye Tracking to Detect Elevated Intracranial Pressure. As principal investigator for this study I am investigating whether eye tracking serves as a physiologic indicator of elevated intracranial pressure. We have recruited 20 patients with intracranial pressure monitors who have undergone more than 60 serial eye trackings to date.

VA Merit Award Oct 2010-Sept 2013; Vagus Nerve Stimulation to Augment Recovery from Traumatic Brain Injury; As Principal Investigator for this prospective randomized blinded pilot study I am investigating whether VNS improves outcome after severe TBI resulting in minimally conscious or persistently vegetative states.

Thrasher Research Fund; July 2013-July 2014; Ocular Motility Assessment to Detect Hydrocephalus or Shunt Malfunction; As mentor for this grant, I supervised a resident investigating whether eye tracking while watching a short film clip detects ocular dysmotility associated with hydrocephalus. The study enrolled more than 100 participants at two sites.

NYU Applied Research Support Fund; Oct 2013-Oct 2014; Eye Movement Tracking as an Outcome Measure for Concussion; As principal investigator for this grant, I supervised all aspects of the study including manuscript generation. This grant recruited more 200 trauma patients making more than 500 visits for validation of eye tracking as a biomarker for concussion and structural brain injury.

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Silbergleit, Robert

eRA COMMONS USER NAME (agency login): SILBERGLEIT

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Massachusetts Institute of Technology, Cambridge, MA	BS	05/1988	Life Sciences
University of Michigan, Ann Arbor, MI	MD	06/1992	
Medical College of Pennsylvania, Philadelphia, PA	Resident	06/1995	Emergency Medicine
George Washington University, Washington, DC	Fellow	06/1997	Brain Resuscitation Research

I am an emergency physician with expertise in organizing and conducting clinical trials in the acute care setting with a focus on neurotrauma. My past experience is as a translational researcher, working on laboratory animal models of brain injury and participating in clinical trials as a site PI and sub-investigator. My laboratory work was particularly relevant to the current proposal because it included studying the effects of hyperbaric oxygen in traumatic brain injury, intracerebral hemorrhage, and brain ischemia. For the past eight years, I have been a leading co-investigator in the formation and organization of the Neurological Emergencies Treatment Trials network where I contribute to the oversight and management of all NETT trials. In the NETT I have developed specific expertise and experience in investigating initial interventions in patients with status epilepticus and neurotrauma. My clinical trial leadership experience includes being the Co-Principal Investigator, along with Dan Lowenstein, of the recently completed Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART), a study of prehospital treatment of status epilepticus. RAMPART completed ahead of schedule and underbudget. I am also a co-investigator in the clinical trial leadership for the Progesterone for Traumatic brain injury: Experimental Clinical Treatment (ProTECT) trial which recruited on schedule with 882 subjects enrolled with moderate to severe traumatic brain injury. I am currently Principal Investigator (MPI) of the Established Status Epilepticus Treatment Trial (ESETT), in which enrollment also takes place in the earliest stages of intervention in the emergency department. In multiple trials I have developed operational and academic expertise in Exception from Informed Consent (EFIC) for Emergency Research and its conduct under FDA regulations. I was also a co-investigator in the leadership of an NIH/FDA co-funded project to investigate the application of adaptive clinical trial designs in the confirmatory trial space. The adaptive design we have developed for HOBIT, the current proposal, builds on our successful ADAPT-IT project experience. These experiences have prepared me well for my responsibilities in the current application. I bring to this application my background in hyperbaric oxygen research, expertise in trial design and organization, protocol implementation, regulatory management, human subjects' protection (including EFIC), and accrual and monitoring.

1. Rosenthal RE, Silbergleit R, Hof PR, Haywood Y, Fiskum G. Hyperbaric oxygen reduces neuronal death and improves neurological outcome after canine cardiac arrest. Stroke. 2003 May;34(5):1311-6. PubMed PMID: 12677019.
2. Qin Z, Xi G, Keep RF, Silbergleit R, He Y, Hua Y. Hyperbaric oxygen for experimental intracerebral hemorrhage. Acta Neurochir Suppl. 2008;105:113-7. PubMed PMID: 19066094.
3. Meurer WJ, Lewis RJ, Tagle D, Fetters MD, Legocki L, Berry S, Connor J, Durkalski V, Elm J, Zhao W, Frederiksen S, Silbergleit R, Palesch Y, Berry DA, Barsan WG. An overview of the adaptive designs accelerating promising trials into treatments (ADAPT-IT) project. Ann Emerg Med. 2012 Oct;60(4):451-7. PubMed PMID: 22424650; PubMed Central PMCID: PMC3557826.
4. Wright DW, Yeatts SD, Silbergleit R, Palesch YY, Hertzberg VS, Frankel M, Goldstein FC, Caveney AF, Howlett-Smith H, Bengelink EM, Manley GT, Merck LH, Janis LS, Barsan WG. Very early

administration of progesterone for acute traumatic brain injury. N Engl J Med. 2014 Dec 25;371(26):2457-66. PubMed PMID: 25493974; PubMed Central PMCID: PMC4303469.

1995 - 1997	Adjunct Instructor, George Washington University, Washington, DC
1995 - 1997	Clinical Instructor, Medical College of Pennsylvania, Philadelphia, PA
1997 - 1998	Lecturer, University of Michigan, Ann Arbor, MI
1998 - 2006	Assistant Professor, University of Michigan, Ann Arbor, MI
2006 - 2013	Associate Professor, University of Michigan, Ann Arbor, MI
2013 -	Professor, University of Michigan, Ann Arbor, MI

1999 - 2003	Principal Investigator, Hyperbaric oxygen in rodent models of cerebral ischemia
2005 - 2006	Co-investigator, Safety of Community Delivery of tPA in Acute Stroke
2005 - 2006	Co-investigator, GIS System Design for Acute Stroke Treatment in Michigan
2006 -	Principal Investigator, Rapid Anticovulsant Medication Prior to Arrival Trial
2006 -	Co-investigator, Neurological Emergencies Treatment Trials (NETT) Network
2009 -	Co-investigator, Progesterone for the Treatment of Traumatic Brain Injury (ProTECT III)
2014 -	Principal Investigator (MPI), Established Status Epilepticus Treatment Trial

1986	Member, Sigma Xi Research Honor Society
1993	Member, Alpha Omega Alpha Honor Society
1995	Best Resident/Fellow Oral Presentation, SAEM National Meeting
1996	Fellow, American Academy of Emergency Medicine
1997	Finalist, NAEMSP Cerebral Resuscitation Abstract Competition
2004	"Top Peer Reviewer" Status, Annals of Emergency Medicine
2006	Fellow, Stroke Council, American Heart Association
2012	Airway Article of the Year, Airway World
2013	Trial of the Year Award, Society for Clinical Trials

1. Neurotrauma. I have contributed to the study of hyperacute treatments for traumatic brain injury and spinal cord injury. I was a leading investigator in the ProTECT study of progesterone as a neuroprotectant in TBI. While the treatment proved ineffective in the study population, the trial methodology has been cited as advancing the field. Key features of the trial included very early enrollment and randomization, tight controls of clinical standardization, and informative prognosis-weighted outcomes. In our NIH/FDA co-funded project to explore adaptive designs in confirmatory clinical trials, we spent substantial effort crafting and simulating a seamless dose-finding and efficacy-testing set of trials of induced hypothermia in acute cervical spinal cord injury. Currently under review, these trials benefit from lessons learned in ProTECT and in the adaptive design planning grant.
   a. Saatman KE, Duhaime AC, Bullock R, Maas AI, Valadka A, Manley GT. Classification of traumatic brain injury for targeted therapies. J Neurotrauma. 2008 Jul;25(7):719-38. PubMed PMID: 18627252; PubMed Central PMCID: PMC2721779.
   b. Cairns CB, Maier RV, Adeoye O, Baptiste D, Barsan WG, Blackbourne L, Burd R, Carpenter C, Chang D, Cioffi W, Cornwell E, Dean JM, Dyer C, Jaffe D, Manley G, Meurer WJ, Neumar R, Silbergleit R, Stevens M, Wang M, Weiner D, Wright D. NIH Roundtable on Emergency Trauma Research. Ann Emerg Med. 2010 Nov;56(5):538-50. PubMed PMID: 21036294.
   c. Meurer WJ, Lewis RJ, Tagle D, Fetters MD, Legocki L, Berry S, Connor J, Durkalski V, Elm J, Zhao W, Frederiksen S, Silbergleit R, Palesch Y, Berry DA, Barsan WG. An overview of the adaptive designs

accelerating promising trials into treatments (ADAPT-IT) project. Ann Emerg Med. 2012 Oct;60(4):451-7. PubMed PMID: 22424650; PubMed Central PMCID: PMC3557826.

d. Wright DW, Yeatts SD, Silbergleit R, Palesch YY, Hertzberg VS, Frankel M, Goldstein FC, Caveney AF, Howlett-Smith H, Bengelink EM, Manley GT, Merck LH, Janis LS, Barsan WG. Very early administration of progesterone for acute traumatic brain injury. N Engl J Med. 2014 Dec 25;371(26):2457-66. PubMed PMID: 25493974; PubMed Central PMCID: PMC4303469.

2. Ethics and Human Subjects Protection. I have contributed to finding better ways to study critically ill and injured patients in ways that provide potential benefit to participants and future patients, are ethically sound, and continue to protect human research subjects. This includes extensive work on exception from informed consent (EFIC) processes, consideration of alternative IRB models for emergency research, as well as work on better ways to consider and conceptualize equipoise in clinical research trials.
   a. Ubel PA, Silbergleit R. Behavioral equipoise: a way to resolve ethical stalemates in clinical research. Am J Bioeth. 2011 Feb;11(2):1-8. PubMed PMID: 21337264.
   b. Silbergleit R, Biros MH, Harney D, Dickert N, Baren J. Implementation of the exception from informed consent regulations in a large multicenter emergency clinical trials network: the RAMPART experience. Acad Emerg Med. 2012 Apr;19(4):448-54. PubMed PMID: 22506949; PubMed Central PMCID: PMC3335290.
   c. Dickert NW, Mah VA, Baren JM, Biros MH, Govindarajan P, Pancioli A, Silbergleit R, Wright DW, Pentz RD. Enrollment in research under exception from informed consent: the Patients' Experiences in Emergency Research (PEER) study. Resuscitation. 2013 Oct;84(10):1416-21. PubMed PMID: 23603291; PubMed Central PMCID: PMC3770787.
   d. Goldkind SF, Brosch LR, Biros M, Silbergleit RS, Sopko G. Centralized IRB models for emergency care research. IRB. 2014 Mar-Apr;36(2):1-9. PubMed PMID: 24783375.

3. Re-engineering the Clinical Trial Enterprise. My work has also included contributions to identifying and implementing better ways to efficiently and effectively conduct clinical investigations. These range from information technology and management, to statistical issues related to design, to reforming the use of screening logs.
   a. Zhao W, Durkalski V, Pauls K, Dillon C, Kim J, Kolk D, Silbergleit R, Stevenson V, Palesch Y. An electronic regulatory document management system for a clinical trial network. Contemp Clin Trials. 2010 Jan;31(1):27-33. PubMed PMID: 19782156; PubMed Central PMCID: PMC2829838.
   b. Durkalski V, Silbergleit R, Lowenstein D. Challenges in the design and analysis of non-inferiority trials: a case study. Clin Trials. 2011 Oct;8(5):601-8. PubMed PMID: 21921062.
   c. Le Roux PD, Cooper J, Guntupalli KK, Silbergleit R, Daily J, Geocadin R, Wijman CA, Suarez JI. The critical care research networks experience. Neurocrit Care. 2012 Feb;16(1):20-8. PubMed PMID: 21796493.
   d. Elm JJ, Palesch Y, Easton JD, Lindblad A, Barsan W, Silbergleit R, Conwit R, Dillon C, Farrant M, Battenhouse H, Perlmutter A, Johnston SC. Screen failure data in clinical trials: Are screening logs worth it?. Clin Trials. 2014 Jun 12;11(4):467-472. PubMed PMID: 24925082; PubMed Central PMCID: PMC4264995.

4. Status Epilepticus. I have contributed to a better understanding of the most effective treatments for the treatment of status epilepticus in the emergency setting. The RAMPART study determined that, in children and adults treated in the prehospital setting, intramuscular midazolam was not only non-inferior, but was superior than intravenous lorazepam at terminating seizures prior to arrival at the hospital. This treatment also leads to fewer hospital and ICU admissions, and has a favorable safety profile. Our current trial is seeking to select the best second line anticonvulsant treatment in the emergency department for those patients in whom status epilepticus does not terminate with first line benzodiazepine therapy.
   a. Silbergleit R, Durkalski V, Lowenstein D, Conwit R, Pancioli A, Palesch Y, Barsan W. Intramuscular versus intravenous therapy for prehospital status epilepticus. N Engl J Med. 2012 Feb 16;366(7):591-600. PubMed PMID: 22335736; PubMed Central PMCID: PMC3307101.
   b. Bleck T, Cock H, Chamberlain J, Cloyd J, Connor J, Elm J, Fountain N, Jones E, Lowenstein D, Shinnar S, Silbergleit R, Treiman D, Trinka E, Kapur J. The established status epilepticus trial 2013. Epilepsia. 2013 Sep;54 Suppl 6:89-92. PubMed PMID: 24001084; PubMed Central PMCID: PMC4048827.

c. Welch RD, Nicholas K, Durkalski-Mauldin VL, Lowenstein DH, Conwit R, Mahajan PV, Lewandowski C, Silbergleit R. Intramuscular midazolam versus intravenous lorazepam for the prehospital treatment of status epilepticus in the pediatric population. Epilepsia. 2015 Feb;56(2):254-62. PubMed PMID: 25597369; PubMed Central PMCID: PMC4386287.

d. Vohra TT, Miller JB, Nicholas KS, Varelas PN, Harsh DM, Durkalski V, Silbergleit R, Wang HE. Endotracheal Intubation in Patients Treated for Prehospital Status Epilepticus. Neurocrit Care. 2015 Jan 27;PubMed PMID: 25623785.

5. Cardiac Arrest. My work has contributed to ensuring that cardiac arrest is understood to be a critical neurological emergency. Through our NIH/FDA co-funded adaptive clinical trial design and planning grant, we have crafted a highly adaptive study of the duration of hypothermia in comatose survivors of cardiac arrest. This trial, currently under review at FDA and NIH, also builds on previous observational study in this field.

a. Majersik JJ, Silbergleit R, Meurer WJ, Brown DL, Lisabeth LD, Morgenstern LB. Public health impact of full implementation of therapeutic hypothermia after cardiac arrest. Resuscitation. 2008 May;77(2):189-94. PubMed PMID: 18249484.

b. Paulsen MJ, Haddock AJ, Silbergleit R, Meurer WJ, Macy ML, Haukoos JS, Sasson C. Empirical hospital and professional charges for patient care associated with out of hospital cardiac arrest before and after implementation of therapeutic hypothermia for comatose survivors. Resuscitation. 2012 Oct;83(10):1265-70. PubMed PMID: 22410427.

c. Terman SW, Hume B, Meurer WJ, Silbergleit R. Impact of presenting rhythm on short- and long-term neurologic outcome in comatose survivors of cardiac arrest treated with therapeutic hypothermia. Crit Care Med. 2014 Oct;42(10):2225-34. PubMed PMID: 25014063; PubMed Central PMCID: PMC4167183.

d. Terman SW, Shields TA, Hume B, Silbergleit R. The influence of age and chronic medical conditions on neurological outcomes in out of hospital cardiac arrest. Resuscitation. 2015 Apr;89:169-76. PubMed PMID: 25640799.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/robert.silbergleit.1/bibliography/10087677/public/?sort=date&direction=ascending

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2014/09/30-2019/08/31
U01 NS088034-01, National Institute of Neurological Disorders and Stroke (NINDS)
Chamberlain, James (PI)
Established Status Epilepticus Treatment Trial (ESETT)
Role: PI

2014/04/01-2019/03/01
1R25NS088248-01, National Institutes of Health
Meurer, William (PI)
Enhancing Scientific Inquiry in Clinical Neurosciences Through Methodology Training, Mentorship, and Trans-Institutional Cooperation
Role: Faculty

2006/09/20-2016/05/30
5U01NS056975-09, National Institutes of Health
Barsan, William (PI)
Neurological Emergencies Treatment Trials – Clinical Coordinating Center
Role: Co-Investigator

2010/09/01-2015/08/01
5U01NS073476-03, National Institutes of Health
Barsan, William (PI)
Accelerating Drug/Device Evaluation through Innovative Clinical Trial Design-Adaptive Design Trial
Role: Co-Investigator

2009/07/01-2015/06/01
5U01NS062778-05, National Institutes of Health
Wright, David (PI)
Progesterone for Traumatic brain injury-Experimental Clinical Treatment
Role: Co-Investigator

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Scott M. Berry, PhD

eRA COMMONS USER NAME (credential, e.g., agency login): STATBERRY

POSITION TITLE: President and Senior Statistical Scientist

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Minnesota, Minneapolis, MN	B.S.	08/1990	Mathematics
Carnegie Mellon University, Pittsburgh, PA	M.S.	05/1991	Statistics
Carnegie Mellon University, Pittsburgh,PA	Ph.D.	12/1994	Statistics

Scott Berry is President and a Senior Statistical Scientist at Berry Consultants, LLC. His research interests include Bayesian methods in clinical trials, adaptive clinical trials, Bayesian computation, and hierarchical models. He earned his Ph.D. in Statistics from Carnegie Mellon University and was an Assistant Professor at Texas A&M University before joining Berry Consultants in 2000. Since 2000, he has been involved in the design of hundreds of Bayesian adaptive clinical trials for pharmaceuticals and medical devices and has become an opinion leader in the field of Bayesian adaptive clinical trials. His groundbreaking work using Bayesian methods to synthesize information from prevention trials of pravastatin and aspirin led to FDA approval of the combination for secondary prevention of cardiovascular events. He has contributed several articles to the statistical and medical literature including several publications in the *Journal of the American Statistical Association*. His book on Bayesian Adaptive Methods in Clinical trials has become a standard in the industry. He gives numerous seminars on Bayesian adaptive clinical trials each year. He is the designer of commercial Bayesian adaptive design software, FACTS (Fixed and Adaptive Clinical Trial Simulator), that is now licensed to 25% of the top 20 pharmaceutical companies in the US.

1994-1995	Visiting Assistant Professor, Statistics and Social and Decision Sciences, Carnegie Mellon University
1995-2000	Assistant Professor, Department of Statistics, Texas A&M University
2000-present	Statistical Scientist, Berry Consultants
2007-present	President and Senior Statistical Scientist, Berry Consultants
2013-present	Adjunct Professor, Department of Biostatistics, University of Kansas Medical Center

1996-1998	Senior Associate Editor, *Chance*
1999-2006	Columnist, “A Statistician Reads the Sports Pages,” *Chance*
2001	Program Chair, Statistics and Sports Section, American Statistical Association

2004 Chair, Statistics and Sports Section, American Statistical Association
2011-present Associate Editor, The American Statistician
2011-2013 Chair Elect, Chair, Past Chair; MDD Section of the American Statistical Association
2012-present Associate Editor, Journal of the American Statistical Association

1993 First prize, best speaker, Graduate Student Seminar Series in Statistics and Biostatistics, Carnegie Mellon University
1999 Applications and Case Studies Invited Paper Award, *Journal of the American Statistical Association*
2007 Statistics in Sports Award, American Statistical Association
2010 Excellence-in-CE Award Winner. JSM Short Course "Bayesian Adaptive Methods in Clinical trials". Joint with Don Berry, Brad Carlin, and Jack Lee.
2013 Elected Fellow of the American Statistical Association

1. An aspect of my research is on Bayesian methodology and modeling. I did a lot of research on the use of hierarchical modeling, modeling different but related treatment arms in a study, and modeling endpoints longitudinally. This advanced modeling and calculation allows for using these techniques to enhance innovative trial designs.
    a. , Berry DA. Accounting for multiplicities in assessing drug safety: A three-level hierarchical mixture model. *Biometrics* 2004;60:418-426.
    b. , Carroll RJ, Ruppert D. Bayesian smoothing and regression splines for measurement error problems. *Journal of the American Statistical Association* 2002;97:160-169.
    c. , Berry DA, Natarajan K, Lin C-S, Hennekens CH, Belder R. Bayesian survival analysis with nonproportional hazards: Metanalysis of pravastatin-aspirin. *Journal of the American Statistical Association* 2004;99:36-44.
    d. Berry DA, , McKellar JJ, Pearson T. Bayesian dose response meta-analysis comparing LDL-C lowering of rosuvastatin and atorvastatin. *American Heart Journal* 2003;145:1036-1045.

2. A second aspect of research involves innovative trial design. Using the Bayesian methodology allows for creating innovative and efficient trial designs. By constructing an adaptive trial design, one that is allowed to evolve towards the accruing information within the trial, allows for the design to be much more efficient. This work includes an industry leading book and example successful trials that were based on innovative trial designs.
    a. , Carlin, BP, Lee, JJ, and Mueller, P (2010) Bayesian Adaptive Methods for Clinical Trials, Chapman & Hall.
    b. Julian TB, Blumencranz P, Deck K, Whitworth P, Berry DA, , Rosenberg A, Chagpar AB, Reintgen D, Beitsch P, Simmons R, Saha S, Mamounas EP, Giuliano A. A Novel Intra-operative Molecular Test for Sentinel Lymph Nodes Metastases in Early Stage Breast Cancer Patients. *Journal of Clinical Oncology* 2008;26:3338-3345.
    c. Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, Macle L, Daoud EG, Calkins H, Hall B, Reddy V, Augello G, Reynolds MR, Vinekar C, Liu CY, , Berry DA; ThermoCool AF Trial Investigators. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *Journal of the American Medical Association* 2010;303(4):333-40.
    d. Lewis RJ, Viele K, Broglio K, , Jones A; An adaptive, Phase II, Dose-finding Clinical Trial Design to Evaluate L-Carnatine in the Treatment of Septic Shock Based on Efficacy and Predictive Probability of Subsequent Phase III Success, Critical Care Medicine, 2013, 41, 7, 1-5. PMCID: PMC4334380

3. A third dimension of research is in clinical trial simulation. As trials get more complicated and efficient they tend to be constructed through complex clinical trial simulation. This is a new burgeoning field of Statistics, the art, science, and practice of clinical trial simulation. This involve the expertise in numeric methods, statistical models, ad designs, as well as software design. I am a creator and developer for an industry

changing clinical trial simulation software package. FACTS (Fixed and Adaptive Clinical Trial Simulator) allows users to design, simulate, and explore the performance of clinical trial designs.

a. FACTS (http://www.berryconsultants.com/software)
b. Video Presentation: In Silico Clinical Trial Design. (https://www.youtube.com/watch?v=-b1eWNEtZ8A)

4. A fourth dimension of research involves modeling the biologic aspects of sports. While sport may seem distinct from clinical trials and biological modeling, it shares many common aspects of biology. In sport there are issues with indirect comparisons, biological variability in performance and outcomes, longitudinal performance, and correlation of outcomes. In fact, the paper on bridging different eras in sports has been reference many times in its similarity to understanding the effect of medical therapies being bridged from different trials.
   a. , Reese CS, Larkey PM. Bridging Different Eras in Sports. *Journal of American Statistical Association* 1999;94:661-684
   b. (2005) Nature, nurture, or culture, *Chance*, 18 (1).
   c. (2004) The cold-foot effect, *Chance*, 17 (4).
   d. (2001) Luck in Sports, *Chance*, 14 (1).

Innovative Medicines Initiative (Europe) Craig Ritchie, Serge Van Der Geyten (Co-PIs) 01/2015-12/2019
EPAD (European Prevention of Alzheimers Consortium) is funded by the IMI and aims to develop an infrastructure that efficiently enables the undertaking of adaptive, multi-arm Proof of Concept studies for early and accurate decisions on the ongoing development of drug candidates or drug combinations. This includes evaluating patients' reactions to a drug early in a clinical trial and modifying the trial according to these reactions. The EPAD project will initially run for five years. (http://www.synapse-managers.com/epad/index.html)
Role: Statistical Work Package Co-Leader

European Commission Herman Goosens (PI) 02/2014-01/2019
PREPARE (Platform for European Preparedness Against (Re-)emerging Epidemics) is an EU funded network for harmonised large-scale clinical research studies on infectious diseases, prepared to rapidly respond to any severe ID outbreak, providing real-time evidence for clinical management of patients and for informing public health responses. PREPARE is funded by the European Commission's FP7 Programme under grant number 602525. (http://www.prepare-europe.eu). I am leading the design of an innovative platform trial for community acquired pneumonia.
Role: Scientific Personnel

U01 NS073476 Barsan, Lewis, and Berry (PIs) 09/27/10-08/31/13
ADAPT-IT is a unique collaboration between Berry Consultants, the University of Michigan, UCLA, and the Neurological emergency treatment trials network, funded by the NIH and FDA. This project explored different aspects of adaptive clinical trial designs, and potential barriers to their use. This project included the construction of five adaptive clinical trials for the NETT.
Role: Key Personnel

PCORI Funding 01/03/12-06/15/12
Funded in a competitive grant from PCORI to address the *Standards in the Design, Conduct, and Evaluation of Adaptive Randomized Clinical Trials*
Role: Statistical Scientist

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OMB Number: 0925-0001

1. Project Director / Principal Investigator (PD/PI)

Prefix:
First Name*: Gaylan
Middle Name:
Last Name*: Rockswold
Suffix:

2. Human Subjects

Clinical Trial? ○ No ● Yes
Agency-Defined Phase III Clinical Trial?* ● No ○ Yes

3. Permission Statement*

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

● Yes ○ No

4. Program Income*

Is program income anticipated during the periods for which the grant support is requested? ○ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

Budget Period*	Anticipated Amount ($)*	Source(s)*

PHS 398 Cover Page Supplement

5. Human Embryonic Stem Cells

Does the proposed project involve human embryonic stem cells?* ● No ❍ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s): Specific stem cell line cannot be referenced at this time. One from the registry will be used.

6. Inventions and Patents (For renewal applications only)

Inventions and Patents*: ❍ Yes ❍ No

If the answer is "Yes" then please answer the following:

Previously Reported*: ❍ Yes ❍ No

7. Change of Investigator / Change of Institution Questions

❑ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

First Name*:

Middle Name:

Last Name*:

Suffix:

❑ Change of Grantee Institution

Name of former institution*:

PHS 398 Research Plan

Please attach applicable sections of the research plan, below.

OMB Number: 0925-0001

1. Introduction to Application (for RESUBMISSION or REVISION only)	
2. Specific Aims	1250-Specific Aims Final.pdf
3. Research Strategy*	1251-Research Strategy Final.pdf
4. Progress Report Publication List	
Human Subjects Sections	
5. Protection of Human Subjects	1252-Protection of Human Subjects FINAL.pdf
6. Inclusion of Women and Minorities	1253-Inclusion of Women and Minorities.pdf
7. Inclusion of Children	1254-Inclusion of Children.pdf
Other Research Plan Sections	
8. Vertebrate Animals	
9. Select Agent Research	
10. Multiple PD/PI Leadership Plan	1255-Shared leadership plan FINAL.pdf
11. Consortium/Contractual Arrangements	1256-Consortium-contractual agreements.pdf
12. Letters of Support	1257-Letters of Support Final.pdf
13. Resource Sharing Plan(s)	1258-Resource-Sharing Plan.pdf
Appendix (if applicable)	
14. Appendix	1259-Appendix A - Protocol.pdf 1260-Appendix B - Treatment Checklist.pdf 1261-Appendix C - Clinical Standardization Guidelines.pdf 1262-Appendix D - Consent Form.pdf 1263-Appendix E - WebDCU.pdf 1264-Appendix F - HOBIT Design.pdf 1265-Appendix G - Data Collection Schedule.pdf

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 (HBO2) is physiologically active in reducing brain injury and improving outcomes in severe TBI. There are peer-reviewed published animal data from well-established research laboratories which indicate that HBO2 potentially improves outcome from TBI by multiple mechanisms. By markedly increasing oxygen (O2) delivery to the traumatized brain, HBO2 can reverse the ischemia that precipitates cellular energy failure and subsequent cell death. Clinical investigations in HBO2 have largely corroborated the experimental work by demonstrating that HBO2 in comparison with standard care significantly improves markers of oxidative metabolism in relatively uninjured brain as well as in pericontusional tissue, reduces intracranial hypertension, demonstrates improvements in markers of cerebral toxicity, and improves clinical outcome. However, prior to a definitive efficacy study, important information is required to optimize the HBO2 treatment paradigm instituted in terms of pressure and frequency, and whether normobaric hyperoxia (NBH) delivered following the HBO2 treatment enhances clinical effectiveness.

1. (Dose selection) The first aim is to select the combination of HBO2 treatment parameters (pressure, frequency, and intervening NBH) that is most likely to demonstrate improvement in the rate of good neurological outcome at 6 months following severe TBI injury versus standard-of-care therapy in a subsequent confirmatory trial.
2. (Signal of efficacy) The second aim is to determine whether there is a >50% probability of HBO2 treatment demonstrating improvement in the rate of good neurological outcome at 6 months following severe TBI injury versus standard-of-care therapy in a subsequent confirmatory trial.

1. To analyze the level and duration of intracranial hypertension (> 20 mmHg) using area under the curve (AUC) methodology in HBO2-treated versus control groups (Vik 2008).
2. To analyze the therapeutic intensity level (TIL) scores for controlling intracranial pressure (ICP) in HBO2-treated patients compared to controls.
3. Utilizing Licox brain tissue partial pressure of oxygen (PO2) monitoring, analyze the level and duration of brain tissue hypoxia (brain tissue PO2 < 15 mmHg) using AUC methodology in HBO2-treated groups versus control (van den Brink 2000).
4. To compare the rate of serious adverse events (SAEs) between HBO2 treatment arms and control.

The trial will utilize an innovative adaptive design. The primary outcome is the severity adjusted Glasgow Outcome Scale-Extended (GOS-E) at 6 months. The trial will explore nine different active treatment arms for relative efficacy and comparison to the control arm. Three pressures (1.5, 2.0 and 2.5 atmospheres absolute [ATA]), two frequencies (everyday versus twice daily), and with or without NBH will be studied. If there is at least one experimental treatment arm promising enough, it will be a candidate and will be compared for superiority to the control in the future phase III trial. Utilizing this 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. The maximum number of subjects to be enrolled is 200 at approximately 15 clinical centers. The trial will utilize response adaptive randomization to favor the better performing experimental arms. Response adaptive randomization (being able to change how subjects are assigned to the treatments during the study based on information gained during the study) will allow for substantially smaller sample sizes and provide better conclusions about the most effective treatment and will let us stop the study early if we find strong signs of efficacy or identify futility before the scheduled end of the study (Gajewski 2015). For the response adaptive randomization, clinical data from 30 days and 3 months will be used to predict 6-month data. Safety of the trial will be carefully assessed including a statistical analysis of severe adverse events (SAEs). 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.

The enormous negative social and economic impact of TBI throughout the world cannot be overemphasized. The major issue is premature death and disability both in civilian and military populations. Conservative estimates of the prevalence of long-term disability due to TBI in the United States of America are well over 3 million people. The economic toll of TBI exceeds $76.5 billion per year (CDC 2010). These sequelae of TBI have led to untold effort in carrying out many unsuccessful clinical trials and the spending of millions of dollars seeking a treatment for severe TBI. Clinical outcome for severe TBI victims has not improved from 1990 to the present (Stein 2010). A successful treatment for severe TBI would result in billions of dollars of savings for the chronically disabled patients, improve the patients' ability to work productively, and relieve a significant amount of human suffering. Prior studies (discussed below) strongly indicate that HBO2 is physiologically active in improving the destructive processes in severe TBI. However, prior to a definitive efficacy study, important information is required regarding optimizing the HBO2 treatment paradigm instituted in terms of the atmospheric pressure, frequency of treatment and whether NBH following HBO2 treatments enhances the treatment effect. Preclinical investigators working with TBI models have used pressures varying from 1.5 to 3.0 ATA. Clinical investigators have used pressures varying from 1.5 to 2.5 ATA. However, the lungs in severe TBI patients have frequently been compromised by direct lung injury and/or acquired ventilator pneumonia and are very susceptible to oxygen toxicity. Working within those constraints, it is essential to determine the most effective HBO2 dose schedule without producing oxygen 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.

The trial design is creative and addresses the appropriate dose and delivery of HBO2 therapy as well as providing probability for a go/no-go threshold for proceeding to a confirmatory phase III trial.

There is peer-reviewed published animal data from well-established research laboratories which indicate that HBO2 potentially improves outcome from TBI by multiple mechanisms (Daugherty 2004, Lin 2012, Miller 1970, Palzur 2004, Palzur 2008, Rogatsky 2005, Soustiel 2008, Vlodavsky 2005, Vlodavsky 2006, Wada 1996, Wada 2001, Zhou 2007). These mechanisms include improved oxidative metabolism and mitochondrial function, reductions in intracranial hypertension, apoptosis, neural inflammation, and free radical mediated damage. 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 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 (Bergsnedier 1997, Lifshitz 2004, Signoretti 2001, Signoretti 2008, Verweij 2000). Diffusion barriers to the cellular delivery of O2 develop and persist. These barriers appear 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). 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, HBO2 markedly increases O2 delivery to traumatized brain (Daugherty 2004, Rockswold 2010). Thus, HBO2 can potentially reverse the ischemia that precipitates cellular energy failure and the subsequent destructive biochemical cascade. Elevated brain tissue oxygen tension favorably influences 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 HBO2 restores the loss of mitochondrial transmembrane potential and that the reduction of apoptotic cell death mediated by HBO2 is achieved by a mitochondrial protective effect (Palzur 2008, Soustiel 2008). These investigators theorize that the increased intracellular O2 bioavailability resulting

from HBO2 may contribute to the preservation of mitochondrial integrity and reduce the activation of the mitochondrial pathway of apoptosis. Clinical trials have shown increased global O2 consumption lasting for at least 6 hours post HBO2 treatment. This may be secondary to improved mitochondrial function. In addition, this effect is seen for at least 5 days post injury in human TBI victims treated with HBO2 (Rockswold 2001, Rockswold 2010). Thus, HBO2 improves oxidative metabolism during the period of prolonged post trauma hypometabolism. In addition, HBO2 has been shown in both experimental and clinical studies to reduce ICP (Brown 1988, Hayakawa 1971, Miller 1971, Rockswold 1992, Rockswold 2001, Sukoff 1982) and cerebral edema after severe brain injury (Mink 1995, Nida 1995, Palzur 2004, Sukoff 1982). These latter studies suggest that HBO2 may promote blood brain barrier integrity, thus reducing cerebral edema and hyperemia and therefore reducing the elevated ICP. In addition, HBO2 improved hippocampal cell loss and reduced intracranial hypertension and the size of hemorrhagic cerebral contusions (Palzur 2004, Zhou 2007). These positive findings were demonstrated in injured rats treated with HBO2 compared to control injured animals.

Daugherty, et al. and Zhou, et al. from Virginia Commonwealth University have produced experimental mechanistic data that provides strong support for clinical observations of the effect of HBO2 in TBI reported by Rockswold, et al. (Daugherty 2004, Rockswold 2001, Rockswold 2010, Rockswold 2013, Zhou 2007). A lateral fluid percussion injury model in rats was used to compare sham injured rats, an injured control group, an injured group treated with NBH (4 hours of 1.0 ATA), and an injured group treated with 1 hour of HBO2 (1.5 ATA followed by 3 hours NBH (HBO2/NBH). Hyperoxia treatment started 15 minutes following injury. HBO2/NBH significantly increased brain tissue PO2 compared to the control group (247 mmHg versus 37.7 mmHg) and also caused a highly significant increase in global O2 consumption in both injured and sham injured animals when compared to control animals receiving 30% fraction of inspired oxygen (FiO2). Mitochondrial redox potential as measured by Alamar blue fluorescence and ATP extracted and measured from the cerebral cortex using high performance liquid chromatography were significantly reduced by the fluid percussion injury when compared to sham injury at the completion of treatment. The reductions in mitochondrial redox potential and ATP were completely reversed at 4 hours post injury in animals receiving HBO2/NBH therapy ($p \leq 0.05$). The injured animals treated with HBO2/NBH had significant improvements in cognitive recovery as characterized by a shorter latency in the Morris Water Maze performance (90.5 seconds for controls, 77.4 seconds for NBH, and 60.5 seconds for HBO2). Decreased neuronal loss in the CA2/3 and hilar regions of the hippocampus was also seen in HBO2/NBH treated animals as compared to controls or animals treated with NBH. There was no significant difference in neuronal cell counts between animals that received 30% FiO2 and those receiving NBH treatment. These data indicate that mitochondrial function is depressed after TBI, but there is a potential for mitochondrial functional recovery that HBO2 can enhance.

A series of elegant experiments conducted by the Tecnion Israel Institute of Technology using a cerebral contusion rat model have provided strong preclinical evidence for the neuroprotective effect of HBO2 (Palzur 2004, Palzur 2008, Soustiel 2008, Vlodavsky 2005, Vlodavsky 2006). A dynamic cortical deformation (DCD) injury model induced by negative pressure applied to the cortex was used. In these studies, DCD injured rats (control group) were compared to an HBO2 (2.8 ATA) treated group. Two consecutive 45-minute HBO2 treatments separated by 5 minute air breaks were given daily for 3 days. The treatment window was 3 hours after injury. In the first two studies, there were two additional groups; DCD and postoperative hypoxia versus DCD and postoperative hypoxia followed by HBO2 (Palzur 2004, Vlodavsky 2005). All animals were sacrificed on day 4 and histological sections taken. Secondary brain damage was assessed by counting the number of terminal deoxynucleotidyl transferase-mediatiad dUTP nick end labeling (TUNEL) and caspase 3-positive cells in 0.5 mm thick successive increase in the TUNEL-positive cell index for apoptosis in each layer of the cortex. HBO2 treatment induced a significant decrease in both the radius of the area of the lesion and severity of the brain damage following DCD. The reduction in lesion volume and severity was even more pronounced in HBO2 treated injured rats exposed to post traumatic hypoxemia (Palzur 2004). The TUNEL-positive cell index in the first layer in DCD injured rats treated with HBO2 was reduced by 53% and 71.7% in the HBO2 group exposed to DCD plus hypoxemia. The apoptosis-related proteins of the Bcl-2 family in the traumatic penumbra area were evaluated (Vlodavsky 2005). The expression of the anti-apoptotic protein Bcl-2 was lower in the animals exposed to DCD plus hypoxemia than animals receiving injury from only DCD. A significant increase in Bcl-2 expression was seen in both groups after HBO2 treatment. The investigators concluded that HBO2 reduces the area of necrosis, cerebral edema and secondary brain damage. It was also concluded that apoptotic mechanisms are important in delayed cell death in TBI and that post traumatic hypoxemia increases

the intensity of apoptosis, probably through a decrease in Bcl-2 and Bcl-xL expression that normally represses apoptosis. HBO2 appears to enhance the expression of Bcl-2 and Bcl-xL, thus suppressing apoptosis.

The effect of HBO2 on neuroinflammation and on the expression of matrix metalloproteinase (MMP)-9 was studied by Vlodavsky (2006). Neutrophils were revealed by myeloperoxidase staining and immunohistochemical staining for MMP-9 also was performed. The HBO2 treated group had a significant decrease in neutrophilic inflammatory infiltration compared to control groups. The expression of MMP-9 also was significantly lower in the HBO2 group. These results demonstrated that HBO2 decreased the extent of secondary cell death and reactive neuroinflammation in this TBI model compared to controls. The decline of MMP-9 expression after HBO2 may also contribute to protection of brain tissue in the perilesional area.

In the final two studies the investigators hypothesized that HBO2 mediated enhancement of Bcl-2 expression and increased intracellular O2 bio-availability may contribute to preserve mitochondrial integrity and reduce the activation of the mitochondrial pathway of apoptosis by involving the 18-kDa translocator protein (TSPO) (Palzur 2008, Soustiel 2008). TSPO is mostly associated with the mitochondrial transition pore and its role in mitochondrial respiration. In mitochondria isolated from injured brain tissue there was a profound loss of mitochondrial transmembrane potential that proved to be substantially reversed (approximately 70%) by HBO2. This finding correlated with a significant reduction of caspase 3 and 9 activation in HBO2 treated animals (60%) but not of caspase 8, indicating that the reduction of apoptotic cell death mediated by HBO2 is achieved by a mitochondrial protective effect. In addition, HBO2 reduced both the number of TSPO-expressing and TUNEL-positive cells in the perilesional area as compared to control groups (-52.7% of TSPO positive cells for HBO2 versus controls, respectively). Hyperoxia resulted in profound decreases in apoptosis in comparison to the control DCD group which was significantly more pronounced with HBO2 compared to controls (-66.5% of TUNEL positive cells for HBO2 compared to controls across the perilesional area).

Wang, et al. have systematically evaluated the effective treatment window for HBO2 following TBI in a rat contusion model (Wang 2010). This was an exhaustive study utilizing over 300 animals which created a standardized parietal contusion using Fenney's weight drop model. The neurological scoring systems proposed by Dixon, et al. and Hall, et al. were adapted, i.e., beam balancing test and prehensile traction test (Dixon 1987, Hall 1988). All neurologic evaluations were carried out by a researcher blinded to study group. Gravimetric analysis of brain water content, the incidence of apoptosis, and hippocampal ischemic cell loss also were evaluated. Time windows of HBO2 effectiveness were evaluated at 3, 6, 12, 24, 48 and 72 hours after TBI. The effectiveness of a single treatment versus three or five treatments on consecutive days was also evaluated. Rats were randomized to either a HBO2 treatment group receiving 3 ATA for 60 minutes or a sham-operated group. It was found that a single HBO2 treatment given at 3, 6 or 12 hours post injury significantly reduced the neurology deficit score and brain water content, improved the preservation of neuronal cells in the hippocampus, and reduced apoptosis in the cortex surrounding the primary injury. There was no notable effect when a single treatment of HBO2 was started at 24, 48 or 72 hours after TBI. However, when the first HBO2 treatment was started up to 24 hours after TBI, multiple HBO2 treatments (either 3 or 5 consecutive days) decreased the neurology deficit score and neuronal cell loss significantly more than compared to a single treatment. When the first HBO2 treatment was carried out at 48 hours after TBI, multiple treatments reduced the neurology deficit score and increased the number of neurons preserved as compared to the control group. However, the improvement was less than that seen with a single HBO2 treatment administered as early 6 hours after TBI. When the first HBO2 treatment was deferred until 72 hours, there was no improvement in these outcome measures.

Our first randomized clinical trial (RCT) (Rockswold 1992) randomized 168 patients within 24 hours of injury equally into two groups: a control group and an HBO2 treatment group (1.5 ATA per 60 minutes). Hyperbaric oxygen treatments were given every 8 hours for 14 days unless the patient began to follow commands or became brain dead. The dichotomized Glasgow Outcome Scale (GOS) was assessed by a blinded independent examiner. This clinical outcome study showed that for severe TBI patients, HBO2 can be administered safely and systematically and that mortality rates were reduced by a relative 50% with HBO2 treatments. This effect was especially dramatic in patients with negative outcome predictors, that is intracranial hypertension, evacuated mass lesions, and Glasgow Coma Scale (GCS) scores of 4 to 6. No improvement occurred in clinical outcome using the dichotomized GOS at 6 months. A reanalysis of the raw data and outcomes was performed by the biostatistical group at the Medical University of South Carolina.

Since the favorable impact on mortality rate by HBO2 occurred in severely injured patients, it was hypothesized that patients with GCS scores of 7 or 8 with diffuse injury were "diluting" the treatment effect. This subgroup (49 patients) had a favorable outcome of 71% using the dichotomized GOS. The reanalysis of the remaining patients showed that 19 of 57 (33.3%) in the control group and 27 of 60 (45%) of the HBO2 treated group had a favorable outcome using the dichotomized GOS. This difference represents an absolute 11.7% improvement in favorable outcome. When the 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 difference represents an absolute 12.7% improvement in favorable outcome. Because of the smaller numbers, these differences did not reach statistical significance.

A second prospective clinical physiologic study to determine the effects of HBO2 on cerebral metabolism and ICP was performed (Rockswold 2001). Thirty-seven patients treated for severe TBI were entered into the study within 24 hours of injury. All patients received HBO2 at 1.5 ATA for 60 minutes. Treatments were administered once every 24 hours for 5 days. Cerebral blood flow (CBF), arterial venous difference of oxygen (AVDO2), cerebral metabolic rate of oxygen (CMRO2), ventricular cerebral spinal fluid (CSF), lactate levels, and ICP measurements were obtained 1 hour before HBO2 and 1 hour and 6 hours after HBO2 treatments. CBF and CMRO2 were increased post treatment in patients who began their HBO2 treatment with a reduced or normal blood flow ($p < 0.05$). Levels of CSF lactate were consistently decreased after HBO2 sessions ($p = 0.01$). Patients with elevated ICP ($\geq$ 15 mmHg) prior to HBO2 showed a consistent and highly significant reduction in their ICP from completion of HBO2 treatment to 6 hours post treatment ($p = 0.006$). Effects occurred whether their HBO2 was delivered in the first 24 hours after injury or up to 5 days after injury.

A third prospective RCT directly compared the effect of HBO2 to NBH on surrogate markers of oxidative cerebral metabolism and O2 toxicity that predict and closely correlate with clinical outcome (Rockswold 2010). Sixty-nine patients sustaining severe TBI (mean GCS score 5.8) were prospectively randomized within 24 hours of their injury into one of three groups: 1) HBO2; 60 minutes of HBO2 at 1.5 ATA 2) NBH; 3 hours of 100% FiO2 at 1 ATA and 3) control. Treatments occurred every 24 hours for 3 consecutive days. Brain tissue PO2 was continuously monitored. Microdialysis lactate, pyruvate, and glycerol as well as ICP were collected hourly. Cerebral blood flow, AVDO2, CMRO2, CSF lactate, F2-isoprostane, bronchial alveolar lavage (BAL) fluid interleukin (IL)-8 and IL-6 assays were obtained pretreatment and at 1 and 6 hours post treatment. Mixed effect linear modeling was used to statistically test differences between the treatment arms as well as changes from pretreatment to post treatment. Data from the study can be summarized as follows. 1) HBO2 had a significantly greater positive post treatment effect than NBH on oxidative cerebral metabolism. 2) Although the treatment effect was not an all-or-nothing phenomenon, a critical brain tissue PO2 level of 200 mmHg was important in achieving a robust positive effect on cerebral metabolism, especially CMRO2, which reflects mitochondrial function. Brain tissue PO2 levels of $\geq$ 200 mmHg were reached in only 51% of the HBO2 treatment sessions and 5% of the NBH treatments. Finding that a brain tissue PO2 of $\geq$ 200 mmHg was required to produce a significantly more robust effect in oxidative cerebral metabolism indicates that higher pressures of HBO2 may be more effective than 1.5 ATA. 3) HBO2 had a post treatment effect lasting between 6 and 24 hours, which suggests that HBO2 can be delivered intermittently to obtain the treatment effect over many days and reduce potential O2 toxicity. 4) The treatment effect was as great on day 3 as it was in the first 24 hours, that is, the treatment effect was the same after the first treatment as after the third which implies that HBO2 is effective in improving mitochondrial function even when ischemia is not overtly present. 5) ICP was reduced after HBO2 treatments in comparison with levels following standard care. The NBH group did not demonstrate a reduction in ICP. 6) There was no evidence of cerebral or pulmonary O2 toxicity in either of the HBO2 or NBH treatment paradigms administered.

Our clinical study described above demonstrated that the positive effect on cerebral oxidative metabolism occurred following, not during, the HBO2 treatment (Rockswold 2001). The CMRO2 is a surrogate marker of mitochondrial function and was improved significantly for 6 hours post HBO2 treatment. The data suggested that the HBO2 treatment improved the brain's ability to utilize baseline O2. This finding led to the testing of this hypothesis in two experimental studies described above by the group led by Ross Bullock at the Virginia Commonwealth University School of Medicine (Daugherty 2004, Zhou 2007). Both studies utilized a lateral fluid percussion injury model in rats and compared sham-injured and injured control rats to an injured group treated with 1 hour of HBO2 (1.5 ATA) followed by 3 hours of NBH (combined HBO2/NBH treatment). Both mitochondrial redox potential, as measured by Alamar blue fluorescence, and ATP, extracted and measured from the cerebral cortex using high-performance liquid chromatography, were significantly reduced by the fluid

percussion injury when compared to sham-injury at the completion of treatment. The reductions in mitochondrial redox potential and ATP were completely reversed at 4 hours post injury in animals receiving combined HBO2/NBH therapy but not after 1 hour of HBO2 treatment. This experimental work led to our receiving a competitive supplemental grant from National Institutes of Neurological Disorders and Stroke (NINDS) to evaluate combining HBO2/NBH (Rockswold 2013).

Forty-two patients who sustained severe TBI (mean GCS score 5.7) were prospectively randomized within 24 hours of injury to either: 1) combined HBO2/NBH; 60 minutes of HBO2 at 1.5 ATA followed by NBH, 3 hours of 100% FiO2 at 1.0 ATA; or 2) control, standard care. Treatments occurred once every 24 hours for three consecutive days. Intracranial pressure, surrogate markers for cerebral metabolism and O2 toxicity were monitored. Clinical outcome was assessed at 6 months using the severity adjusted dichotomized GOS score. Mixed-effects linear modeling was used to statistically test differences between the treatment and control groups. Functional outcome and mortality rates were compared using chi-squared tests. There were no significant differences in demographic characteristics between the two groups.

This study using combined HBO2/NBH demonstrated improvement in surrogate markers of oxidative cerebral metabolism and a previously unreported finding was the fact that oxidative cerebral metabolism improved in pericontusional areas as well as relatively “non-injured” cerebral tissue. Although the study was relatively small in terms of numbers, it showed a dramatic statistically significant improvement in functional outcome and mortality rate. The mortality rate was 16% for the combined HBO2/NBH group as compared with 42% for the control group or an absolute percentage reduction of 26% (p=0.048). Thirty-eight percent of the control group and 74% of the HBO2/NBH group had a favorable outcome based on the sliding dichotomized GOS for an absolute 36% improvement (p=0.024). Based on the dichotomized GOS, 33% of the control group and 58% of the combined HBO2/NBH group had a favorable outcome for a 25% absolute improvement (p=0.077).

Data in this study can be summarized by the following key points: 1) The combined HBO2/NBH treatment significantly improved markers of oxidative cerebral metabolism in relatively uninjured brain tissue but, importantly, also in pericontusional tissue. 2) The combined HBO2/NBH treatment reduced intracranial hypertension and thereby decreased the therapeutic intensity of treatment of intracranial hypertension. 3) There was no evidence for O2 toxicity either in the brain or lungs and there was actual demonstrated improvement in markers of cerebral toxicity. 4) Combining HBO2 and NBH into a single treatment potentially has a synergistic therapeutic effect. 5) The combined HBO2/NBH treatment reduced mortality and improved favorable outcome as measured by the GOS at 6 months. This improvement was significantly better than past clinical outcome observed with either of the treatments used separately. The clinical outcome portion of this study is limited by a relatively small number of patients.

The treatment window is a significant issue in designing the HOBIT trial. It is considerably more difficult to initiate a complex treatment like HBO2 as compared to initiating a drug therapy intravenously. HBO2 treatment cannot occur until resuscitation, including intubation, hemodynamic stabilization, emergency surgery as needed, and management of other traumatic injuries has occurred. Informed consent must be obtained from the legal authorized representative (LAR). Based on our past experience, patients not requiring craniotomy/craniectomy or any other major surgical procedure will be enrolled and the first HBO2 treatment initiated within 6 hours of admission. If the patient does require craniotomy/craniectomy or major surgical procedure, the enrollment and initial HBO2 treatment shall be initiated within 12 hours. Under no circumstances will a patient be enrolled more than 24 hours after the injury occurs. Prior investigations of HBO2 have used a 24-hour treatment window (Rockswold 1992, Rockswold 2001, Rockswold 2010, Rockswold 2013).

This trial is designed as a 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 to 8 (age 16 to 65 years) are initially eligible for inclusion. Patients with a GCS score of 7 or 8 and a Marshall computerized tomography (CT) score 1 or 2, as well as patients with a GCS score of 3 AND bilaterally mid-position nonreactive pupils will be excluded. Patients in previous RCTs with GCS scores of 7 or 8 or GCS motor score of 4 or 5 with mildly abnormal CT scores have had a favorable outcome on the dichotomized GOS in the 70 to

80% range; in these patients it is difficult to show clinical benefit for treatment (Maas 2006, Marshall 1998, Morris 1999). Patients with a GCS of 3 and bilateral unreactive pupils are excluded because of their inability to respond to any treatment. No exclusion criteria will be based on race, ethnicity, or gender.

GCS score ≤ 6 or GCS score 7 or 8 and Marshall CT score ≥ 3	Patients most likely to benefit from treatment
Age ≥ 16 and ≤ 65	Safety not established in children. Elderly have relatively poor outcome.
Patients not requiring craniotomy or major surgical procedures will be enrolled and HBO2 treatment initiated within 6 hours of admission. Patients requiring a craniotomy or major surgical procedure will be enrolled and HBO2 treatment initiated within 12 hours.	Pre-clinical/clinical data support this treatment window
Informed consent obtained	Required
Blunt mechanism only	Pathophysiologic and anatomic differences with penetrating injury

GCS 3 bilaterally unreactive pupils ≥ 4 mm	Death highly likely
Severe pre-existing neurological deficits, e.g., previous TBI, stroke	Prevent good recovery
Acute spinal cord injury	Alters neurologic recovery
Fixed coagulopathy. INR > 1.4 despite correction attempts.	Poor prognosis; appropriate procedures can't be done
Pregnancy	Effects of HBO2 on fetus uncertain

Adequate recruitment has been a major issue in previous clinical trials. We are basing our conservative enrollment numbers on previous Neurological Emergency Treatment Trials (NETT), particularly the recently concluded Progesterone for the Treatment of Traumatic Brain Injury (ProTECT) III trial. However, the HOBIT trial has more restrictive inclusion criteria than ProTECT and the treatment is more complex. In our best case scenario, we are anticipating that each of our 15 enrolling sites will enter one patient every other month into the HOBIT trial. This is taking into consideration the inclusion criteria which exclude TBI patients with GCS scores 7 and 8 and Marshall CT scores 1 or 2. The 15 enrolling sites are expected to enroll approximately 90 patients per year or 1.75 patients per week. This would give us an enrollment time of 114 weeks plus another 26 weeks to complete follow up for a total of 140 weeks. We would anticipate a 3-year enrollment period, including final 6-month assessments. In the ProTECT III trial, the lost to follow up rate was under 6%. Our observed recruitment and retention rate will provide predictive value for a subsequent phase III trial.

The following table lists the number of severe TBI patients (GCS 3 to 8) per site and the number of patients anticipated to be enrolled in the HOBIT trial. The numbers for the NETT enrolling sites are based on the ProTect trial.

	HCMC/U of Minnesota	93	6	0.5	U Utah	80	6	0.5
	Med College of Wisconsin	84	12	1	U Tennessee	128	6	0.5
	U Pittsburgh	80	6	0.5	Duke	75	6	0.5
	U Maryland	250	12	1	Loma Linda	84	6	0.5

	Ohio State	108	6	0.5	U Iowa	98	6	0.5
	U Kentucky	93	6	0.5	U Nebraska	65	6	0.5
	U Texas – Houston	220	12	1	McMaster, Canada	65	6	0.5
	Mass Gen Hospital	84	6	0.5				

Total all sites HOBIT: 108 pts/year and 9.0 pts/month

If the patient meets inclusion criteria and informed consent is obtained, they will be randomized to one of nine HBO2 treatment paradigms.

1. 2.0 ATA no NBH once daily
2. 2.5 ATA no NBH once daily
3. 1.5 ATA with NBH once daily
4. 2.0 ATA with NBH once daily
5. 2.5 ATA with NBH once daily
6. 1.5 ATA no NBH twice a day
7. 2.0 ATA no NBH twice a day
8. 2.5 ATA no NBH twice a day
9. 1.5 ATA with NBH twice a day
10. Control (no HBO2 treatment)

HBO2 treatments will be delivered in both monoplace and multiplace chambers. Compression and decompression will occur at a standard 2 feet per minute. Each treatment will be 60 minutes at the specified pressure. NBH will consist of the patient breathing 100% O2 for 3 hours following HBO2 decompression. The treatment paradigm will be continued for five days or until the patient is following commands or determined to be brain dead.

David Wright, MD, PI for the ProTECT III trial evaluating progesterone in the treatment of TBI, has allowed the HOBIT trial to utilize the Clinical Standardization Guidelines (CSG) developed for the ProTECT trial. The guidelines were established by the ProTECT III Clinical Standardization Team (CST), a national committee of experts in neurological surgery, trauma surgery, neurological critical care and emergency medicine. They are based on the Guidelines for the Management of Severe Traumatic Brain Injury (Brain Trauma Foundation 2007) as well as the expertise of the CST.

The baseline severity adjusted dichotomized GOS-E score will be used as the primary outcome measure to assess recovery. At 3 and 6 months, a blinded assessment using the structured GOS interview will be completed by either the patient or, if the patient is unable to participate, the patient's closest family member or legal guardian (Wilson 1998). The primary outcome measure will be at 6 months. The Disability Rating Scale (DRS) using the TBI national database collection form will be obtained at the same time the interview for the GOS-E is obtained. Information can be obtained during the phone interview with either the patient or the patient's closest family member or legal representative.

A SAE is defined as any adverse event that occurs during the course of the trial that results in any of the following outcomes: death, a life-threatening adverse experience, prolongation of existing hospitalization or inpatient hospitalization subsequent to initial hospital discharge, or a persistent or significant disability/incapacity. All SAEs will be judged independently to be unlikely, possibly, probably, or certainly related to the HBO2 treatment. A statistical comparison of the incidence of SAEs in the HBO2 treated groups versus control will be done.

Inaccurate Determination of GCS Scores. All severe TBI patients require early intubation which requires sedation and muscle relaxants which may lead to inaccurate neurological evaluation (Stocchetti 2004). Stocchetti, et al. found significant improvement in post stabilization GCS score as compared to the pre-hospital or admission GCS score (Stocchetti 2004). Marmarou, et al found that the GCS score and pupil reactivity assessment have the greatest prognostic association when determined at the time of enrollment into a clinical trial (after resuscitation) as compared to pre-hospital, first in-hospital assessment, or study hospital admission (Marmarou 2007). In this proposed clinical trial, a post resuscitation/enrollment GCS score will be the one recorded for randomization and subsequent evaluation of GOS-E.

Slow Patient Accrual. Recruitment and enrollment is a major challenge for any multisite trial. We have addressed this issue in the following ways.

1. We've utilized actual enrollment data from previous NETT trials (specifically ProTECT) to establish conservative enrollment rates.
2. The budget for the clinical sites is based on a per patient reimbursement model with clear milestones set prior to disbursement of funds. This model will encourage the sites to meet recruitment goals.
3. Low performing sites will be subject to oversight by the Executive Committee (EC) and will potentially be dropped from the trial.
4. The clinical sites were selected in part for their experience with HBO2.
5. The per-patient reimbursement model allows for expansion to other centers if needed on a relatively cost neutral basis.

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

We have carefully examined problems with previous clinical trials.

1. The HOBIT trial has adapted the ProTECT III CSG developed by a multidisciplinary team of experts in the management of severe TBI. These guidelines are straightforward and are in use in most major TBI treatment centers and follow a goal-direct therapy approach.
2. The External Steering Committee (ESC) is made up of a group of experts, including Drs. Lindell Weaver, Lori Shutter, and David Wright, who will help to ensure standardization of TBI care.
3. The EC plans to conduct pretrial meetings with the lead staff at the enrolling sites to discuss and emphasize the importance of providing consistent, state-of-the-art care.
4. The EC will implement a protocol based online examination through the Web DCU that will be required for personnel involved in patient care prior to participation in the study.
5. The Statistical and Data Management Center (SDMC) is experienced in tracking performance based on key data elements entered daily into the study database to monitor each site's adherence to the management protocol. The system will alert the principal investigator (PI) and other appropriate EC members to violations and deviations.
6. The EC will assess site performance via a site report card that will be generated on a regular basis with predetermined minimal site guidelines for patient care and adherence to the protocol. As part of the report card process, there are provisions to drop a participating site if a pattern of willing disregard for the protocol is identified.
7. Periodic ongoing onsite visits by the PI and the Clinical Project Coordinator (CPC) will be conducted to ensure quality assurance throughout the trial.
8. The HOBIT trial statistical plan includes randomization adjusted for enrolling sites.
9. The EC has secured written assurances of cooperation from our research partners at each enrolling site.

The _____ is of the six-month GOS-E response and will be that a treatment arm is superior to control, meaning that the rate of response with GOS-E is greater for one experimental arm compared to the

control. 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. Specifically, the currently proposed Phase II trial will be considered conclusive if one of the three following cases occurs. is if at any interim analysis the most likely arm has at least a 0.975 posterior probability of being better than control.
happens if at the conclusion of accrual of the 200 patients, the most likely arm has at least a 0.94 posterior probability of being better than control. is if at any interim analysis the most likely arm has at most a 0.55 posterior probability of being better than control. Prediction of Phase III success is if recommended novel treatment has a greater than 50% probability of HBO2 treatment demonstrating improvement versus placebo in a subsequent confirmatory trial. *The intent-to-treat* (ITT) patient population will include all patients randomized, where patients will be classified by the group in which they are randomized, regardless of the treatment received. The design is a novel Phase II adaptive design. The trial will utilize response adaptive randomization to favor the better performing experimental arms. If there is at least one experimental treatment arm that shows promise based on the above description, it will advance to a Phase III trial and be compared for superiority to the control arm. ***The Phase II trial will have*** initial burn-in period of 50 subjects in which these patients are enrolled in a fixed randomization ratio to the control and each of the experimental arms. A ratio of 1:1:1:1:1:1:1:1:1 will be used for the burn-in period. After the initial burn-in period, response adaptive randomization will be utilized. A constant proportion of 20% of patients will be enrolled to the control arm throughout the study. Interim analyses will take place quarterly to adjust the randomization probabilities based on the current data. The probabilities will be set to be proportional to the probability each experimental arm is the maximally effective treatment arm. There is a possibility of early stop for efficacy and advancing to planning a Phase III trial. The trial can stop for futility if the probability of Phase II success drops below 50% for all experimental treatment arms. The final analysis will be conducted after all subjects have completed six-month GOS-E response. Phase II information will be used to predict the probability of a successful Phase III clinical trial (equally randomized to usual care or novel treatment) to confirm the efficacy of novel treatment to increase response and confirm the safety of treating severe TBI with optimal HBO2 compared to usual care. The primary outcome for a hypothetical Phase III trial will be the same as in Phase II (sliding dichotomized GOS-E at 6 months). The primary analysis in Phase III investigates, with two sample proportions test (chi-square test), whether there is a difference between usual and novel treatment. The sample size for Phase III is assumed to be 500 in control and 500 in the novel treatment, and alpha =.05 2-tailed).

The ***Statistical Modeling*** is Bayesian in nature. *For the response model for six-month GOS-E response we* label the observations of the six-month GOS-E response for subject *i*, at the six-month visit as $Y_{i,6}$. We model the six-month primary outcomes as Bernoulli distributed. The model is $[Y_{i,6}]$~Bernoulli(θ_{ai}), where a_i is the treatment arm for subject *i*. We label the six-month GOSE response for arm *a* as θ_a. Based on prior studies, it is expected GOS-E response for control group and novel treatment have the following prior distributions logit(θ_1)~N(-.41,.75^2), the control arm, and logit(θ_a)~N(0,1.75^2), novel treatments *a*=2,3,4,…,10. The control prior is equivalent to eight observations worth of weight the novel treatment's prior is equivalent to two observations. The main effects model is $[Y_{i,6}]$~Bernoulli(P_i), for subject *i*. We construct a main effects model for the GOS-E response rate that is a function of pressure, NBH, and duration. The logit transformation of P_i is modeled with a linear equation. By assuming no interaction among the main factors, this model has a lower number of parameters and is designed to increase ability to predict phase III success. The structure is $logit(\mathrm{P_i}) = X_{i1}\mu + X_{i2}\alpha_{1.5ATA} + X_{i3}\alpha_{2.0ATA} + X_{i5}\gamma_{NBH} + X_{i6}\gamma_{no\ NBH} + X_{i7}\beta_{BID} + X_{i8}\beta_{QD}$. The *X*s are 0 or 1 depending on the treatment combination subject *i* is assigned. μ represents the effect of control. The α's represent the additional effect of pressure relative to control. The γ's and β's represent the additional effect of NBH and BID respectively. Note: to identify, set $\gamma_{no\ NBH} = 0$ and β_{QD}=0. Based on prior studies, it is expected GOS-E response for control group and novel treatment have the following prior distributions logit(μ)~N(-.41,.75^2), the control arm, and logit(*all other parameters*)~N(0,10^2). The control prior is equivalent to eight observations worth of weight the novel treatment's prior is equivalent to close to 0 observations. At each interim analysis there will be subjects who could have complete or incomplete information. Some subjects will have complete information on their six-month observation, $Y_{i,6}$. These subjects may also have their interim value, $Y_{i,1}$. There will be subjects with interim observations response, but no six-month value. There will be subjects with no observations. We utilize the information from subjects with incomplete information to the extent that the interim values are predictive of the final six-month values. A Bayesian model is built to learn from the accruing information (those subjects with complete six-month data) in the early response values to the final endpoint of six-month response. Estimate transition probabilities from outcome at early time point to final outcome. The

number of transitions to final outcome given early outcome is distributed as Binomial. Let p21 and p22 be conditional on a patient showing early response, the respective final probabilities of response and not responsive. For these we use a Beta prior on transition probabilities, (p21,p22)~Beta(20,5). Similarly for a patient that shows no response early, the final prior probabilities are (p31,p32)~Beta(5,20).

The following are calculated at each interim analysis. These quantities are used in the adaptive design. From the joint posterior distribution the posterior probability that each arm, *a*=2,3,4,…,10 is the maximally effective arm, P_a^{max}, is calculated. The arm with the largest P_a^{max} is labeled the *most likely maximum effective novel treatment.* The posterior mean and variance for each GOS-E response rate is calculated. We label $V(\theta_a)$ as the posterior variance of the parameter θ_a. For GOS-E response rate the posterior probability that each arm is superior (larger response rate) to the control arm is calculated $\Pr(\theta_a > \theta_1|\text{data})$. Each of these Bayesian quantities is calculated at each interim analysis point. Each of these quantities are calculated using the data from all subjects in the trial—those with complete data and those with interim data. Taking the maximum arm from Phase II trial simulations we calculated the posterior predictive probability whether there is a >50% probability of hyperbaric treatment demonstrating improvement in the rate of good neurological outcome versus control in a subsequent Phase III confirmatory trial. This is calculated with the main effects model among the successful treatment combinations. During the defined burn-in period (50 subjects) the allocation is set at 1:1:1:1:1:1:1:1:1. During the adaptive allocation in Phase II randomization will be used in which the allocation probabilities are updated monthly to favor those durations most likely to be the maximum effective treatment arm. The specification of the vector of probabilities for randomization is defined in this section. The randomization vector is created by selecting a vector based on the posterior distribution of the GOS-E response for each arm. The number of subjects enrolled in arm *a* is n_a. The goal of the adaptive randomization is to allocate subjects to the arms most likely to be the maximum effective arm. In addition, the goal is to learn how good the effective maximum arm is relative to the control arm. A *component,* V_a, is constructed for each arm. Set V_1=1, assuring 1/5 probability for control arm throughout the trial. The component for arms *a*=2,3,4,…,10 is $V_a=P_a^{max}$. The randomization vector, $\boldsymbol{q}$, is set as $q_a=V_a/10$.

In this section we summarize the results of several simulation cases and an additional scenario of a null scenario in order to ensure type I error control of the design. For each of the cases 1,000 trials are simulated. We present the results as a function of the final six-month GOS-E response for each of the arms. For all simulations in this section we assume an accrual rate of 1.75 subjects per week. No drop outs are assumed. The study is classified as a success if a target duration arm is identified and recommended to be carried to Phase III. In the simulations if a trial enters the possible success or futility stage the trial is stopped in the simulation. Several cases are presented in Table 1. The value in each cell is the GOS-E response at 6 months. The first case is referred to as the *null hypothesis* as each of the arms have identical GOS-E responses—the novel treatment has no effect on GOS-E response relative to the control arm. The remaining six cases explore scenarios with different GOS-E responses for the experimental arms, including one case where harm is exhibited. The six cases involved are small, medium, and large. Also investigated is a case where the GOS-E response is the factor pressure both as medium and large effects.

Case	Control	1.5, NBH, QD	2.0, NBH, QD	2.5, NBH, QD	1.5, no NBH, BID	2.0, no NBH, BID	2.5, no NBH, BID	1.5, NBH, BID	2.0, no NBH, QD	2.5, no NBH, QD
1. None	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
2. Small Main	0.4	0.45	0.5	0.43	0.45	0.5	0.43	0.48	0.48	0.4
3. Medium Main	0.4	0.5	0.55	0.48	0.5	0.5	0.48	0.55	0.5	0.43
4. Large Main	0.4	0.57	0.7	0.52	0.57	0.7	0.52	0.65	0.63	0.45
5. Harm	0.4	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35

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

For the purposes of this investigation power for this phase II trial, futility probability, sample size, time (duration), and subject allocation is calculated for the several different cases. We performed five sets of trial

simulations based on the various cases of response. Each set involved 1000 trial simulations. We highlight four cases. The first uses a medium case. If there is a medium effect, we estimated (identified) that 65% power, 6% futility, the sample size of this trial scenario was on average 187 (36% of these in one of the three 2.0 ATA treatments), and probability greater than 50% probability of Phase III success 71%. The average length of this trial scenario was 131 weeks. The second uses a large case. If there is a large effect, we estimated (identified) that 96% power, 1% futility, the sample size of this trial scenario was on average 174 (45% of these in one of the three 2.0 ATA treatments), and probability greater than 50% probability of Phase III success 98%. The average length of this trial scenario was 125 weeks. The third is the highly unlikely scenario that serves as our null hypothesis. In this scenario there is no difference between the treatments. Therefore, the extent to which this scenario is "successful" actually reflects our Type I error rate. Thus this trial scenario produced an appropriate expected Type I error (α=20%). The sample size of this scenario on average was 186 subjects (equally allocated across groups). The average length of the trials under this scenario was 119 weeks. The futility probability is 34%. The probability greater than 50% probability of Phase III success is 20%.

This study, in addition to identifying the optimal dose, offers the opportunity to explore the treatment effect in other important outcome domains using the ICP, TIL scores and brain tissue PO2. These analyses will allow us to explore the impact of treatment on other potential outcomes that may be more patient-oriented for use in future confirmatory trials and to further support a go/no-go decision regarding a subsequent definitive efficacy trial. Analyses of these secondary outcomes will be conducted using the ITT principle and will follow a similar analysis plan as the primary outcome using the results from all HBO2 treatment paradigms in the comparison of the selected treatment and the control (i.e. main effects model). The level and duration of intracranial hypertension (> 20 mmHg) will be analyzed using AUC methodology in HBO2-treated versus control groups (Vik 2008). The TIL scores for controlling ICP in HBO2-treated patients compared to controls will be analyzed. Utilizing Licox brain tissue PO2 monitoring, the level and duration of brain tissue hypoxia (brain tissue PO2 < 15 mmHg) using AUC methodology in HBO2-treated groups versus control will be analyzed (van den Brink 2000). Finally, the cumulative incidences of specific SAEs as well as SAEs will be compared versus using a main effects model.

Overall. The HOBIT trial will be conducted in the NETT network funded by the NINDS. The Clinical Coordinating Center (CCC) for HOBIT will be the NETT CCC at the University of Michigan and the SDMC will be the NETT SDMC at the Medical University of South Carolina working with the lead statistician at 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. Multiple PIs will serve the HOBIT trial. Dr. William Barsan will serve as the PI at the CCC, Dr. Renee Martin, the PI at the SDMC, and Dr. Byron Gajewski will be the PI for the implementation of the Bayesian adaptive designs and statistical analysis. Dr. Gaylan Rockswold will be the contact PI and will be responsible for the overall conduct of the study. This arrangement allows for a balance split of the overall research project management, the site management, and the data analysis (see Multiple PI Leadership Plan).

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

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

Analytic Center. The AC statistical team will provide the Bayesian adaptive design modeling, using blinded data, at each interim analysis and the randomization probabilities. It will be performing the final Bayesian analysis (see the SDMC parallel application for details).

Scientific Coordinating Center. The SCC consists of the PI, the CPC, the Internal Medical Monitor (IMM), and the HOBIT trial financial manager (FM). The SCC provides overall leadership to the entire HOBIT trial to ensure a successful implementation. It 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 HBO2 administration. The CPC assists the PI in day-to-day implementation in various trial activities. The FM, together with the PI, is responsible for the budgetary management of the grant which funds the CCC, the AC, and all United States and Canadian clinical sites. The IMM will be responsible for reviewing and coding AEs prior to forwarding them to the external Medical Safety Monitor (MSM). The IMM will also assist in monitoring protocol compliance.

Executive Committee. The EC consists of the leadership of the SCC, the CCC, the SDMC, the lead statistician at the University of Kansas, and an NINDS-appointed liaison. The TMC 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, SDMC, SCC, clinical sites, and the NINDS).

External Steering Committee. The ESC membership given above is composed of nationally recognized leaders in the fields of HBO2 critical care, TBI, and clinical trials. The ESC has already played an important role in study design and project development. Individuals have reviewed the grant and protocol and provided advice and insight. The ESC will continue this role during the planning and implementation phase of the trial.

Medical Safety Monitor The MSM is a neurointensivist experienced in severe TBI management as well as serving as a MSM. She is not affiliated with any of the institutions participating in the HOBIT trial. The MSM responsibilities are to review all SAEs and determine whether they are possibly related to HBO2 administration and to adjudicate adverse outcome events.

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

The planning and startup phase will require six months for the identified 15 clinical sites. Activities will include, but are not limited to, finalizing the protocol and the Study Procedural Manual. Contracts with the clinical sites will be done along with training of study personnel and adaptation of the monoplace chambers for ICP monitoring. A run-in or trial period will be required for each clinical enrolling site to ensure that the procedures are learned without jeopardizing patient safety or data quality (Choi 2001). We anticipate the run-in period will occur during the second half of the first year of funding. All patients (up to two) will receive HBO2 during the run-in period and none will be controls. At least one of the patients must be entered without significant protocol violation and meet study data quality requirements. This run-in trial period will optimize the HBO2 treatments at all enrolling sites. This schedule allows for up to two patients per clinical site in the six-month run-in period. Each of the 15 sites will be required to enroll an average of one patient every other month for approximately 30 months. The following table is a timeline for the 5 years.

	30					30
	0	71	95	34	0	200
	0	47	96	57	0	200
	0	25	94	81	0	200

Protection of human subjects in HOBIT is paramount. The NETT dedicates substantial resources to human subjects' protection (HSP) efforts. There is a full time NETT HSP coordinator that provides support, guidance, and oversight to ensure that appropriate high quality processes are in place at sites across the network to protect human subjects, and to help ensure full regulatory compliance. The NETT also has a very active working group of investigators that advise on trial development and operations with special regard to human subject vulnerabilities, and that has been active in performing empirical research to better understand the ethics of clinical trials. This enhances both the implementation and performance of HSP activities. As such, the NETT participates in funded research on the ethics of clinical trials. This resource is of particular value to HOBIT because the NETT HSP working group includes experts that have studied and published on methods to enhance the meaningfulness of informed consent processes conducted in the emergency setting under time constraints, pain, and emotional stress.

All participants in this research understand the importance of protecting human subjects participating in clinical research protocols and will comply with all regulations related to these protections. Key regulations and ethical standards governing the protection of human subjects include:

- Title 45 CFR Part 46: Protection of Human Subjects, "Common Rule";
- Title 21 CFR Part 50, Subpart A: General Provisions and Subpart B Informed Consent, Federal Drug Administration (FDA);
- Title 21 CFR Part 56, Subparts A-E: Institutional Review Boards (IRB);
- FDA Information Sheets: Guidance for IRB and Clinical Investigators, 1998 Update;
- The Belmont Report;
- International Conference on Harmonization; Good Clinical Practice: Consolidated Guideline, May 9, 1997.

There continues to be an overarching problem of high mortality and poor outcome for victims of severe TBI. Preclinical and clinical investigations indicate that HBO2 is physiologically active in reducing brain injury and improving outcomes in severe TBI. Preclinical investigations working with TBI models have used pressures varying from 1.5 to 3.0 atmospheres absolute (ATA). Clinical investigators have used pressure varying from 1.5 to 2.5 ATA. However, the lungs in severe TBI patients have frequently been compromised by direct lung injury and/or acquired ventilator pneumonia and are susceptible to O2 toxicity. Working within these constraints, it is essential to determine the most effective HBO2 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 efficacy trial. Based in part on our previous clinical investigations, as well as a review of the reasons for failure of previous trials in severe TBI, the HOBIT trial will focus on patients who have sustained a severe TBI (GCS score $\leq$ 6) and patients with GCS scores of 7 or 8 and a Marshall CT scan score $\geq$ 3. This strategy will exclude patients with a previous demonstrated high probability of favorable outcome without any intervention, i.e., patients with a GCS score of 7 or 8 and a mildly abnormal CT scan (Marshall score 1 or 2). Patients with a GCS score of 3 and midpoint fixed pupils also will be excluded due to the high probability of treatment futility. No exclusion criteria will be based on race, ethnicity or gender. Detailed eligibility criteria are below. Potential subjects also must be able to be treated within 12 hours of admission to the hospital and in not less than 24 hours of the injury. All subjects with a severe TBI, whether eligible or not, who are evaluated by study

team physician will be recorded in a HOBIT trial screening log. It is anticipated that a significant number of the subjects who arrive in the emergency department with a severe TBI will be excluded from trial participation due to failure to meet the eligibility criteria set out below.

GCS score $\leq$ 6 or GCS score 7 or 8 and Marshall CT score $\geq$ 3	Patients most likely to benefit from treatment
Age $\geq$ 16 and $\leq$ 65	Safety not established in children. Elderly have relatively poor outcome.
Patients not requiring craniotomy or major surgical procedures will be enrolled and HBO2 treatment initiated within 6 hours of admission. Patients requiring a craniotomy or major surgical procedure will be enrolled and HBO2 treatment initiated within 12 hours.	Pre-clinical/clinical data support this treatment window
Informed consent obtained	Required
Blunt mechanism only	Pathophysiologic and anatomic differences with penetrating injury

GCS 3 bilaterally unreactive pupils $\geq$ 4 mm	Death highly likely
Severe pre-existing neurological deficits, e.g., previous TBI, stroke	Prevent good recovery
Acute spinal cord injury	Alters neurologic recovery
Fixed coagulopathy. INR > 1.4 despite correction attempts.	Poor prognosis; appropriate procedures can't be done
Pregnancy	Effects of HBO_2 on fetus uncertain

Sample informed consent documents will be developed in Year 1 of this project period. These documents will contain all elements required by Title 21 CFR Part 50. The documents will be available for use by all participating clinical centers. The individual center's informed consent documents will be reviewed at the CCC prior to submission to the IRB at each participating center. Copies of the locally approved informed consent documents, as well as documentation of IRB approval, and all other regulatory or essential documents will be provided to the SDCC prior to enrollment of study subjects. The SDCC will upload the documents into the WebDCU™, verify, and monitor all regulatory documents. Written informed consent from the legally authorized representative (LAR) of that patient will be required for enrollment. The patient will not be enrolled into the trial if consent cannot be obtained from a competent legal representative. A waiver of consent is not being sought for this study.

Randomization Procedures

A web-based central randomization system will be developed by the SDMC and installed on the WebDCU™ HOBIT study website. The objective of randomization is to prevent possible selection bias by providing random treatment assignment to each subject, and to prevent

accidental treatment imbalances for the known prognostic variables. Balancing of prognostic variables will be conducted using the Minimal Sufficient Balance randomization algorithm which aims to maximize the treatment allocation randomness while containing the baseline covariate imbalances within a pre-specified limit.[35] The randomization scheme will be equal allocation balanced across pre-specified covariates during a burn-in period (first 50 randomizations; 5 per arm). Imbalances in the following baseline covariates between the treatment groups will be controlled: age and GCS score. Once 50 subjects are randomized (in order to accrue outcome information in each arm), response-adaptive randomization (RAR) will be utilized for a maximum of 200 subjects with the goal of maximizing the likelihood of identifying the most effective treatment arm with regards to the GOSE-E response. The allocation probabilities will be proportional to the probability that the arm is the best. The target allocation ratio will be updated every 13 weeks. To ensure proper randomization, the unblinded statistical programmer will have access to the randomization information in order to oversee the quality control of the computer program. Randomization will occur via the study-specific password-protected website accessed by an authorized research coordinator or investigator at the clinical site. If, in rare circumstances, the web system is not available, the coordinator or investigator will have access to emergency randomization procedures that will allow the site to randomize the patient. Upon randomization by the authorized person at each center, an e-mail notification will be sent to the Study EC, Site PI, Site Primary Study Coordinator and relevant NETT CCC and SDMC personnel. Subjects will be considered enrolled in this trial at the time of randomization, regardless of whether or not they start or complete study treatment. The entire randomization process will be blind to all study team members.

The primary responsibilities of the clinical sites will be to:

1. Screen and enroll patients.
2. Manage enrolled patients according to protocol.
3. Collect and transmit acute care data of high quality and integrity.
4. Report adverse events/serious adverse events, protocol deviations/violations, and any other unusual situations to the CCC promptly.
5. Conduct outcome assessments with a high degree of inter-rater reliability.

The clinical sites will be staffed with acute care staff and outcome personnel. The acute care staff includes the center investigators, study coordinator (SC), and HBO_2 personnel. These individuals will be responsible for screening and enrolling appropriate patients, managing clinical care of the patient to conform to the study protocol, conducting HBO_2 treatments, and collecting data about the acute care phase of the patient's care. These individuals will be under the supervision of the clinical site investigators. Outcome personnel, who are blinded to the treatment assignment, will be trained in the structured Glasgow Outcome Scale interview which will be conducted at 3 and 6 months.

The following data will be collected from human subjects: (1) clinical data regarding clinical history, clinical course, diagnostic tests, and clinical outcomes; (2) imaging of the brain for independent review at HCMC; and (3) GOS-E and DRS assessments at 3 and 6 months. Each subject for whom consent is obtained and who meets the study eligibility criteria will have a unique study identifier assigned to them by the WebDCU™ system upon enrollment into the study. The SDCC computers and servers will not house any personal health identifiers (*i.e.*, name, medical record number), rather the subject will be tracked during the study period through the assigned unique identifier. All collected information regarding a given subject will be stored using the unique identification code. Only authorized local site study personnel will have access to a subject's personal identifying information. Source documents and case report forms

(CRFs) will remain at the participating sites. All data will be stored in a manner that is Health Insurance Portability and Accountability Act of 1996 (HIPPA) compliant, without the ability to track the information back to a specific subject except through a password protected system. All study personnel will have Protection of Human Research Subjects certification.

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 favorable outcome if their 6 month Glasgow Outcome Scale-Extended (GOS-E) score is good recovery to severe disability; subjects with less severe injury and whose initial GCS scores are 6 to 8 are considered to have a favorable outcome if their 6 month GOS-E score is good recovery to moderate disability.

Secondary outcomes include 1) control and prevention of intracranial hypertension (> 20 mmHg) in HBO2 treated versus control patients, 2) prevention of brain tissue hypoxia (< 15 mmHg) in HBO2 treated versus control patients, 3) analysis of the therapeutic intensity level (TIL) scores to control intracranial pressure (ICP), and 4) incidence of SAEs in HBO2 compared to control treated patients.

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

Security, Privacy, and Confidentiality

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

The network and system security is ensured by implementing multiple layered firewalls and a network intrusion prevention system for identifying and blocking malicious network activity in real time. Vulnerability scans are also run daily to ensure server and network hardening

preventing known application and Operating Systems (OS) vulnerabilities. Antiviral, Trojan and worm protection is achieved by using Microsoft Forefront, updated on a daily basis. All communication with the web server and client is encrypted via Secure Socket Layer (SSL) to make certain network traffic 'sniffing' poses no threat.

Patient Confidentiality

Protection of patient confidentiality is essential in human clinical trials. A HIPAA compliant de-identification process will be utilized. HOBIT patient data maintained outside of the study site and within the WebDCU™ will be stored in a de-identified format with the key maintained with the NETT site PI. Furthermore, NETT databases, including electronic formats and study binders, will be maintained in locked physical facilities and all data will be password protected to ensure data integrity and to protect patient privacy.

Study Modifications/Discontinuation

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

The major risks to human subjects of this trial are: 1) Potential oxygen toxicity to the lungs. Specific criteria for withholding or terminating HBO_2 treatment will be adhered to strictly in order to avoid any permanent pulmonary complications related to the HBO_2 treatments. In two recently completed prospective trial (Rockswold 2010, Rockswold 2013), there was no increased incidence of pneumonia, increased FiO_2 requirements, or need for positive end expiration pressure (PEEP) requirements in the HBO_2 patients as compared to the control group. 2) Cerebral oxygen toxicity. This is most commonly manifested by seizures. There have been no occurrences of seizures related to HBO_2 treatment in our past three clinical trials. In fact, the results of the last three clinical studies utilizing HBO_2 in severe TBI documents significant improvement in cerebral oxidative metabolism (Rockswold 2001, Rockswold 2010, Rockswold 2013). 3) Transport of the severe TBI patients to and from the HBO_2 chamber could potentially be associated with adverse events. However, the protocol for the HBO_2 treatments indicates that no patient should be transported if hemodynamically unstable. It is essential that the same level of care provided in the ICU, including monitoring, be continued throughout the patient's transport and the HBO_2 treatment per our protocol (Weaver 1999, Gossett 2010). 4) Fire hazard is a potential risk in HBO_2 chambers. The National Fire Protection Association (NFPA) has produced a hyperbaric safety standard since 1967 (NFPA 1999, Healthcare Facilities). In facilities that carefully follow these standards, there have been no fatalities due to hyperbaric chamber fire in North America. None of the clinical centers expected to participate in the HOBIT Trial have experienced fires.

If any subject should develop study-related complications, appropriate medical care will be carried out at that participating clinical center, including immediate access to emergency care in the ICUs of all participating clinical centers.

No other substantial risk is anticipated in this trial. Women of childbearing potential will not be eligible to participate in this trial. A pregnancy test will be done to make sure that a female subject is not pregnant before starting the treatment. Children (under the age of 16) are not eligible to participate in the trial because there is no safety profile for HBO treatment for persons under the age of 16. In addition, children under 16 require an entirely different team of

providers and are in a different ICU than adults. Prisoners and wards of the state will not be eligible for this trial.

Currently there is no approved specific treatment for severe TBI patients. Participating in the HOBIT trial will not preclude the patient from getting the standard treatments.

Potential subjects for this trial will be recruited from all patients with a severe TBI presenting to the 15 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. Upon confirmation of a patient's eligibility for the trial, consent is obtained by either the clinical site PI or by individuals to whom the clinical site PI has delegated authority to obtain informed consent. The delegation of authority must be documented and a current copy of this document must be maintained at the clinical site. As with most clinical trial responsibilities delegated by the clinical site PI, it is his/her responsibility to ensure that the delegation is made only to those individuals who are qualified to undertake the delegated tasks, and that there is adherence to all federal regulatory requirements and Good Clinical Practice (GCP) Guidelines. Additionally, it is the investigator's responsibility to ensure that the patient's LAR has been given an adequate explanation of the purpose, methods, risks, potential benefits and patient responsibilities of the study. The consent form must be an up-to-date document that has been approved by the clinical site's IRB/Ethics Committee. A written signed and dated informed consent is required prior to randomization.

Prior to enrolling patients at any study sites, the site investigators will have obtained local IRB approval. In recognition of the potential for differences in practice due to geographical locale, clinical setting, and patient populations, sites will be required to submit applications and obtain approval from their respective IRB's. Sites will also be expected to comply with their local IRB practices to ensure adequate protection of patient/study subject rights. This will typically require annual reporting and reviews of study subject enrollment, outcomes, and adverse events. IRB and consent form templates will be provided for sites to aid in the submission process, and also to ensure greater consistency in the protocols between centers. The HOBIT PI (Dr. Rockswold), the University of Minnesota Trial Coordinator, and the NETT HSP coordinator will assist sites with IRB submissions and protocol revisions. Representatives of the University of Minnesota HOBIT team will travel to all study sites prior to patient enrollment to confirm site training completion and IRB approval.

The informed consent document will be submitted to each participating IRB/Ethics Committee (EC) for review and approval before the study is initiated. The final IRB/EC approved document from each clinical site will be provided to the CCC. In the HOBIT Trial, all subjects will be comatose, therefore, informed consent will be obtained from a LAR or person with power of attorney for the patient. Every attempt will be made to contact the patient's family as soon as possible after the patient's admission, and in accordance with the individual hospital's protocol. To the extent possible, these discussions should be carried out in a private setting without distraction. No coercion will be applied, and the LAR and other family members will be given an opportunity to read the informed consent document, ask and have answered any questions they may have about the study.

Note that the process for obtaining consent must be in compliance with the local institution's IRB/EC guidelines and policies for obtaining informed consent for research participation. A subject will not be enrolled if consent cannot be obtained. A copy of the informed consent document must be provided to the subject's LAR. Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time. There are no plans to seek waiver of consent for the HOBIT Trial.

Additionally, all research personnel, investigators, and staff involved with this clinical research will be mandated to complete, if they have not previously done so or do not have a current certificate, some type of human subject protection training. This training may be accomplished by taking prescribed modules via the Collaborative Institutional Training Initiative, academic courses in clinical research, or attendance at responsible conduct research seminars. Study team members at each U.S. participating clinical center will be expected to comply with their individual institution's requirements established for compliance with the HIPAA with regard to research processes and respect for subject personal health information (PHI). The CCC will be responsible for reviewing and verifying compliance with human subject protection training before a clinical site can begin enrollment of patients.

Due to the critical nature of communication during the consent process, alternative language consent forms will be provided as appropriate for each enrolling site. The use of fluent language translators will be utilized for patients who are unable to speak or understand English. Medical and technical language will be minimized and replaced with simple sentences written at about a sixth grade reading level. Suspects in police custody or prisoners will not be enrolled in the study, given their potential vulnerability in medical research. This study will include minors under the age of 21. Patients who have not reached their majority (ages 16-17) will be required to have a legal representative (parent, guardian, or custodian) give consent.

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We have had extensive experience with the use of HBO_2 in severely brain-injured patients (Rockswold 1985; Rockswold 1992; Rockswold 2001; Rockswold 2010; Rockswold 2013, Gossett 2010). Over the course of four clinical trials, we have delivered 1,984 HBO_2 treatments to 167 patients (Gossett 2010). There were no permanent complications related to the HBO_2 treatment with no patient emergently evacuated from the chamber. This exemplary safety record has been accomplished by strict adherence to the inclusion/exclusion criteria listed in this application as well as considering the HBO_2 treatment area an extension of the ICU. In our two recent prospective randomized trials, patients with decompressive craniectomies who underwent HBO_2 treatment had no difficulties or complications (Rockswold 2010, Rockswold 2013). A myringotomy will not be performed if there is blood in the external ear or otorrhea present. This is not a contraindication to HBO_2 treatment. Thirty-seven patients were treated in our phase II trial without a myringotomy (Rockswold 1992).

Although no seizures related to HBO_2 treatments have occurred in the past three trials, all patients were intravenously loaded with phenytoin for seizure prophylaxis. In our last two prospective trials, cerebral spinal fluid (CSF) F2-isoprostane, which is a marker of lipid peroxidation in the brain due to oxygen toxicity or ischemia, showed no evidence of increased levels following HBO_2 treatments (Rockswold 2010, Rockswold 2013). With regard to pulmonary toxicity, the unit pulmonary toxic dose (UPTD) is a theoretic method for calculating relative O2 doses (Bardin 1970, Wright 1972, Rockswold 2010). One UPTD is equal to 1

minute of 100% O2 at 1 ATA. Appropriate conversion factors, that is multipliers of 1 minute of 100% O2 at 1 ATA, allow one to quantitate the pressure of the O2 exposure. It is recommended that total O2 exposure in a single treatment be limited to $\leq$ 615 UPTD. Total O2 exposure of any of the single HBO2 treatments in this protocol are well within this limit. Maximum UPTD for a single treatment in this trial is 476 UPTD. It is important to note that interruptions to an O2 exposure between treatments are known to increase O2 tolerance and improve safety. For example, 600 UPTD per day in two treatment sessions have been administered for weeks with no evidence of accumulative pulmonary toxicity (Ref 43 Kindall 2004).

Hyperbaric facility safety depends on a number of interrelated issues: proper staffing, appropriate training, development of operational procedures, effective maintenance, and rigid adherence to the principles of oxygen safety. Specific criteria for withholding or terminating HBO_2 treatment will be adhered to strictly in order to continue to avoid any permanent complications related to the HBO_2 treatments. Enrolling centers involved in this trial have superb safety records. The HBO_2 personnel are certified by the Undersea Hyperbaric Medicine Society (UHMS).

If any patient should develop study-related complications, appropriate medical care will be carried out at that clinical center. All of the enrolled patients will be in the ICU at that particular enrolling site throughout the five days of this treatment protocol. Immediate access to emergency care will be available in the ICU at all of the enrolling sites.

Human subjects in the proposed trial may directly benefit from their participation by being randomized to whichever intervention arm(s) are most effective. The use of response adaptive randomization in the proposed trial increases the likelihood of allocation to the more favorable intervention. Subjects may also benefit from the increased vigilance associated with daily rounding by the study team and with visits from the local and central study monitors.

The Center for Disease Control estimates that there were 300,000 individuals hospitalized with a TBI in the USA in 2012. Approximately 10% of patients admitted to hospitals have sustained a severe TBI, as defined by the Glasgow Coma Scale (GCS) (Kraus 1993, Thurman 2001). Approximately 30% of these individuals die and 40% achieve a favorable outcome as defined by the dichotomized Glasgow Outcome Scale (GOS). Therefore, approximately 30% of severe TBI patients are permanently severely disabled or vegetative. The average age of an individual sustaining a TBI is about 40 years, and the average life expectancy after TBI is an additional 20 years. The annual average cost of a TBI victim requiring custodial care in the state of Minnesota is $80,000 ($1.6 million on average per disabled severe TBI patient over their lifetime). Using the above suppositions, we can therefore calculate that of the approximately 30,000 severe TBI patients there would be 9,000 left severely disabled or vegetative. Supposing there is a 10% improvement to favorable or functional abilities in 900 patients, this would translate into a savings of $1.44 billion over the lifetime of the increased number of functional survivors per year. 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 placing 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 which would be substantial.

The enormous negative social and economic impact of TBI throughout the world cannot be overemphasized. The major issue is premature death and disability both in civilians and military

populations. These sequelae of TBI have led to untold effort in carrying out many (approximately 30) unsuccessful clinical trials and the spending of millions of dollars seeking a treatment for severe TBI. Clinical outcome for severe TBI victims has not improved from 1990 to approximately the present. Mortality rates persist at approximately 35% with only 40% of severe TBI patients achieving a functional recovery. Our extensive preclinical and clinical preliminary data document that HBO2 is a positive physiologic effect on the severely traumatized brain. This adaptive phase II trial is an essential step toward the goal of a subsequent confirmatory phase III trial which could lead to the first definitive treatment for sevre TBI.

The NINDS will appoint an independent Data and Safety Monitoring Board (DSMB) who will be given the responsibility of assuring the safety of trial participants as well as the continued relevance of the research question, integrity of the data, and appropriateness of the treatment protocol. The DSMB will follow the guidelines as described in the NIH issued policy on data and safety monitoring. The DSMB will receive monthly safety reports from the SDMC and will meet twice yearly with at least one meeting being face to face. Bi-annual meetings will commence with the enrollment of patients and will end after last follow-up. Monthly safety reports provided by the NETT SDMC to the DSMB will include summary tables of all AEs (serious and non-serious) by treatment arm. Severity and relationship to study treatment will be included. In addition to the monthly safety reports, semi-annual reports will be generated by the SDCC. These reports will include details on patient enrollment, baseline characteristics of patients, adverse events, clinical outcomes, losses to follow up, and any other information requested related to data integrity, continued relevance of the research questions, or patient safety.

The results of all DSMB deliberations will be summarized to the study PI's via the meeting minutes that will be forwarded to the sites. The DSCB will also review safety data from all nine treatment arms at the end of the study to provide recommendations regarding safety to the NINDS in consideration of a go/no-go decision.

To facilitate rapid review of safety data, Claudia Robertson, MD will function as the independent medical safety monitor (MSM). Dr. Robertson is a neurointensivist and Professor of Neurological Surgery at the Baylor College of Medicine. She serves as the Medical Director at The Center for Neurosurgical Intensive Care at Ben Taub General Hospital. Dr. Robertson is an expert in neurocritical care with extensive experience in the investigation of Neuroprotection strategies and has served as a MSM for other NINDS sponsored clinical trials. The MSM will review complete tables of safety data regularly throughout the study (provided by SDCC) and will receive automatic e-mail notification of SAEs as they are reported into the study database. Dr. Robertson will not be blinded to the treatment allocation for SAE's. An alternate MSM will be appointed at the start of the trial given the potential need for timely SAE reviews in the event that Dr. Robertson is unavailable.

Adverse events (AE) will be defined as any undesirable sign, symptom or medical condition that occurs after initiation of study therapy or which worsens after initiation of study therapy through hospital discharge. Each adverse event will be captured by the treating team and the study team based upon history, physical exam, medical records, and laboratory findings. All AEs will be recorded and assessed for date of onset, duration, severity, seriousness, relationship to

study therapy, action or treatment required and resolution date. The MSM will receive a periodic summary of AEs (provided by SDCC). Participating sites will submit adverse event reports to their local IRB according to local IRB guidelines.

Serious adverse events (SAE) are undesirable signs, symptoms, or medical conditions that are fatal, life threatening, require or prolong hospitalization, result in persistent or significant disability/incapacity, require additional surgical intervention, or is determined to be serious and medically significant based on the investigator's judgment. All SAE's will be captured throughout the 6 month study period. Participating sites are required to data enter SAE information into the study database within 1 business day of discovery followed immediately with entry of pertinent patient information via the web based system. Upon data entry, the system will trigger an automatic e-mail notification to the MSM stating that an SAE has occurred. The MSM will access the information via the password protected web based system and will review the SAE data within 2 business days of being notified for completeness of reporting. The MSM will report safety concerns to the DSMB via the NINDS DSMB liaison.

Plans for stopping the trial for safety or futility are discussed in the SDCC application. The proposed stopping rules will be established with the DSMB prior to the onset of the trial. However, the trial can be stopped at any time for safety concerns, and there is a mechanism in place to keep the MSM and DSCB well-informed on safety events in a timely manner. Statistical guidelines for stopping the trial for futility are in place and detailed in the SDCC application. Futility monitoring will be conducted on a frequent basis in order to stop the trial if there is a low probability that any arm will be superior to the control. Prior to the initiation of the trial, the safety plan and stopping guidelines will be reviewed with the DSMB and modified if warranted. The explicit and robust stopping rules in this adaptive exploratory trial are designed to replace a single decision at a single milestone with an iterative process. By asking the stopping rule frequently, we can stop the trial as soon as the data indicate futility, or as soon as a clear winning arm is evident.

Study personnel may be at risk for exposure to blood or bodily fluids during examinations and neurological testing. Thus, HOBIT will require the research personnel to adhere to universal protection policies and local and federal guidelines for occupational safety and health. Medical personnel are not exposed to hyperbaric conditions when a monoplace chamber is utilized. In the case of the sites using multiplace chambers, all medical personnel who will attend to the patients in the multiplace chamber must undergo medical clearance according to the standards of the Undersea and Hyperbaric Medical Society. The various HBO2 treatment paradigms to be evaluated in the HOBIT trial are well within the normal limits of HBO2 treatments utilized for standard indications.

This trial has been registered on clinicaltrials.gov and updates will be maintained in a timely manner.

HOBIT will enroll consecutive eligible patients with traumatic brain injury in the racial, ethnic, and gender distributions in which they present to clinical centers. The clinical centers are geographically dispersed across the United States and serve racially and ethnically diverse communities. As such, enrollment of subjects is anticipated to reflect that diversity. The ethnic composition of the centers is reflected in the 'Planned Enrollment Report' table. Eligibility for entry into the trial will not be influenced by race, ethnicity, or gender. For communities with large minority populations that are non-English speaking, consent and enrollment will be achieved by utilizing the appropriate translators and language-specific informed consent documents, as determined by their local IRB's. Subjects will only be excluded from the trial on the basis of language if the consent process is precluded because appropriate medical translation for the particular language cannot be made available in the required time window. As with other NETT studies, race, ethnicity, and gender are tracked and monitored in the study database and in the study screening log, both of which are part of the online data and trial management system, to ensure that the distribution among enrolled subjects is not skewed from the distribution among eligible patients. This allows us to monitor for disparities which can then be investigated to determine if any intervention is necessary to prevent disproportionate enrollment. (See Planned Enrollment Report for Targeted/Planned Enrollment based on sex and gender/ethnicity). Pregnant woman are excluded from this protocol because of potential risk to the fetus.

OMB Number: 0925-0002

Planned Enrollment Report

Study Title: Hyberbaric Oxygen Brain Injury Treatment (HOBIT) Trial: A Multi-center, Randomized, Prospective Phase II Adaptive Clinical Trial Evaluating the Most Effective Hyberbaric Oxygen Treatment Paradigm for Severe Traumatic Brain Injury

Domestic/Foreign: Domestic

Comments: Expected enrollment by sex, ethnicity, and race has been projected based on demographics of the regions in which planned clinical sites are located, weighted by the proportion of patients expected from each site. Data for US sites is based on the 2010 US Census.

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	1	1	0	0	**2**
Asian	4	4	0	0	**8**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	10	12	0	0	**22**
White	74	82	2	4	**162**
More than One Race	0	0	2	4	**6**
Total	**89**	**99**	**4**	**8**	**200**

Study 1 of 1

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This study will include minors under the age of 21, but will not include minors younger than age 16. Patients aged 16 to 21 are included in the study because they have injury patterns and recovery responses that are more like those of adults than it is like those of younger children.

Children under the age of 16 are not included in this study because they have patterns of TBI and a natural history of recovery that are so qualitatively different from those of adults, that they prevent meaningful inclusion in the study sample. Furthermore children under the age of 16 require a different team of providers and ICU compared to adults. Therefore it would be inappropriate to include this age group.

Patients who have not reached their majority (ages 15-17) will be required to give informed assent or consent and also have a legal representative (parent or guardian) give consent to participate.

The submission of this proposal with Drs. Gaylan Rockswold, William Barsan, and Byron Gajewski as multiple principal investigators represents a unique collaboration of three scientists with a strong interest in the treatment of severe TBI but representing different key disciplines and experiences to work together to conduct an adaptive clinical trial to select the best combination of HBO2 treatment for the improvement of neurological outcome. We embrace the NIH Implemented Multiple Principal Investigator policy. The availability of the multiple PD/PI option encourages interdisciplinary and other team approaches to biomedical research.

Dr. Rockswold is a neurosurgeon and will serve as the contact PI. He will supervise the overall conduct of the study, experimental design, data analysis, and manuscript preparation. He has extensive experience in investigating the potential of hyperbaric oxygen (HBO2) in the treatment of severe traumatic brain injury (TBI) and has been Chief of Neurosurgery at the Hennepin County Medical Center for the past 30 years with a focus on neurotrauma, particularly TBI. He has held a professorship in neurosurgery at the University of Minnesota for the past 25 years. He will meet regularly with and assure communication among all key personnel on a daily or weekly basis. He will be available at all times to sites to answer questions regarding appropriate enrollment, inclusion/exclusion criteria, and management issues.

Dr. Barsan is an emergency medicine physician and the Principal Investigator for the NETT Clinical Coordinating Center. He will be principal investigator responsible for the clinical coordination of the trial at the NETT clinical coordinating center. Working with the other NETT coordinating center investigators and with the Hub investigators, he will oversee protocol implementation, regulatory management, human subjects' protection, and accrual and monitoring during the day-to-day operations of the trial. He will also be participating in data analysis and manuscript preparation. Dr. Barsan has focused on translational research in stroke and neurological emergencies for many years and has experience founding and directing the Hyperbaric Oxygen Center at the University of Cincinnati in the late 1980's. He was also co-PI on the Adaptive Designs Advancing Promising Treatments into Trials (ADAPT-IT) project funded by NIH and FDA and has extensive experience in adaptive clinical trial design. He has served as a professor of emergency medicine at the University of Michigan Medical School for over two decades.

Dr. Gajewski is a biostatistician. His role is to design and govern the Bayesian Adaptive Design. He has expertise in the design and implementation of Bayesian adaptive designs. He has published several new Bayesian clinical trials methodologies in top tier biostatistics journals (e.g. *Statistics in Medicine*), of which one was quoted in NHLBI's RFA-HL-08-013. He has also published two papers showcasing novel Bayesian predictors of clinical trials accrual. He was also successful in gaining PCORI (CER-1306-02496) funding using a novel Bayesian adaptive design.

We will set up a teleconference at least once per month (more frequently initially and as needed) to discuss any study issues (e.g. recruitment and retention at any site). The teleconference will include the PIs (Rockswold, Barsan, Gajewski) and the key personnel at the CCC and the Statistical and Data Monitoring Center (SDMC) at the Medical University of South Carolina (PI, Dr. Renee Martin). The teleconferences will be used to review and provide updates on enrollment, testing, and data collection over the previous month provided by the leaders of each of the teams. Rockswold, Barsan, Gajewski will communicate on a regular basis through email or telephone conversation. The PIs have already developed open channels of dialogue that were exercised frequently in the writing of this proposal (e.g., biweekly phone conference).

Given that Rockswold, Barsan, and Gajewski spheres of expertise are disparate (i.e., they have unique roles and knowledge they bring to this proposal and team), intellectual disagreements are unlikely to arise. Drs. Rockswold, Barsan, and Gajewski have worked closely and effectively for the last six months in designing HOBIT. If there is uncertainty with respect to scientific issues, however, the PIs have enough common experience that they should be able to explain the matters at hand to one another.

Actual conflict is not anticipated. However, should they occur, we expect that it will be resolved through a significant effort on the part of all three PIs with the conduct of the project's science maintained as the highest priority. If a dispute arises with no apparent resolution, an online or in person meeting of the entire executive research team for this project will be called, issues will be described, and the committee will make a majority decision that will be fully binding.

The data generated by this project will be entered at the individual site into a system developed and managed by the SDMC. The de-identified data will be fully accessible to the PIs at all times. Typically, with longitudinal projects like this one, decisions as to how and when to publish empirical reports is a difficult one. To resolve this issue, the PIs will map out a preliminary dissemination plan that is principled yet flexible enough to allow for the clearest manner of presenting the results and to determine the extent of authorship.

Dr. Rockswold will be the contact PI and provide 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 the HBO2 administration. He will coordinate communication between the multiple PIs, as well as the PI for the SDMC and other key personnel. He or a qualified surrogate will be available at all times to enrolling sites to answer questions regarding appropriate enrollment, inclusion/exclusion criteria, and management issues. Dr. Barsan will be responsible for leading and supervising the CCC and its responsibilities to the trial. These responsibilities include site management, trial management, and management of study operations. The CCC personnel include administrative leadership, project managers, site monitors, educators and coordinators for human subjects' protection and for education. Dr. Gajewski will be responsible for the Bayesian adaptive portion of the project. With de-identified data provided by the SDMC, he will write and conduct the computer code for the adaptive design procedure and perform final statistical analyses for the first two aims of the protocol. Dr. Gajewski will conduct the Bayesian adaptive design modeling and the creation of the randomization probabilities that will be provided to the SDMC. Dr. Gajewski will also be responsible for providing initial adaptive design study interpretations and reviewing and verifying all conclusions drawn from these analyses for abstracts and manuscripts resulting from this study. This arrangement allows for a balanced split of the overall research project management, the site management, and the statistical analysis.

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The HOBIT trial will be conducted in the Neurological Emergency Treatment Trial (NETT) network funded by the NINDS. The CCC for the HOBIT trial will be the NETT CCC at the University of Michigan and SDMC will be the NETT SDMC at the Medical University of South Carolina working with the Analytical Center at the University of Kansas for adaptive design component. The Scientific Coordinating Center will be the University of Minnesota/Hennepin County Medical Center. The CCC is responsible for coordinating the network and HOBIT enrolling site leadership and for overall organization, administration and communication. These responsibilities include site management, trial management and management of study operations. The main responsibilities of the SDCC will be data management, statistical analysis, and project management, including maintaining regulatory documentation, site monitoring and safety monitoring.

This proposal will involve 15 clinical centers. These sites will receive a small amount of infrastructural support to maintain regulatory documentation and education regarding the trial, as well as “per patient” payments to cover study-related patient care costs, data collection, and account for screen failures that lead to each enrollment. If this application is awarded, budgets will be agreed to, subaward agreements drafted and executed, adherence to compliance issues addressed, scope of work documented, study conduct initiation arrangements made, work conducted by the subawardees will be regularly reviewed and invoices reviewed and approved, and every effort will be made to ensure that finances and reporting will be done in a timely manner as put forth in the subaward agreement.

KU MEDICAL CENTER RESEARCH INSTITUTE
The University of Kansas

May 13, 2015

Dr. Gaylan Rockswold, M.D., Ph.D.
Minneapolis Medical Research Foundation
701 Park Ave, Suite PP7.701
Minneapolis, MN 55415

Dear Dr. Gaylan Rockswold, M.D., Ph.D

The University of Kansas Medical Center Research Institute, Inc. (KUMCRI) agrees to participate as a subcontractor in Minneapolis Medical Research Foundation proposed research project entitled "Hyperbaric Oxygen Treatment Trial." The KUMCRI portion of the work will be under the primary direction of Dr. Byron Gajewski.

The amount requested for KUMCRI's participation in this research project is $569,812 for anticipated project period 04/01/2016-03/31/2021. Please see the attached budget and budget justification for a detailed explanation of costs.

The appropriate programmatic and administrative personnel of each organization involved in this grant application are aware of the NIH consortium agreement policy and are prepared to establish the necessary inter-organizational agreement(s) consistent with the policy. We understand that a subcontract agreement will be negotiated between the University of Kansas Medical Center Research Institute, Inc. and Minneapolis Medical Research Foundation should an award result from the proposal being submitted.

KUMCRI certifies that it has implemented and is enforcing the new PHS regulations on Conflict of Interest as of August 24, 2012 and is in compliance with the updated provisions of 42 CFR Part 50, Subpart F & 45 CFR Subtitle A, Part 94.

We appreciate your consideration of this request and look forward to a rewarding and productive research effort.

Sincerely,

Deborah Maloney
Assistant Director, Sponsored Programs Administration

Mailing Address
Mail Stop 1039 | 3901 Rainbow Boulevard | Kansas City, KS 66160 | (913) 588-1261 | FAX (913) 588-3225 | www.kumc.edu/kumcri.html
Physical Address
4330 Shawnee Mission Parkway | Fairway, KS 66205

OMB Number: 4040-0001
Expiration Date: 6/30/2016

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION

☐ Pre-application ☒ Application ☐ Changed/Corrected Application

2. DATE SUBMITTED | **Applicant Identifier**

4. a. Federal Identifier

b. Agency Routing Identifier

c. Previous Grants.gov Tracking ID

5. APPLICANT INFORMATION

Organizational DUNS: 073133571

Legal Name: Regents of the University of Michigan

Department: | Division:

Street1: 3003 South State Street

Street2:

City: Ann Arbor | County / Parish: Washtenaw

State: MI: Michigan | Province:

Country: USA: UNITED STATES | ZIP / Postal Code: 48109-1274

Person to be contacted on matters involving this application

Prefix: | First Name: Tracey | Middle Name:

Last Name: Larkin | Suffix:

Position/Title: Administrative Specialist-OSRP

Street1: 3003 S. State Street

Street2: 1061 Wolverine Tower

City: Ann Arbor | County / Parish:

State: MI: Michigan | Province:

Country: USA: UNITED STATES | ZIP / Postal Code: 48109-1274

Phone Number: 734-764-7237 | Fax Number:

Email: larkint@umich.edu

6. EMPLOYER IDENTIFICATION *(EIN) or (TIN)*: 38-6006309

7. TYPE OF APPLICANT: H: Public/State Controlled Institution of Higher Education

Other (Specify):

Small Business Organization Type ☐ Women Owned ☐ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION:

☐ New ☒ Resubmission

☐ Renewal ☐ Continuation ☐ Revision

If Revision, mark appropriate box(es).

☐ A. Increase Award ☐ B. Decrease Award ☐ C. Increase Duration ☐ D. Decrease Duration

☐ E. Other (specify):

Is this application being submitted to other agencies? Yes ☐ No ☒ What other Agencies?

9. NAME OF FEDERAL AGENCY: National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER: 93.853

TITLE: Extramural Research Programs in the Neurosciences and Neurological Disorders

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT:

Hyperbaric Oxygen Brain Injury Treatment (HOBIT) Trial

12. PROPOSED PROJECT:

Start Date: 04/01/2016 | Ending Date: 03/31/2021

13. CONGRESSIONAL DISTRICT OF APPLICANT

MI-012

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: | First Name: William | Middle Name:
Last Name: Barsan | Suffix: M.D.
Position/Title:
Organization Name: Regents of the University of Michigan
Department: | Division:
Street1: 3003 South State Street
Street2:
City: Ann Arbor | County / Parish: Washtenaw
State: MI: Michigan | Province:
Country: USA: UNITED STATES | ZIP / Postal Code: 48109-1274
Phone Number: 734-232-2142 | Fax Number: 734-232-2122
Email: wbarsan@umich.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested	4,858,662.00
b. Total Non-Federal Funds	0.00
c. Total Federal & Non-Federal Funds	4,858,662.00
d. Estimated Program Income	0.00

16. IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?

a. YES ☐ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
DATE:

b. NO ☐ PROGRAM IS NOT COVERED BY E.O. 12372; OR
☒ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious. or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

☒ I agree

**The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL (Disclosure of Lobbying Activities) or other Explanatory Documentation

Add Attachment | Delete Attachment | View Attachment

19. Authorized Representative

Prefix: | First Name: Daryl | Middle Name:
Last Name: Weinert | Suffix:
Position/Title: Associate Vice President for Research
Organization: Regents of the University of Michigan
Department: | Division:
Street1: 3003 South State Street
Street2:
City: Ann Arbor | County / Parish: Washtenaw
State: MI: Michigan | Province:
Country: USA: UNITED STATES | ZIP / Postal Code: 48109-1274
Phone Number: 734-936-1361 | Fax Number:
Email: larkint@umich.edu

Signature of Authorized Representative: Kathryn A. DeWitt for Completed on submission to Grants.gov

Date Signed: 3 June 2015 Completed on submission to Grants.gov

20. Pre-application | Add Attachment | Delete Attachment | View Attachment

21. Cover Letter Attachment | Add Attachment | Delete Attachment | View Attachment

Kathryn A. DeWitt
Managing Project Rep.
Office of Res. & Spon. Proj.

Medical Director, NICU
1504 Taub Loop
Room 4IN 51 019D
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Department of Neurosurgery

Claudia S. Robertson, M.D.
Professor

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May 15, 2015

Dr. Gaylan Rockswold, M.D., Ph.D
Minneapolis Medical Research Foundation
701 Park Ave, Suite PP7.700
Minneapolis, MN 55415

Dear Dr. Rockswold,

I am writing to enthusiastically support your NIH R01 application entitled trial. Participation in a trial to find a more effective way to treat TBI patients is compelling. I very excited about the possibilities of this project and am looking forward to being a part of this research.

I am happy to serve as medical monitor for the trial.

I am delighted to serve as a consultant for your proposed research project. I am committed to providing the resources outlined in this proposal as well as committed to the time adequate to accomplish all the proposed activities of the project. I look forward to working together on this important research.

Sincerely,

Claudia Robertson, MD

UPMC | University of Pittsburgh Medical Center
Department of Critical Care Medicine

613 Scaife Hall
3550 Terrace Street
Pittsburgh, PA 15261
412 647-3136
412 647-8060
www.ccm.upmc.edu

May 29, 2015

Dr. Gaylan Rockswold, MD, PhD
Minneapolis Medical Research Foundation
701 Park Ave, Suite PP7.700
Minneapolis, MN 55415

Dear Dr. ~~Rockswold~~, *Gaylan*

This letter is to express my enthusiastic support and confirm my willingness to serve as a consultant for your NIH R01 application entitled ***Hyperbaric Oxygen Brain Injury Treatment (HOBIT)*** trial. It is critical that we continue to seek more effective ways to treat patients with traumatic brain injury (TBI). The possibilities of this treatment are extremely exciting.

I am an academic neurocritical care physician, Professor of Critical Care Medicine, Neurology and Neurosurgery at the University of Pittsburgh School of Medicine, and Medical Director of the Neurovascular Intensive Care Unit. My research has focused on the study of traumatic brain injury (TBI) with the help of advanced neuro-imaging, neuro-monitoring, and on development of interventions to improve clinical outcomes. These experiences support my qualifications to serve as the neurocritical care (NCC) consultant for the planned study. My role as the NCC consultant will be to provide advice to the trial Principal Investigators (PIs) and participating centers regarding critical care management issues for patients enrolled in this study. In addition, I will serve as a backup to review SAEs as necessary during the trial. My extensive experience in neurocritical care and managing patients with TBI provides me with the knowledge and skills necessary to successfully fulfill these roles.

Thank you for asking me to participate in this project. I am delighted to assist, and am committed to providing the services outlined in this proposal as well as the time necessary to accomplish all proposed activities. I look forward to working together on this important research.

Sincerely,

Lori Shutter, MD
Professor, Critical Care Medicine, Neurology & Neurosurgery
Director, Neurocritical Care Program
Medical Director, Neurotrauma & Neurovascular Intensive Care Units
University of Pittsburgh School of Medicine/UPMC

EMORY UNIVERSITY SCHOOL OF MEDICINE
DEPARTMENT OF EMERGENCY MEDICINE
49 Jesse Hill Jr. Dr. FOB Suite 126 Atlanta, GA 30303

EMERGENCY NEUROSCIENCES
DEPARTMENT OF EMERGENCY MEDICINE

Phone: (404) 778-1709
FAX: (404) 778-1604

June 1st, 2015

Dr. Gaylan Rockswold, M.D., Ph.D
Minneapolis Medical Research Foundation
701 Park Ave, Suite PP7.700
Minneapolis, MN 55415

Dear Dr. Rockswold,

I am delighted to support and serve as a consultant on your NIH R01 application entitled **Hyperbaric Oxygen Brain Injury Treatment (HOBIT)** trial. As you know, I have devoted my career to finding effective treatments for the treatment of acute traumatic brain injury. Your data are compelling and I am excited to be a part of your team.

As you know, traumatic brain injury (TBI) is a devastating condition that afflicts over 1.7 million persons in the US annually. Over 50,000 deaths and 235,000 hospitalizations are caused by TBI each year, with another 80,000 Americans disabled. The CDC estimates that 5.3 million civilian Americans are living with some degree of disability from a traumatic brain injury. Yet we have still not identified a treatment that can reduce the morbidity of TBI.

With strong preclinical and pilot data, it is appropriate to begin the process of translating this potential treatment to human study. The HOBIT study will provide critical information needed to proceed to an efficacy trial, such as the most optimal HBO2 treatment protocol (e.g. pressure, duration, and frequency of the HBO2 treatments). The adaptive design lends itself to this type of study. Armed with the results from this trial, a Phase III efficacy trial can be designed with the maximum probability for success.

Over my past 18 years of TBI research, in both the basic sciences and clinical trials, I have gained significant insight into the challenges of translating preclinical findings into effective clinical treatments. Indeed, my experience as the PI of the NINDS funded multicenter clinical trial, ProTECT III, provides me with the intimate knowledge of how to successfully conduct these large scale trials. ProTECT III was a major undertaking and despite the negative results, was a very successful clinical trial. In addition, I am very familiar with many of the stakeholders and investigators that you will eventually need to conduct your efficacy trial. I believe that my experience in operationalizing such a large and complex trial will be of benefit to your project.

I am committed to supporting the HBO approach and believe it to be meritorious for further study. I am honored to serve as a consultant and committed to providing the time and resources required to make this trial a success. I look forward to working together on this important research.

Sincerely,

David W. Wright, MD, FACEP
Vice Chair for Research, Associate Professor,
Department of Emergency Medicine
Emory University School of Medicine
Director, Emergency Neurosciences
PI, ProTECT III Clinical Trial

Scott M. Berry, PhD
President
4301 Westbank Drive, Bldg B, Suite 140
Austin, TX 78746
979-690-1242
scott@berryconsultants.com

May 27, 2015

Dr. Gaylan Rockswold, M.D., Ph.D
Minneapolis Medical Research Foundation
701 Park Ave, Suite PP7.700
Minneapolis, MN 55415

Dear Dr. Rockswold,

I am pleased to propose support as a consultant for your NIH R01 application entitled **Hyperbaric Oxygen Brain Injury Treatment (HOBIT)** trial. Participation in finding an effective way to treat TBI patients is very compelling. I am a co-founder, President, and Senior Statistical Scientist at Berry Consultants, and have been involved in hundreds of Bayesian adaptive clinical trials for pharmaceuticals and medical devices.

Our team at Berry Consultants includes senior biostatisticians, computer programmers, and analysts who have been directly involved in advising on the design of HOBIT and helped provide resources for the initial simulation. We are excited to continue our collaboration, and assist with the more any additional computation, algorithmic, and logistical aspects of running a sophisticated adaptive trial.

Berry Consultants has done extensive work in adaptive clinical trials. We have experience working in TBI and with conducting federally funded trials in the emergency room setting. We have experience working on the ADAPT-IT grant (with NETT) for trials in the intensive care and emergency room space. The adaptive aspects of this trial, including response adaptive randomization, arm-dropping, and early stopping have the potential to create a very efficient design, helping to answer some critical questions for the treatment of TBI. We are committed to providing the resources needed to help make this trial a success.

I enthusiastically support this work and commit to contributing the resources of Berry Consultants necessary to make this the transformative work it can be.

Sincerely,

Scott M. Berry, PhD
President

Intermountain Healthcare

Division of Hyperbaric Medicine
Intermountain Hyperbaric Medicine Department

Intermountain Medical Center
PO Box 577000
5121 S. Cottonwood Street
Murray, Utah 84157-7000
Office: 801.507.5370
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LDS Hospital
8th Avenue & C Street
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Fax: 801.408.8578

Division Chief & Medical Director
Lindell K. Weaver, MD

William Tettelbach, MD
Susan Churchill, NP
Gail Wilson, NP
Rebecca Cable, NP

May 28, 2015

Gaylan L. Rockswold, MD, PhD
Medical Director, Traumatic Brain Injury Program
Hennepin County Medical Center
701 Park Avenue
Minneapolis, MN 55415
(Tel) 612-873-2810
(Fax) 612-904-4297
gaylan.rockswold@hcmed.org

RE: Consultant for Critical Care and Hyperbaric Oxygen

Dear Dr. Rockswold;

I am willing to serve as a critical care and hyperbaric oxygen consultant for your planned future multi-center trial of hyperbaric oxygen for severe acute traumatic brain injury. As you know, I am a recognized expert in this regard, having treated intubated patients, often requiring pressors and even blood gas and Swan-Ganz catheter measures during hyperbaric oxygen. I anticipate some of the centers in this planned hyperbaric oxygen and traumatic brain injury trial may need consultation and guidance regarding treating critically ill brain injured patients inside hyperbaric chambers. I offer to help provide this consultation and guidance.

Sincerely,

Lindell Weaver

Lindell K. Weaver, MD, FACP, FCCP, FCCM, FUHM
Study Director (Lead Principal Investigator):
Department of Defense Brain injury and mechanisms of action randomized trial of HBO2 and mild TBI
Medical Director and Division Chief, Hyperbaric Medicine
LDS Hospital, Salt Lake City, UT and
Intermountain Medical Center, Murray, UT
Professor of Medicine, Univ. of Utah School of Medicine
Adjunct Professor, Depart. of Anesthesiology, Duke Univ. School of Medicine
Office (LDS Hospital): 801-408-3623
Office (IMC): 801-507-5370
Cell: 801-718-2835
Email: lindell.weaver@imail.org

DukeMedicine

Department of Anesthesiology

May 28th, 2015

Dr. Gaylan Rockswold, M.D., Ph.D
Minneapolis Medical Research Foundation
701 Park Ave, Suite PP7.700
Minneapolis, MN 55415

Dear Dr. Rockswold,

We are writing on behalf of our site to enthusiastically support your NIH R01 application entitled Hyperbaric Oxygen Brain Injury Treatment (HOBIT) trial. Participation in finding a more effective way to treat TBI patients is compelling. We are very excited about the possibilities of this project and are looking forward to being a part of this research.

We believe this trial can fully leverage the abilities of our research organization to enroll subjects, provide the highest standards of care throughout the trial, and collect the necessary data for analysis.

The clinicians, investigators and facilities Duke University Medical Center would be delighted to serve as a site for your proposed research project. We are committed to providing the resources outlined in this proposal as well as committed to the staff time adequate to accomplish all the proposed activities of the project. We look forward to working together on this important research and we are eager to test this promising treatment for TBI patients.

Sincerely,

Michael L. "Luke" James, MD FAHA
Associate Professor of Anesthesiology
Program Director, Neuroanesthesia Fellowship
Associate Director, Multidisciplinary Neuroprotection Laboratories
Associate Director, Brain Injury Translational Research Center
Departments of Anesthesiology & Neurology

Richard E. Moon, MD, FACP, FCCP
Professor of Anesthesiology
Professor of Medicine
Medical Director, Center for Hyperbaric Medicine & Environmental Physiology

BOX DUMC 3094, Durham, NC 27710 URL anesthesia.duhs.duke.edu dukemedicine.org

UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

Barney J. Stern, MD
Professor and Interim Chairman
Stewart J. Greenebaum Endowed Professor in Stroke Neurology

Department of Neurology
110 S. Paca Street
Baltimore, MD 21201
410 328-6483/6485 PHONE/410 328 5999 FAX/410 328 9600 TDD

bstern@som.umaryland.edu
www.umm.edu

May 21, 2015

Dr. Gaylan Rockswold, MD, PhD
Minneapolis Medical Research Foundation
701 Park Ave, Suite PP7.700
Minneapolis, MN 55415

Dear Dr. Rockswold:

We are writing on behalf of the University of Maryland School of Medicine to enthusiastically support your NIH R01 application entitled **Hyperbaric Oxygen Brain Injury Treatment (HOBIT)** trial. Participation in finding a more effective way to treat TBI patients is compelling. We are very excited about the possibilities of this project and are looking forward to being a part of this research.

We believe this trial can fully leverage the abilities of our research organization to enroll subjects, provide the highest standards of care throughout the trial, and collect the necessary data for analysis.

The University of Maryland Medical Center houses a large hyperbaric oxygen chamber under the direction of Dr. Robert Rosenthal, an emergency medicine physician. The chamber is located very near the Shock Trauma Center which is the largest facility caring for head injured patients in the region and which has a worldwide reputation for excellence in trauma care and research. The Center contains a dedicated neurotrauma ICU staffed by a multidisciplinary team. Dr. Howard Eisenberg, Chair of the Department of Neurosurgery is a recognized expert in TBI.

The University of Maryland Medical Center would be delighted to serve as a site for your proposed research project. We are committed to providing the resources outlined in this proposal as well as committed to the staff time adequate to accomplish all the proposed activities of the project. We look forward to working together on this important research and we are eager to test this promising treatment for TBI patients.

Sincerely,

Barney J. Stern, MD
Hub PI, the Maryland/DC Consortium of the NETT Network
Interim Chair, Department of Neurology
The Stewart J. Greenebaum Endowed Professor in Stroke Neurology

UNIVERSITY of IOWA
CARVER COLLEGE
OF MEDICINE

University of Iowa Health Care

Merete Ibsen, M.D.

Assistant Professor
Department of Anesthesia
Roy J. and Lucille A.
Carver College of Medicine
200 Hawkins Drive, 6 JCP
Iowa City, IA 52242-1079
319-384-5423 Tel
319-356-2940 Fax
www.uihealthcare.com

Dr. Gaylan Rockswold, MD, PhD
Minneapolis Medical Research Foundation
701 Park Ave, Suite PP7.700
Minneapolis, MN 55415

Dear Dr. Rockswold,

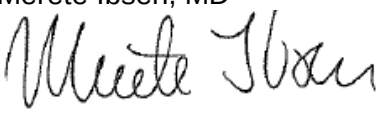
We are writing on behalf of The University of Iowa to enthusiastically support your NIH R01 application entitled Hyperbaric Oxygen Brain Injury Treatment (HOBIT) trial. Participation in finding a more effective way to treat TBI patients is compelling. We are very excited about the possibilities of this project and are looking forward to this collaborative effort.

We believe this trial can fully leverage the abilities of our research organization to enroll subjects, provide the highest standards of care throughout the trial, and collect the necessary data for analysis.

The University of Iowa Department of Neurosurgery and Department of Anesthesia would be delighted to serve as a site for your proposed research project. We are committed to providing the resources outlined in this proposal as well as committed to the staff time adequate to accomplish all the proposed activities of the project. We look forward to working together on this important research and we are eager to test this promising treatment for TBI patients.

Sincerely,

Merete Ibsen, MD



Clinical Assistant Professor
Medical Director
Hyberbaric Medicine Service

MEDICAL COLLEGE OF WISCONSIN
EMERGENCY MEDICINE

June 3, 2015

Dr. Gaylan Rockswold, M.D., Ph.D
Minneapolis Medical Research Foundation
701 Park Ave, Suite PP7.700
Minneapolis, MN 55415

Dear Dr. Rockswold,

On behalf of the Milwaukee Clinical Site Hub (MCSH), it is an absolute pleasure to enthusiastically support your NIH R01 application entitled Hyperbaric Oxygen Brain Injury Treatment (HOBIT) trial.

Participation in finding a more effective way to treat TBI patients is compelling. We are very excited about the possibilities of this project and are looking forward to contributing to this research. We believe this trial can fully leverage the abilities of our research organization to enroll subjects (as we have 24/7 coordinator coverage), provide the highest standards of care throughout the trial, and collect the necessary data for analysis.

The MCSH would be delighted to serve as a site for your proposed research project. We are committed to providing the resources outlined in this proposal as well as committed to the staff time required to accomplish all the proposed activities of this project. We look forward to working together on this important research and having the opportunity to test this promising treatment and ultimately further improving outcomes for TBI patients.

Sincerely-

Tom P. Aufderheide, M.D., M.S., FACEP, FACC, FAHA
Professor of Emergency Medicine
Associate Chair of Research Affairs
PCIR Director, CTSI of Southeastern Wisconsin
Director, Resuscitation Research Center
Medical College of Wisconsin
Department of Emergency Medicine
9200 West Wisconsin Avenue, Pavilion 1P
Milwaukee, Wisconsin 53226
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Email: taufderh@mcw.edu

DEPARTMENT OF NEUROLOGY

9200 W. Wisconsin Avenue
Milwaukee, WI 53226-3596

Froedtert & Medical College of Wisconsin

414-805-3666 Patient Access
800-272-3666

414-805-4700 Physician Access
877-804-4700

June 3, 2015

Dr. Gaylan Rockswold, M.D., Ph.D
Minneapolis Medical Research Foundation
701 Park Ave, Suite PP7.700
Minneapolis, MN 55415

Dear Dr. Rockswold,

We are writing on behalf of the Milwaukee Clinical Site Hub(MCSH), for the Neurological Emergency Treatment Trials network, to enthusiastically support your NIH R01 application entitled Hyperbaric Oxygen Brain Injury Treatment (HOBIT) trial. Participation in finding a more effective way to treat TBI patients is compelling. We are very excited about the possibilities of this project and are looking forward to being a part of this research.

We believe this trial can fully leverage the abilities of our research organization to enroll subjects, provide the highest standards of care throughout the trial, and collect the necessary data for analysis.

The MCSH would be delighted to serve as a site for your proposed research project. We are committed to providing the resources outlined in this proposal as well as committed to the staff time required to accomplish all the proposed activities of this project. We look forward to working together on this important research and having the opportunity to test this promising treatment and ultimately further improving outcomes for TBI patients.

Sincerely,

Ann K. Helms, MD
Associate Professor of Neurology
Medical College of Wisconsin
Department of Neurology
9200 W Wisconsin Ave
Milwaukee, Wisconsin 53226
Office: 414-805-5204
Email: ahelms@mcw.edu

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

The Ohio State University
Wexner Medical Center
Department of Neurology

333 W. 10th Ave, 3rd Floor
Columbus OH, 43210-1228

May 27, 2015

Dr. Gaylan Rockswold, M.D., Ph.D
Minneapolis Medical Research Foundation
701 Park Ave, Suite PP7.700
Minneapolis, MN 55415

Dear Dr. Rockswold,

We are writing on behalf of The Ohio State University – Wexner Medical Center to enthusiastically support your NIH R01 application entitled **Hyperbaric Oxygen Brain Injury Treatment (HOBIT)** trial. Participation in finding a more effective way to treat TBI patients is compelling. We are very excited about the possibilities of this project and are looking forward to being a part of this research.

We believe this trial can fully leverage the abilities of our research organization to enroll subjects, provide the highest standards of care throughout the trial, and collect the necessary data for analysis.

Wexner Medical Center would be delighted to serve as a site for your proposed research project. We are committed to providing the resources outlined in this proposal as well as committed to the staff time adequate to accomplish all the proposed activities of the project. We look forward to working together on this important research and we are eager to test this promising treatment for TBI patients.

Sincerely,

Michel T. Torbey, MD, MPH
Professor, Department of Neurology

Jeffrey Caterino, MD
Associate Professor, Department of Emergency Medicine

H. Francis Farhadi, MD, PhD
Assistant Professor, Department of Neurological Surgery

UKHealthCare

May 20, 2015

Dr. Gaylan Rockswold, M.D., Ph.D
Minneapolis Medical Research Foundation
701 Park Ave, Suite PP7.700
Minneapolis, MN 55415

Dear Dr. Rockswold,

We are writing on behalf of the University of Kentucky Neurological Emergencies Treatment Trial Network (NETT) Hub to enthusiastically support your NIH R01 application entitled, **Hyperbaric Oxygen Brain Injury Treatment (HOBIT)** trial. Participation in finding a more effective way to treat TBI patients is compelling. We are very excited about the possibilities of this project and are looking forward to being a part of this research.

We have an active Hyperbaric Oxygen program here at UK and the Department of Emergency Medicine has operated our chamber for the last 20 years. Through the NETT, we have established a 24/7/365 research infrastructure. UK HealthCare has the capability to conduct emergency HBO treatments with in 2 hours of notification of an emergent treatment. We are fortunate to have an outstanding NETT research team including three full-time research nurses and we recently conducted the ProTECT III trial here at UK, enrolling about 30 subjects during the trial.

Our team is multi-disciplinary and experienced. Dr. Humphries, Chair of the Department of Emergency Medicine is trained in the administration of HBO treatments and will serve as the PI for this trial. Dr. Justin Fraser, Director of Neurovascular Surgery, Department of Neurosurgery will be will be the key point person for coordinating the efforts of Neurosurgical faculty and residents to support the identification, enrollment and protocol adherence of study subjects in the trial. Dr. Kevin Hatton, Chief of Neurointensiviist Division in the Department of Anesthesia will coordinate the day-to-day neurocritical care of HOBIT study subjects and will work with the Neurocritical Care faculty, residents and advanced practice providers to ensure that we adhere closely to the study protocol.

In summary, our site has significant experience conducting complicated, high impact, multicenter phase III trials, especially in the area of neurotrauma. We are very excited to be included in this important trial proposal so we can advance the field of neurotrauama treatment.

Sincerely,

Roger L Humphries MD

Roger L. Humphries, MD
Professor and Chair
Department of Emergency Medicine
Principal Investigator UK NETT Hub

Department of Emergency Medicine

University of Kentucky • Room M53 • Lexington, Kentucky 40536-0298
Phone: (859) 323-5908 • Fax: (859) 323-8056 • www.mc.ukhealthcare.uky.edu/emergencymedicine

UKHealthCare

Justin F. Fraser, MD
Assistant Professor of Cerebrovascular, Endovascular, and Skull Base Surgery
Director, Cerebrovascular Surgery
Department of Neurological Surgery

Kevin W. Hatton, MD, FCCM
Director, Neurocritical Care Service
Chief, Division of Anesthesiology Critical Care Medicine
Associate Professor of Anesthesiology and Surgery

Department of Emergency Medicine

University of Kentucky • Room M53 • Lexington, Kentucky 40536-0298
Phone: (859) 323-5908 • Fax: (859) 323-8056 • www.mc.ukhealthcare.uky.edu/emergencymedicine

UTHealth
The University of Texas
Health Science Center at Houston

Medical School
Department of Emergency Medicine

June 1, 2015

Dr. Gaylan Rockswold, M.D., Ph.D
Minneapolis Medical Research Foundation
701 Park Ave, Suite PP7.700
Minneapolis, MN 55415

Dear Dr. Rockswold,

We are writing on behalf of University of Texas Health Science Center at Houston(UT Houston) to enthusiastically support your NIH R01 application entitled **Hyperbaric Oxygen Brain Injury Treatment (HOBIT)** trial. Participation in finding a more effective way to treat TBI patients is compelling. We are very excited about the possibilities of this project and are looking forward to being a part of this research.

We believe this trial can fully leverage the abilities of our research organization to enroll subjects, provide the highest standards of care throughout the trial, and collect the necessary data for analysis.

Our main teaching hospital Memorial Hermann Hospital has a multiplace hyperbaric chamber with a critical care lock. Our trauma service admits more than 400 patients each year with severe TBI. Our site at Memorial Hermann enrolled 64 patients in the ProTECT trial. The study would be done through our Department of Emergency Medicine as the HBO facility will be moving from the Department of Internal Medicine to the Department of Emergency Medicine. We coordinate research studies with our neurosurgical colleagues through a TBI Research committee.

UT Houston would be delighted to serve as a site for your proposed research project. We are committed to providing the resources outlined in this proposal as well as committed to the staff time adequate to accomplish all the proposed activities of the project. We look forward to working together on this important research and we are eager to test this promising treatment for TBI patients.

Sincerely,

Elizabeth B. Jones, MD
Associate Professor of Emergency Medicine

Renie Guilliod

Renie Guilliod, MD
Assistant Professor of Internal Medicine,

713.500.7878 phone 713.500.0758 fax
6431 Fannin Street, JJL 433
Houston, Texas 77030

LOMA LINDA UNIVERSITY
Research Affairs

May 29, 2015

Dr. Gaylan Rockswold, M.D., Ph.D
Minneapolis Medical Research Foundation
701 Park Ave, Suite PP7.700
Minneapolis, MN 55415

Dear Dr. Rockswold,

We are writing on behalf of Loma Linda University to enthusiastically support your NIH R01 application entitled, ***Hyperbaric Oxygen Brain Injury Treatment (HOBIT)*** trial. Participation in finding a more effective way to treat TBI patients is compelling and necessary. We are very excited about the possibilities of this project and are looking forward to collaborating and contributing to this important research.

We are confident that this trial can fully leverage the abilities of our research organization to enroll subjects, provide the highest standards of care throughout the trial, and collect the necessary data for analysis.

In addition, Loma Linda University appreciates the opportunity to serve as a site for your proposed research project. We are committed to providing the resources outlined in this proposal as well as committed to the staff time adequate to accomplish all the proposed activities of the project. We look forward to working together on this important research and we are eager to test this promising treatment for TBI patients.

Sincerely,

Michael A. Kirby, PhD
Associate Vice President for
Research Affairs

Hamilton Health Sciences
237 Barton Street East
Hamilton, ON L8L 2X2
P.905-521-2100 E.46426
F.905-525-6773

May 19, 2015

Dr. Gaylan Rockswold, M.D., Ph.D
Minneapolis Medical Research Foundation
701 Park Ave, Suite PP7.700
Minneapolis, MN 55415

Dear Dr. Rockswold,

We are writing on behalf of Hamilton Health Sciences-Hamilton General Division to enthusiastically support your NIH R01application entitled **Hyperbaric Oxygen Brain Injury Treatment (HOBIT)** trial. Participation in finding a more effective way to treat TBI patients is compelling. We are very excited about the possibilities of this project and are looking forward to being a part of this research.

We believe this trial can fully leverage the abilities of our research organization to enroll subjects, provide the highest standards of care throughout the trial, and collect the necessary data for analysis.

Hamilton Health Sciences-Hamilton General Division would be delighted to serve as a site for your proposed research project. We are committed to providing the resources outlined in this proposed activities of the project. We look forward to working together on this important research and we are eager to test this promising treatment for TBI patients.

Sincerely,

Dr. P. Gregor, MD, FRCP
General Surgeon, Chief Hyperbaric Medicine

Hamilton Health Sciences
237 Barton Street East
Hamilton, ON L8L 2X2
P.905-521-2100 E.46426
F.905-525-6773

May 19, 2015

Dr. Gaylan Rockswold, M.D., Ph.D
Minneapolis Medical Research Foundation
701 Park Ave, Suite PP7.700
Minneapolis, MN 55415

Dear Dr. Rockswold,

We are writing on behalf of Hamilton Health Sciences-Hamilton General Division to enthusiastically support your NIH R01application entitled **Hyperbaric Oxygen Brain Injury Treatment (HOBIT)** trial. Participation in finding a more effective way to treat TBI patients is compelling. We are very excited about the possibilities of this project and are looking forward to being a part of this research.

We believe this trial can fully leverage the abilities of our research organization to enroll subjects, provide the highest standards of care throughout the trial, and collect the necessary data for analysis.

Hamilton Health Sciences-Hamilton General Division would be delighted to serve as a site for your proposed research project. We are committed to providing the resources outlined in this proposed activities of the project. We look forward to working together on this important research and we are eager to test this promising treatment for TBI patients.

Sincerely,

K. Reddy

Dr. K. Reddy, MD, FRCS
Division Head for Neurosurgery, Chief of Surgery

Hamilton Health Sciences
237 Barton Street East
Hamilton, ON L8L 2X2
P.905-521-2100 E.46426
F.905-525-6773

May 19, 2015

Dr. Gaylan Rockswold, M.D., Ph.D
Minneapolis Medical Research Foundation
701 Park Ave, Suite PP7.700
Minneapolis, MN 55415

Dear Dr. Rockswold,

We are writing on behalf of Hamilton Health Sciences-Hamilton General Division to enthusiastically support your NIH R01application entitled **Hyperbaric Oxygen Brain Injury Treatment (HOBIT)** trial. Participation in finding a more effective way to treat TBI patients is compelling. We are very excited about the possibilities of this project and are looking forward to being a part of this research.

We believe this trial can fully leverage the abilities of our research organization to enroll subjects, provide the highest standards of care throughout the trial, and collect the necessary data for analysis.

Hamilton Health Sciences-Hamilton General Division would be delighted to serve as a site for your proposed research project. We are committed to providing the resources outlined in this proposed activities of the project. We look forward to working together on this important research and we are eager to test this promising treatment for TBI patients.

Sincerely,

D Jichici

Dr. D. Jichici, MD, FRCS
Neurology, Critical Care Medicine

HARVARD MEDICAL SCHOOL **MASSACHUSETTS EYE AND EAR ASSOCIATES**

Otology:

Joseph B. Nadol, Jr., M.D.
Ronald K. de Venecia, M.D., Ph.D.
Daniel J. Lee, M.D.
Michael J. McKenna, M.D.
Saumil N. Merchant, M.D.
Steven D. Rauch, M.D.
Felipe Santos, M.D.
Jennifer L. Smullen, M.D.
Konstantina M. Stankovic, M.D., Ph.D.

Head and Neck Surgery:

Daniel G. Deschler, M.D.
Kevin S. Emerick, M.D.
Derrick T. Lin, M.D.
Gregory W. Randolph, M.D.
James W. Rocco, M.D., Ph.D.

Thyroid and Parathyroid Surgery:

Gregory W. Randolph, M.D.
Jean M. Bruch, D.M.D., M.D.
Daniel G. Deschler, M.D.
Derrick T. Lin, M.D.

Otolaryngology:

Gregory W. Randolph, M.D.
Benjamin S. Bleier, M.D.
Jean M. Bruch, D.M.D., M.D.
Nicholas Y. Busaba, M.D.
Richard E. Gliklich, M.D.
Allan J. Goldstein, M.D.
Stacey T. Gray, M.D.
Eric Holbrook, M.D.

Pediatric Otolaryngology:

Christopher J. Hartnick. M.D.
Michael S. Cohen, M.D.
Donald G. Keamy, Jr., M.D.
Daniel J. Lee, M.D.
Leila A. Mankarious, M.D.

Laryngology:

Ramon A. Franco, Jr., M.D.
Jean M. Bruch, D.M.D., M.D.
Nicholas Y. Busaba, M.D.
Daniel G. Deschler, M.D.
Christopher J. Hartnick. M.D.
Gregory W. Randolph, M.D.
Phillip C. Song, M.D.

Facial Plastic and Reconstructive Surgery:

Theresa A. Hadlock, M.D.
Mack L. Cheney, M.D.
Jaimie DeRosa, M.D.
Daniel G. Deschler, M.D.
Richard E. Gliklich, M.D.

Mohs/Dermatology Surgery:

Jessica L. Fewkes, M.D.

Laser Surgery/Dermatology:

Oon T. Tan, M.D., Ph.D.

Oto-Neurology:

Richard F. Lewis, M.D.
Adrian J. Priesol, M.D.

Otolaryngology - Head and Neck Surgery
Massachusetts Eye and Ear Associates
243 Charles Street
Boston, Massachusetts 02114
(617) 523-7900
Fax: (617) 573-3914
http://www.masseyeandear.org

May 27, 2015

Dr. Gaylan Rockswold, M.D., Ph.D
Minneapolis Medical Research Foundation
701 Park Ave, Suite PP7.700
Minneapolis, MN 55415

Dear Dr. Rockswold,

We are writing on behalf of our group at Massachusetts General Hospital (MGH) to enthusiastically support your NIH R01 application entitled **Hyperbaric Oxygen Brain Injury Treatment (HOBIT)** trial. Participation in finding a more effective way to treat TBI patients is compelling. We are very excited about the possibilities of this project and are looking forward to being a part of this research.

We believe this trial can fully leverage the abilities of our research organization to enroll subjects, provide the highest standards of care throughout the trial, and collect the necessary data for analysis.

We believe that MGH will be an outstanding site for your proposed research project. Our hospital is a high volume level 1 Trauma Center with an available hyperbaric chamber. We look forward to working together on this important research and we are eager to test this promising treatment for TBI patients.

Sincerely,

Jean Bruch, DMD, MD

Assistant Director
Norman Knight Hyperbaric Unit
Massachusetts Eye and Ear Infirmary
Boston, MA 02114

MASSACHUSETTS GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL

Joshua N. Goldstein, MD, PhD
Associate Professor, Harvard Medical School
Director, Center for Neurologic Emergencies

Department of Emergency Medicine
Zero Emerson Place, Suite 3B
Boston, Massachusetts 02114
Tel: 617-726-7622
Fax: 617-724-0917
E-mail: jgoldstein@partners.org

May 28, 2015

Dr. Gaylan Rockswold, M.D., Ph.D
Minneapolis Medical Research Foundation
701 Park Ave, Suite PP7.700
Minneapolis, MN 55415

Dear Dr. Rockswold,

We are writing on behalf of our group at Massachusetts General Hospital (MGH) to enthusiastically support your NIH R01 application entitled **Hyperbaric Oxygen Brain Injury Treatment (HOBIT)** trial. Participation in finding a more effective way to treat TBI patients is compelling. We are very excited about the possibilities of this project and are looking forward to being a part of this research.

We believe this trial can fully leverage the abilities of our research organization to enroll subjects, provide the highest standards of care throughout the trial, and collect the necessary data for analysis.

We believe that MGH will be an outstanding site for your proposed research project. Our hospital is a high volume level 1 Trauma Center with an available hyperbaric chamber. We look forward to working together on this important research and we are eager to test this promising treatment for TBI patients.

Sincerely,

Joshua N. Goldstein, M.D., Ph.D.

University of Nebraska Medical Center

May 18, 2015

Dr. Gaylan Rockswold, M.D., Ph.D
Minneapolis Medical Research Foundation
701 Park Ave, Suite PP7.700
Minneapolis, MN 55415

Dear Dr. Rockswold,

We are writing on behalf of Nebraska Medicine and the University of Nebraska Medical Center (UNMC) to enthusiastically support your NIH R01 application entitled **Hyperbaric Oxygen Brain Injury Treatment (HOBIT)** trial. Participation in finding a more effective way to treat TBI patients is compelling. We are very excited about the possibilities of this project and are looking forward to being a part of this research.

We believe this trial can fully leverage the abilities of our research organization to enroll subjects, provide the highest standards of care throughout the trial, and collect the necessary data for analysis.

Nebraska Medicine and UNMC would be delighted to serve as a site for your proposed research project. We are committed to providing the resources outlined in this proposal as well as committed to the staff time adequate to accomplish all the proposed activities of the project. We look forward to working together on this important research and we are eager to test this promising treatment for TBI patients.

Sincerely,

Jeffrey Cooper, MD, FAAEM
PI
Assistant Professor Emergency Medicine
Director, Hyperbaric Medicine

PJ Schenarts, MD, FACS
Professor of Surgery
Director of Trauma and Critical Care Surgery

Ken Follett, MD, PhD, FACS
Professor and Chief of Neurosurgery

981150 Nebraska Medical Center / Omaha, NE 68198-1150
402.559.5413 / fax 402.559.9659 / unmc.edu/emergency

University of Pittsburgh

School of Medicine
Department of Emergency Medicine

Iroquois Building , Suite 400 A
3600 Forbes Avenue
Pittsburgh, PA 15261
412-647-3078
Fax: 412-647-6999

May 20, 2015

Dr. Gaylan Rockswold, M.D., Ph.D
Minneapolis Medical Research Foundation
701 Park Ave, Suite PP7.700
Minneapolis, MN 55415

Dear Dr. Rockswold,

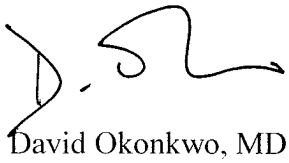
We are writing on behalf of the University of Pittsburgh to enthusiastically support your NIH R01 application entitled **Hyperbaric Oxygen Brain Injury Treatment (HOBIT)** trial. Participation in finding a more effective way to treat TBI patients is compelling. We are very excited about the possibilities of this project and are looking forward to being a part of this research.

We believe this trial can fully leverage the abilities of our research organization to enroll subjects, provide the highest standards of care throughout the trial, and collect the necessary data for analysis.

The University of Pittsburgh would be delighted to serve as a site for your proposed research project. We are committed to providing the resources outlined in this proposal as well as committed to the staff time adequate to accomplish all the proposed activities of the project. We look forward to working together on this important research and we are eager to test this promising treatment for TBI patients.

Sincerely,

Clifton Callaway, MD, PhD
Professor of Emergency Medicine
Executive Vice Chairman of Emergency Medicine
Ronald D. Stewart Endowed Chair of Emergency Medicine Research
NETT Hub PI



David Okonkwo, MD, PhD
Professor of Neurological Surgery
Clinical Director, Brain Trauma Research Center
Executive Vice Chairman, Clinical Operations
Director, Neurotrauma Program
Director, Scoliosis and Spinal Deformity Program

Kevin O'Toole, MD
Associate Professor of Emergency Medicine
Associate Chief, UPMC Presbyterian Emergency Department
Director, Hyperbaric Medicine

The primary results of the clinical trial will be disseminated by publication in the peer reviewed medical literature. In accordance with the NIH Public Access Policy, the investigators will submit an electronic version of their final, peer-reviewed manuscripts (directly or through the publisher) to the National Library of Medicine's PubMed Central, no later than 12 months after the official date of publication. The trial will be registered with http://www.clinical trials.gov, and results of HOBIT will be reported there within a year of trial completion.

After completion of the study and dissemination of primary study results, a public use dataset will be created. The public use dataset will be made available for download through a platform to be designated by the NINDS. The public use dataset, along with the study protocol, the data dictionary, and a brief set of instructions ("Readme" file) will be provided. Release of the public use dataset will be determined by the HOBIT Executive Committee, consistent with the NETT publications standard operating procedure, with the goal of allowing investigators a short protected period to perform secondary analyses, followed by timely public release.

The public use dataset will be stripped of any and all personal identifiers and will undergo a de-identification process. HIPAA compliant deidentification will include removal of study ID numbers and assignment of a random number to each subject, deletion of clinical center ID numbers and assignment of a random number to each clinical center, deletion of investigator or assessor name/ID, deletion of the randomization date but retention of the month and year and the order in which patients enrolled, and conversion when necessary of dates and times to the number of days/minutes from the date and time of randomization.

Derived variables necessary to reproduce the primary analysis will be included. Files will be made available in an accessible data format (SAS, XML, or other). All manuscripts, abstracts and press releases using the study data must acknowledge HOBIT NETT investigators and the NINDS as the study sponsor with the relevant grant numbers.

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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N/A

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The IND/IDE submission to the FDA is under review.

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

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

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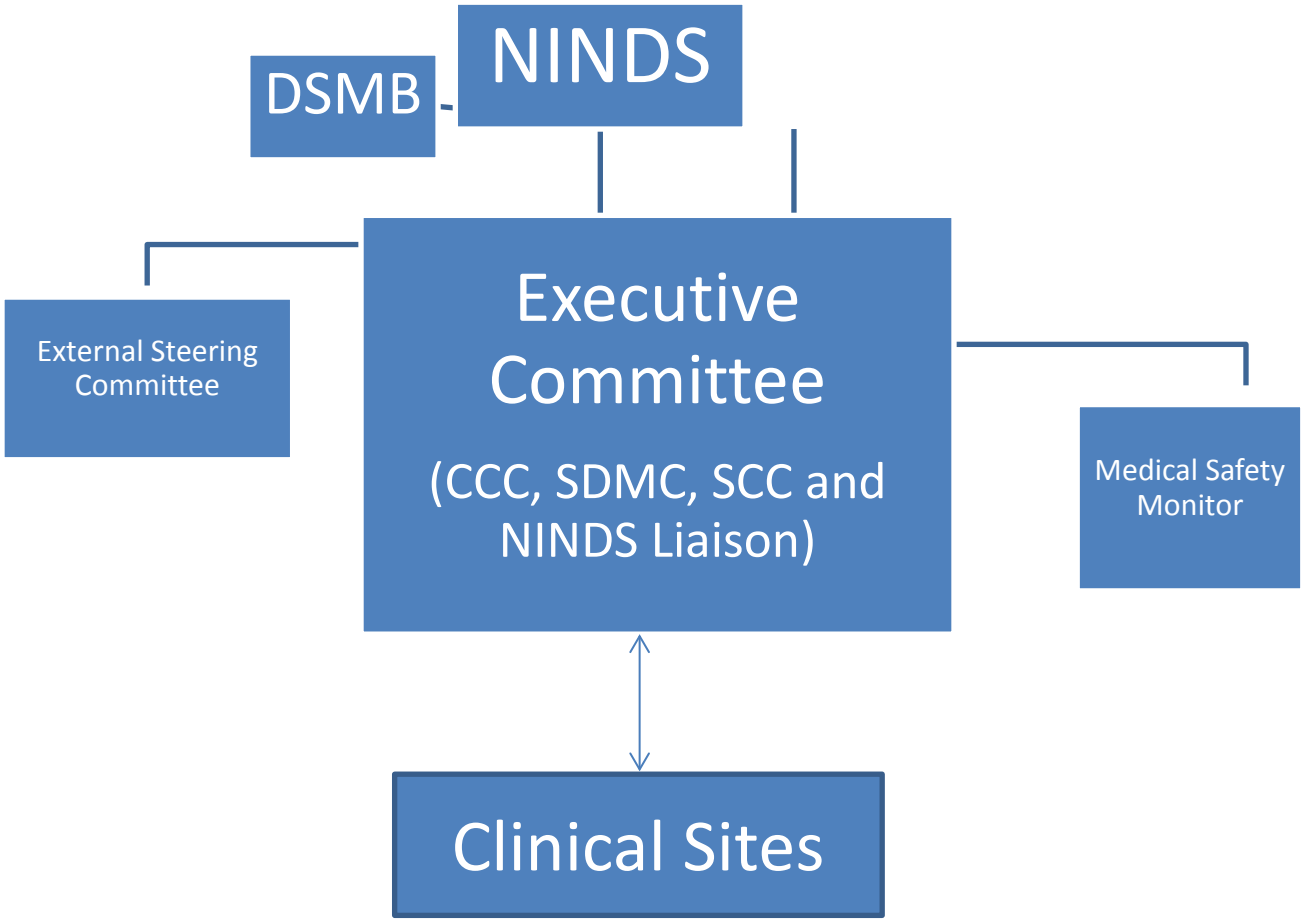


Overall. The HOBIT trial will be conducted in the Neurological Emergency Treatment Trial (NETT) Network funded by the National Institutes of Neurological Disorders and Stroke (NINDS). The Clinical Coordinating Center (CCC) for the HOBIT trial will be the NETT CCC at the University of Michigan and the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

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

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

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

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

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

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

Medical Safety Monitor The MSM is a neurointensivist experienced in severe TBI management as well as serving as a MSM. She is not affiliated with any of the institutions participating in the HOBIT trial. The MSM responsibilities are to review all SAEs and determine whether they are possibly related to HBO2 administration and to adjudicate adverse outcome events. The MSM will have a backup neurointensivist in the unlikely event she is unable to review the SAEs in a timely manner.

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

	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
	1. (Dose selection) To select, in patients with severe TBI, the combination of HBO2 treatment parameters (pressure, frequency, and intervening normobaric hyperoxia [NBH]) that is most likely to demonstrate improvement in the rate of good neurological outcome versus control in a subsequent confirmatory trial. 2. (Signal of efficacy) To determine, in patients with severe TBI, whether there is a >50% probability of HBO2 treatment demonstrating improvement in the rate of good neurological outcome versus control in a subsequent confirmatory trial.
	Phase II
	This trial is designed as a multicenter, prospective, randomized, adaptive Phase II trial.
	To assess efficacy, the treatment groups will be compared with respect to the proportion of subjects with favorable outcome at 6 months post-randomization. Favorable outcome is defined based on the sliding dichotomy methodology whereby subjects with the most severe injury and whose initial Glasgow Coma Scale (GCS) scores are 3-5 are considered to have a favorable outcome if their 6-month Glasgow Outcome Scale – Extended (GOS-E) score is good recovery to severe disability; subjects with less severe injury and whose initial GCS scores are 6-8 are considered to have a favorable outcome if their 6-month GOS-E score is good recovery to moderate disability.
	1. Control and prevention of intracranial hypertension (> 20 mmHg) in HBO2-treated versus control patients. 2. Prevention of brain tissue hypoxia (< 15 mmHg) in HBO2-treated versus control patients. 3. The therapeutic intensity level (TIL) scores to treat intracranial pressure in HBO2-treated versus control patients (Table 3) (Maset 1987). 4. Incidence of severe adverse events in HBO2 compared to control treated patients.
	All individuals presenting to a collaborating institution with a severe TBI defined as a GCS score of 3 to 8 (age 16 to 65 years) are potential candidates for inclusion. Patients with GCS score 7 or 8 will be required to have a clearly abnormal computerized tomography (CT) scan ($\geq$ Marshall score 3) (Table 1). A central randomization module will be developed within the web-based trial management system.
	Patients not requiring a craniotomy/craniectomy or any other major surgical procedure will be enrolled and the first HBO2 treatment initiated within 6 hours of admission. If the patient does require a craniotomy/craniectomy or major surgical procedure, the enrollment and initial HBO2 treatment shall be initiated within 12 hours.
	Fifteen clinical centers in the United States and Canada.

	Planned enrollment period - 3 years Planned duration of the study - 5 years
	Maximum of 200
	The trial design is adaptive. The primary outcome is the severity adjusted GOS-E at 6 months. However, clinical data from 30 days and 3 months will be used to predict 6 month data. The trial will explore nine different active treatment arms for relative efficacy and comparison to the control arm. Three pressures (1.5, 2.0 and 2.5 atmospheres absolute [ATA]+), two frequencies (everyday versus twice daily), and with or without NBH will be studied. If there is at least one experimental treatment arm promising enough, it will be a candidate and will be compared for superiority to the control in the future phase III trial. The maximum number of subjects to be enrolled is 200 at approximately 15 clinical centers. The trial will utilize response adaptive rate randomization to favor the better performing experimental arms. Also, using adaptive randomization (being able to change how we assign subjects to the groups during the study based on information gained during the study) allows for substantially smaller sample sizes and provides better conclusions about the most effective treatment because it lets us stop the study early if we find strong results or identify futility before the scheduled end of the study.

6.1

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

6.2

1. To analyze the level and duration of intracranial hypertension (> 20 mmHg) using area under the curve (AUC) methodology in HBO2-treated versus control groups (Vik 2008).
2. To analyze the TIL scores for controlling intracranial pressure (ICP) in HBO2-treated patients compared to controls.
3. Utilizing Licox brain tissue partial pressure of oxygen (PO2) monitoring, analyze the level and duration of brain tissue hypoxia (PO2 < 15 mmHg) using AUC methodology in HBO2-treated groups versus control (van den Brink 2000).
4. To compare the incidence of SAEs between HBO2 treatment arms and control.

7.1

One of the significant factors in the failure of previous clinical trials to show efficacy in severe TBI may be the fact that the patient population was “frontloaded” with patients who have a relatively good prognosis (Narayan 2002). If one pools the patients from three large multisite trials, approximately 50% of the patients enrolled had either a GCS of 7 or 8 or a GCS motor score of 4 or 5 (Maas 2006, Marshall 1998, Morris 1999). Forty-four percent of the patients had

a “diffuse injury” or a Marshall CT score of 2 (Marshall 1991). These patients had a favorable outcome on the dichotomized Glasgow Outcome Scale (GOS) score in the 70-80% range.

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

Based on the above considerations, all individuals, aged 16 to 65, presenting to a collaborating institution with a severe TBI defined as a GCS score 3 to 8 are potential candidates for inclusion. Patients with a GCS score of 7 or 8 with a Marshall CT score of 1 or 2 are excluded. Patients with a GCS score of 3 ____ 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. Patients over 65 years old are excluded because they have increased co-morbidity and a higher mortality from severe TBI that would tend to obscure the positive effect from treatment.

7.2 _____

The Center for Disease Control estimates that there are 300,000 individuals hospitalized for a TBI in the USA in 2012. Approximately 10% of patients admitted to hospitals have sustained a severe TBI as defined by the GCS (Kraus 1993, Thurman 2001). Approximately 30% of these individuals die and 40% achieve a favorable outcome as defined by the dichotomized GOS. Therefore, approximately 30% of severe TBI patients are permanently severely disabled or vegetative. The average age of an individual sustaining a TBI is about 40 years, and the average life expectancy after TBI is an additional 20 years. The annual average cost of a TBI victim requiring custodial care in the state of Minnesota is $80,000 ($1.6 million on average per disabled severe TBI patient over their lifetime). Using the above suppositions, we can therefore calculate that of the approximately 30,000 severe TBI patients there would be 9,000 left severely disabled or vegetative. Supposing there is a 10% improvement to favorable or functional abilities in 900 patients, this would translate into a savings of 1.44 billion over the lifetime of the increased number of functional survivors per year. 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.

7.3 _____

7.3.1 ***Potential Mechanisms of Action of HBO2 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 very selective neuroprotective effect with respect to the complexity of the process leading to brain cell death. On the other hand HBO2 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, Miller 1970, Palzur 2004, Palzur 2008, Rockswold 1992, Rockswold 2001, Rockswold 2010, Rockswold 2013, Rogatsky 2005, Soustiel 2008, Vlodavsky 2005, Vlodavsky 2006, Wada 1996, Wada 2001, Zhou 2007).

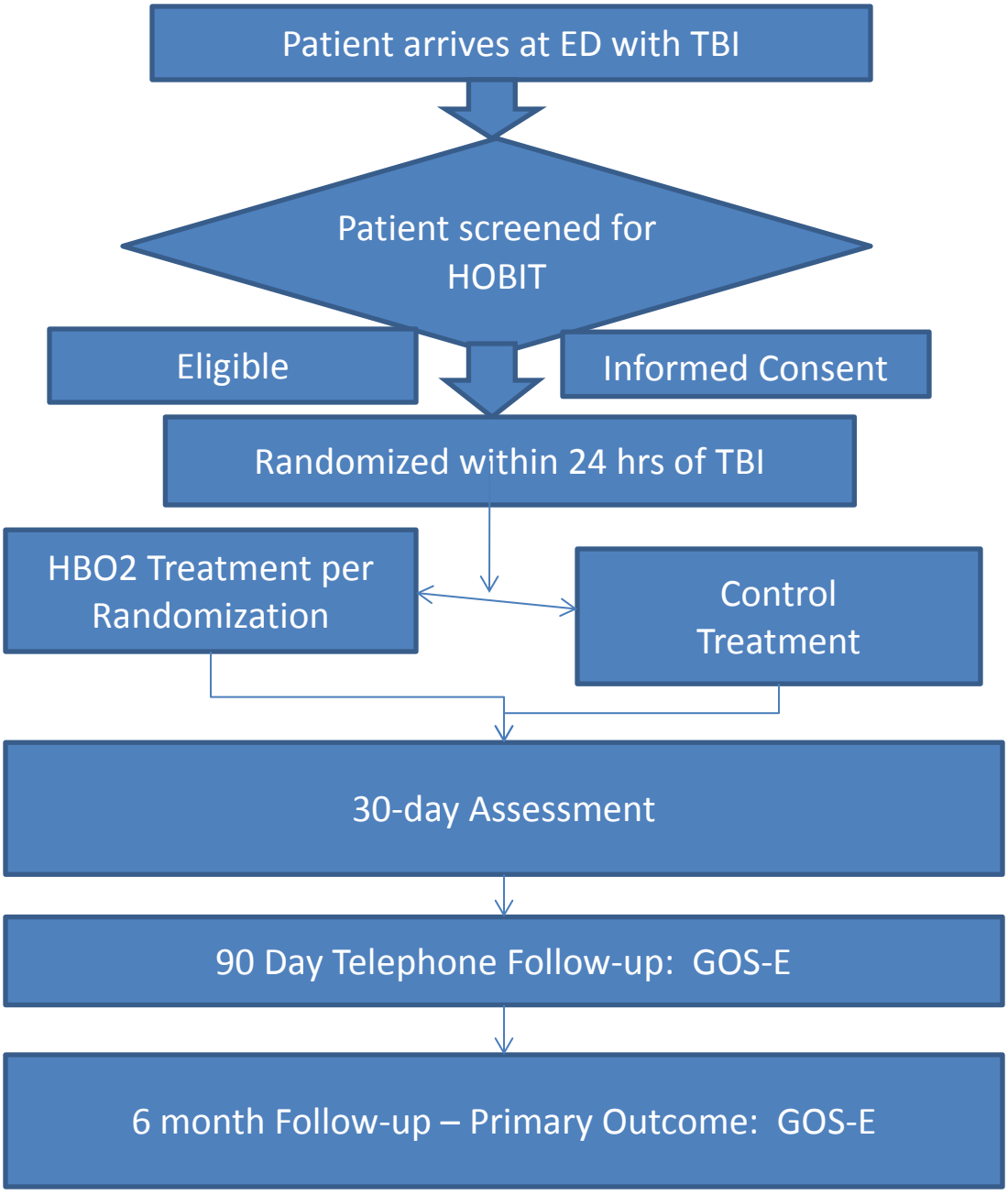
Cellular energy failure appears to be the initiating event in the complex processes leading to brain cell death (Saatman 2008, Signoretti 2008, Tisdall 2008, Zauner 1997). In the first 24 hours after brain injury, ischemia is present, leading to decreased oxygen (O2) delivery that is inadequate to maintain 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). 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, HBO2 markedly increases O2 delivery to traumatized brain (Daugherty 2004, Rockswold 2010, Rockswold 2013). Thus, HBO2 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 HBO2 restores the loss of mitochondrial transmembrane potential, and that the reduction of apoptotic cell death mediated by HBO2 is achieved by a mitochondrial protective effect (Palzur 2008, Soustiel 2008). These investigators theorize that the increased intracellular O2 bioavailability resulting from HBO2 may contribute to the preservation of mitochondrial integrity and reduce the activation of the mitochondrial pathway of apoptosis. Clinical trials have shown increased global O2 consumption lasting for at least 6 hours post HBO2 treatment; this would be secondary to improved mitochondrial function. In addition, this effect is seen for at least 5 days post injury in human TBI victims treated with HBO2 (Rockswold 2001, Rockswold 2010). Thus, HBO2 improves oxidative metabolism during the period of prolonged post trauma hypometabolism. In addition, HBO2 has been shown in both experimental and clinical studies to reduce ICP (Brown 1988, Hayakawa 1971, Miller 1971, Rockswold 1992, Rockswold 2001, Rockswold 2010, Rockswold 2013, Sukoff 1982) and cerebral edema after severe brain injury (Mink 1995, Nida 1995, Palzur 2004, Sukoff 1968). These latter studies suggest that HBO2 may promote blood-brain barrier integrity, thus reducing cerebral edema and hyperemia, and therefore reducing the elevated ICP.

7.3.2 ***Safety Record for HBO_2 Treatment.*** An exemplary safety record for HBO2 treatment has been demonstrated over the course of four clinical trials. There were 1,984 HBO2 treatments delivered to 167 patients with no permanent complications related to the HBO2 treatment and no patient emergently evacuated from the chamber (Gossett 2010, Rockswold 1992, Rockswold 2001, Rockswold 2010, Rockswold 2013). In large part, this safety record was accomplished by strict adherence to inclusion/exclusion criteria that are identical to those included in this application. Additionally, the HBO2 treatment areas were considered an extension of the intensive care unit (ICU), providing further assurance that any potential complication could be addressed immediately. In our recent prospective randomized trial, patients with decompressive craniectomies who underwent HBO2 treatment had no difficulties or complications (Rockswold 2010).

Fire hazard is a potential risk in HBO2 chambers. The National Fire Protection Association (NFPA) has produced a hyperbaric safety standard which has been in place since 1967 (NFPA 99, Standard for Health Care Facilities 2005). In facilities that rigidly follow these standards, there have been no fatalities due to hyperbaric chamber fire in North America.

This trial is designed as multicenter, prospective, randomized, adaptive phase II clinical trial. All individuals presenting at an enrolling site with a severe TBI defined as a GCS score of 3-8 (age 16 to 65 years) are initially eligible for inclusion. Patients with a GCS score of 7 or 8 and a Marshall CT score of 1 or 2, as well as patients with a GCS score of 3 and bilaterally mid position, non-reactive pupils will be excluded. No exclusion criteria will be based on race, ethnicity, or gender. The trial design is adaptive. The primary outcome is a severity adjusted GOS-E at 6 months. However, clinical data from 30 days and 3 three months will be used to predict 6-month data. The trial will explore nine different active treatment arms for relative efficacy in comparison of the control arm. Three pressures (1.5, 2.0 and 2.5 ATA), two frequencies (every day versus twice daily), and with or without NBH will be studied. If there is at least one promising experimental treatment, it will be a candidate and will be compared for superiority to the control in the future phase III trial. Utilizing this 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. The maximum number of subjects to be enrolled is 200 at approximately 15 clinical centers. The trial will utilize response adaptive rate randomization to favor the better performing experimental arms. Also, using adaptive randomization (being able to change how we assign subjects to the groups during the study based on information gained during the study) allows for substantially smaller sample size and provides better conclusions about the most effective treatment because it lets us stop the study early if we find strong results or identified futility before the scheduled end of the study. For the response adaptive randomization, clinical data from 30 days in 3 months will be used to predict 6-month data. 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.



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

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

hr treatment window. If major procedure required = 12 hr	
Informed consent obtained	Required
Blunt mechanism only	Pathophysiologic and anatomic differences with penetrating injury

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

9.2 _____

9.2.1. ***Identifying and Recruiting Candidates*** Potential subjects for this trial will be recruited from all patients with a severe TBI presenting within 24 hours of injury to the 15 clinical sites participating in this trial. All participating clinical sites are staffed by trained research personnel capable of performing careful screening of each potential subject according to the inclusion/exclusion criteria described above.

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

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

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

9.2.4 ***Randomization Procedures.*** A web-based central randomization system will be developed by the SDMC and installed on the WebDCU™ HOBIT study website. The objective of randomization is to prevent possible selection bias by providing random treatment assignment to each subject, and to prevent accidental treatment imbalances for the known prognostic variables. Balancing of prognostic variables will be conducted using the Minimal Sufficient Balance randomization algorithm which aims to maximize the treatment allocation randomness while containing the baseline covariate imbalances within a pre-specified limit. The

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

10.1

10.1.1 ***Hyperbaric Chamber Adaptations and Availability.*** Although there are over 900 hyperbaric facilities in the continental United States, a very small proportion actually practice critical care hyperbaric therapy or have a hyperbaric facility strategically located to treat critically ill patients. Several authors have noted that although HBO2 has shown beneficial effects in animals and humans, this treatment option remains limited because of the expense and very limited availability of HBO2 chambers (Tisdall 2008, Tolias 2004). Two types of HBO2 delivery systems exist. One is the traditional multiple-occupancy large compartment chamber. It is designed to accommodate several patients and attendant medical personnel and has long represented the technology standard. Advantages include the fact that multiple patients can be treated at one time and there is direct patient attendance during each HBO2 treatment. There are no modifications needed to a multiplace chamber to treat TBI patients. There are significant disadvantages, including the greater degree of technology and related support requirements, a larger physical plant footprint, and higher capitalization and operating costs.

An alternate delivery system is the monoplace chamber. It supports a single patient with attendance and support provided from the chamber exterior. The monoplace chamber has been employed across a broad range of patient conditions to an increasing degree over the past two decades. Our institution has found it entirely adequate for the safe care and management of critically ill and ventilator-dependent patients sustaining severe TBI and multiple injuries (Gossett 2010). The major advantages of the monoplace chamber are 1) minimal physical space footprint, 2) easily incorporate in and adjacent to a critical care support area, 3) minimal technology demands, 4) the delivery system can be effectively and safely operated by existing nursing, respiratory, and standard medical support staff upon appropriate training and preceptorship, 5) lower capitalization and operating costs, and 6) no risk of iatrogenic decompression sickness in support staff. It should be emphasized that the monoplace chamber becomes an extension of the critical care environment. The cost of an HBO2 monoplace chamber with appropriate adaptations for monitoring critically ill patients and installation is

approximately $250,000. To modify an existing monoplace chamber to accommodate and monitor severe TBI patients costs approximately $25,000. However, as indicated in *Section 7.7.2 Relevance and Priority of the Study*, the economic impact of a successful treatment for severe TBI far outweighs the cost of installation of multiple monoplace chambers in or near selected ICUs.

10.1.2 ***Treatment Window.*** It is considerably more difficult to initiate a complex treatment like HBO2 as compared to initiating a drug therapy intravenously. HBO2 treatment cannot occur until acute resuscitation, including intubation, hemodynamic stabilization, emergency surgery as needed and management of other traumatic injuries has occurred. Informed consent must be obtained from the LAR. Based on our past experience, patients not requiring a craniotomy/craniectomy or any other major surgical procedure will be enrolled and the first HBO2 treatment initiated within 6 hours of admission. If the patient does require craniotomy/craniectomy or a major surgical procedure, the enrollment and initial HBO2 treatment shall be initiated within 12 hours.

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

10.1.4 ***HBO2 Treatments.*** Compression and decompression will be carried out at a standard rate of 2 feet/minute. It will take 24.75 minutes to reach 2.5 ATA; 16.5 minutes to reach 2.0 ATA; and 8.25 minutes to reach 1.5 ATA. Treatment duration will be 60 minutes at these pressures. Treatments will occur once or twice per day. The HBO2 treatments will either be given in isolation or 3 hours of NBH (100% FiO2 at 1.0 ATA) will follow the HBO2 treatments. Treatments will continue for 5 days or until patient follows commands or is determined to be brain dead. The patient is ventilated with 100% O2 for the entire treatment period. A record of the chamber pressures, FiO2 levels, as well as all data collected during the dive will be maintained. Patients will be randomized to one of nine HBO2 treatment paradigms to be evaluated.

1. 2.0 ATA no NBH once daily
2. 2.5 ATA no NBH once daily
3. 1.5 ATA with NBH once daily
4. 2.0 ATA with NBH once daily
5. 2.5 ATA with NBH once daily
6. 1.5 ATA no NBH twice a day
7. 2.0 ATA no NBH twice a day
8. 2.5 ATA no NBH twice a day
9. 1.5 ATA with NBH twice a day
10. Control (no HBO2 treatment)

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

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

10.2 _____

10.2.1 ***Preparation of the Severe TBI Patient for HBO2.*** There are many details requiring special attention prior to the placement of the patient in the HBO2 chamber (Gossett 2010, Weaver 1999). All clinical sites expected to participate in the HOBIT Trial have trained personnel who are very cognizant of these critical procedures. The EC also will maintain strict oversight of protocol and assessment adherence at each participating clinical site. The procedures include ensuring that: chest tubes are connected to a Heimlich valve and drained passively into a sterile receptacle such as a Foley drainage bag or a sterile glove; the air from the endotracheal tube cuff is completely evacuated and replaced with sufficient normal saline to achieve an appropriate seal with a minimum pressure; gastric tubes are attached to a sputum trap or drainage bag; and, subdural Jackson-Pratt drains are securely occluded for the duration of treatment. In the monoplace chamber, all intravenous (IV) lines in use must have specialized hyperbaric tubing extensions. Each IV line requires its own pump, and only one line can be used for each penetration. IV check valves are positioned inside the chamber door on each line.

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

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

outside of the monoplace chamber to turn the ventriculostomy stopcock valve either open for draining (if ICP is elevated) or closed for intermittent ICP monitoring.

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

Monoplace Chamber

Adequate mechanical ventilation throughout the hyperbaric treatment is essential for TBI patients with severe injury (Gossett 2010). Monoplace ventilators are generally kept on the outside of the chamber. The monoplace ventilator has to overcome the pressure differential between the outside and the inside of the chamber in order to properly ventilate the patient. A common problem with monoplace ventilators is that at any set tidal volume the delivered tidal volume decreases during compression and increases during decompression (Weaver 1988, Weaver 1999). This fluctuation is because the volume of gas changes inversely with pressure (Boyle's Law V=1/P). The slow compression/decompression rate used in this protocol reduces this effect. Therefore, respiratory rate, tidal volume, inspiratory to expiratory ratio, and peak inspiratory pressures is monitored closely throughout the hyperbaric treatment with particular vigilance during pressure changes. Arterial blood gasses can be obtained during HBO2 treatment and are especially important in patients with borderline pulmonary function (Ratzenhofer-Komedna 2003, Weaver 1994).

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

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

Multiplace Chambers

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

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

10.3 _____

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

10.4 _____

10.4.1 ***Management Guidelines***. It is critical that a uniform management plan among the enrolling sites is instituted. Treatment variability among enrolling sites is thought to have been a significant factor in the failure of previous multisite clinical trials involving severe TBI. Adherence to the following guidelines is imperative for a successful trial. David Wright, M.D., PI for the Progesterone for the Treatment of Traumatic Brain Injury (ProTECT) III trial, has agreed to allow the HOBIT Trial to utilize the CSG developed for the ProTECT Trial. This is important for two reasons. 1) The ProTECT III CSGs were developed by a national committee of experts in neurosurgery, trauma surgery, neuro critical care, and emergency medicine. They are based on both their expertise as well as the Guidelines for the Management of Severe TBI (Brain Trauma Foundation 2007). Therefore, they represent the "state-of-the-art" and would be hard to improve upon. 2) Since there are eight enrolling sites that participated in the ProTECT III trial, the management of the patients will be standard care. The guidelines developed by the ProTECT III Clinical Standardization team follow a Goal-Directed Therapy approach. Since all of the potential enrollees in the HBO2 study have suffered severe TBI, all patients will require ventriculostomy and ICP monitoring.

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

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

1. The HOBIT trial has adapted the ProTECT III CSGs developed by a multidisciplinary team of experts in the management of severe TBI. These guidelines are straightforward and are in use in most major TBI treatment centers and follow a goal-direct therapy approach.
2. An ESC made up of a group of experts including Drs. Lori Shutter, Lindell Weaver, and David Wright will help ensure standardization of TBI care.
3. The EC plans to conduct pre-trial meetings with the lead staff at the enrolling sites to discuss and emphasize the importance of providing consistent, state-of-the-art care.
4. The EC will implement a protocol based online examination through the WebDCU which will be required for all personnel involved in patient care prior to participation in the study.
5. The SDMC has had a great deal of experience in tracking performance based on key data elements entered daily into the study database to monitor each site's adherence to the management protocol. The system will alert the PI and other appropriate EC members to violations and deviations.

6. The EC will assess site quality and performance via a site Report Card that will be generated on a regular basis with pre-determined minimal site guidelines for patient care and adherence to the protocol. As part of the "Report Card" process, there are provisions to drop a participating clinical site if a pattern of willing disregard for the protocol is identified at any site.
7. Periodic ongoing onsite visits by the PI and CPC will be conducted to ensure quality assurance throughout the trial.
8. The HOBIT trial statistical plan includes randomization adjusted for enrolling sites.
9. The EC has secured written assurances of cooperation from our research partners at each enrolling site.

10.5

To ensure that each center learns the procedures without jeopardizing patient safety or data quality, and to avoid compromising the trial by poorly-performing centers, a run-in trial period will be required for each clinical center (Choi 2001). The run-in period will occur during the seventh and ninth months of the first year of funding or as clinical centers are prepared to enroll patients. All patients (up to two) will receive HBO2 during the run-in period and none will be randomized. At least one of the patients must be entered without major protocol violations and meet study data quality requirements in order for the participating clinical center to be able to randomize into the trial.

11.1

Screening	X									
Inclusion/Exclusion Criteria	X									
Demographics	X									
Medical History	X									
Pre-hospital Events	X									
Informed consent	X									
GCS	X	X	X	X	X	X	X			
AIS	X									
ISS	X									
Revised Trauma Score	X									
Randomization		X								
Enrollment Head CT	X									
ICP Monitor Insertion	X									

Licox Monitor Insertion Option	X									
Check Licox Monitor Function q HBO_2 Rx	X	X X	X X	X X	X X	X X				
Head CT to Check Placement	X	X								
1st HBO2 Rx		X								
HBO2 Rxs		X	X X	X X	X X	X X				
ICP Monitoring		X	X	X	X	X				
Licox Monitoring Option		X	X	X	X	X				
TILS Recording		X	X	X	X	X				
Vitals	X	X	X	X	X	X				
Labs		X	X	X	X	X				
Concomitant Medications		X	X	X	X	X				
Hospital Discharge							X			
Surgical Procedures		X	X	X	X	X	X			
GOS-E							X	X	X	
DRS								X	X	
AE (only SAEs after Day 5/Discharge)		X	X	X	X	X	X	X	X	
End of Study										X

11.2 _____

Extensive data will be collected in this clinical trial. Data collection is grouped in the following three sections.

Screening and Enrollment

a. ***Baseline:*** The data collected during the Baseline phase of the trial is used to validate eligibility for enrollment into the trial, including, but not limited to, the inclusion/exclusion criteria. Additionally, demographic information and a medical history are collected to identify pre-existing conditions and other information that may prove to be relevant to later treatment decisions. Information related to the accident (e.g., mechanism of injury, medications and fluids administered, transport mode) also is collected to ensure that all relevant information is available for assessments of the patients and their injuries. If a patient is not randomized, the reason is captured on the Screen Failure Log.

b. ***Consent:*** A written, signed, and dated informed consent document is required for this trial and will provide documentation of the date and time of the LAR's agreement to allow the patient to be a participant in the trial.

c. ***CT scans:*** The Baseline CT scan will be sent to the HCMC for review.
d. ***Prognostic Scoring:*** The Abbreviated Injury Score (AIS), Injury Severity Score (ISS), and the Revised Trauma Score are collected to allow quantitative and consistent characterization of associated injuries. .

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

Follow up (Discharge through End of Study)

   a. ***Adverse Events:*** All AEs will be recorded through 5 days following the last treatment or discharge (whichever occurs first). All SAEs will be recorded through the end of study.
   b. ***Outcome/GOS:*** The GOS-E and Disability Rating Scale (DRS) score will be obtained at 3 and 6 months by telephone interview.

11.3 _____

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

12.1 _____

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

Some examples of AEs are:

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

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

- Evidence of barotrauma, such as subcutaneous emphysema

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

12.2 _____

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

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

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

12.2.3. ***Complications that occur as a result of protocol-mandated interventions.*** Events that represent complications of study-related procedures (e.g., pneumothorax secondary to barotrauma) are considered AEs.

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

12.3 _____

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

- death;
- a life-threatening adverse experience;
- prolongation of existing hospitalization or inpatient hospitalization subsequent to initial hospital discharge; or

- a persistent or significant disability/incapacity

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

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

Reports of SAEs, as defined above, require submission to the WebDCU™ (within 24 hours of the site personnel's awareness of the event), whether or not the clinical site PI believes that the experience is related to the study treatment or an expected event. Additionally, study personnel will evaluate subjects daily while in the hospital and at each telephone communication and follow-up for the presence of SAEs. Serious AEs will be reported and recorded throughout the course of the subject's participation in the trial (6 months).

The IMM will be responsible for reviewing and coding AEs prior to being forwarded to the MSM. The IMM will also assist the PI, the CPC, and the SDMC in monitoring protocol compliance. An external MSM will review all SAEs to provide her opinion on whether the AE was a) serious, b) unexpected, and c) related to the study treatment. MSM reports that identify a possible relationship to the study treatment will be sent immediately to the HOBIT Trial PI and the Project Manager (PM). The determination of a probable or possible relationship to the HBO2 treatment will be discussed with the EC and the NINDS liaison to the DSMB to determine what, if any, action should be taken with regard to continuation of the trial. Following that determination, the PM will distribute all appropriate information to the clinical site PIs and study coordinators. The PI at each participating center is responsible for ensuring appropriate reporting of safety events to their individual IRB according to the procedures and requirements established by that IRB.

12.4 _____

Baseline FiO2 requirements will be continuously monitored, and chest radiographs are obtained daily to screen for signs of pulmonary O2 toxicity, pneumonia, and/or other pulmonary pathology. The HBO2 treatments will be discontinued if the FiO2 requirement is > 50% to maintain a PaO2 > 70 mmHg (Rockswold 1992). If there are progressive chest x-ray changes suggesting O2 toxicity, treatment will be temporarily discontinued. If the patient improves to the point that the FiO2 requirement is $\leq$ to 40%, treatments will be resumed. However, if O2 requirements again increase to FiO2 > 50%, treatments will be permanently terminated. Likewise, if PEEP requirements are > 10 cm of water, HBO2 treatments are temporarily discontinued. If requirements become < 6 cm of water, HBO2 treatments are resumed. However, if PEEP requirements again increase to > 10 cm of water, treatments are permanently terminated. Daily chest radiography is performed, and if there are changes suggesting O2 toxicity, treatment is temporarily discontinued until the chest x-ray improves.

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

13.1.0
The goal of the trial is to determine if HBO2 administered either 1.5, 2.0, or 2.5 ATA are effective every day or once a day and with NBH in the treatment of severe TBI.

13.1.1
There are ten treatment arms in the trial;

1. control (no HBO2 treatment)
2. 2.0 ATA no NBH everyday
3. 2.5 ATA no NBH everyday
4. 1.5 ATA with NBH everyday
5. 2.0 ATA with NBH everyday
6. 2.5 ATA with NBH everyday
7. 1.5 ATA no NBH twice a day
8. 2.0 ATA no NBH twice a day
9. 2.5 ATA no NBH twice a day
10. 1.5 ATA with NBH twice a day

We label the control arm as a = 1, and the experimental arms as a = 2, 3, 4, 5, 6, 7, 8, 9, and 10 respectively.

13.1.2
The primary endpoint is the 6-month GOS-E response (success or failure). Additionally each patient will have earlier, possibly associated outcome of 1-month prediction of GOS-E response.

We label the 6-month GOS-E response as Y_6. The 1-month prediction response value as Y_1.

13.1.3
The primary analysis is of the 6-month GOS-E response. The primary analysis will be that a treatment arm is superior to the control arm, meaning that the rate of response with GOS-E is greater for one experimental arm compared to the control arm. The final analysis will also identify the best treatment arm to advance to a future Phase III trial for . 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.
2. End of Enrollment Success: If at the conclusion of accrual of the 200 patients, the most likely arm has at least a 0.94 posterior probability of being better than control.
3. Early Futility: If at any interim analysis the most likely arm has at most a 0.55 posterior probability of being better than control.

Additionally a prediction of Phase III success will be calculated. If recommended novel treatment has a greater than 50% probability of HBO2 treatment demonstrating improvement versus placebo in a subsequent confirmatory trial.

13.1.4
The following subject groups or analysis populations will be used to complete the analysis of data:

Intent-to-treat patient population: The ITT patient population will include all patients randomized,

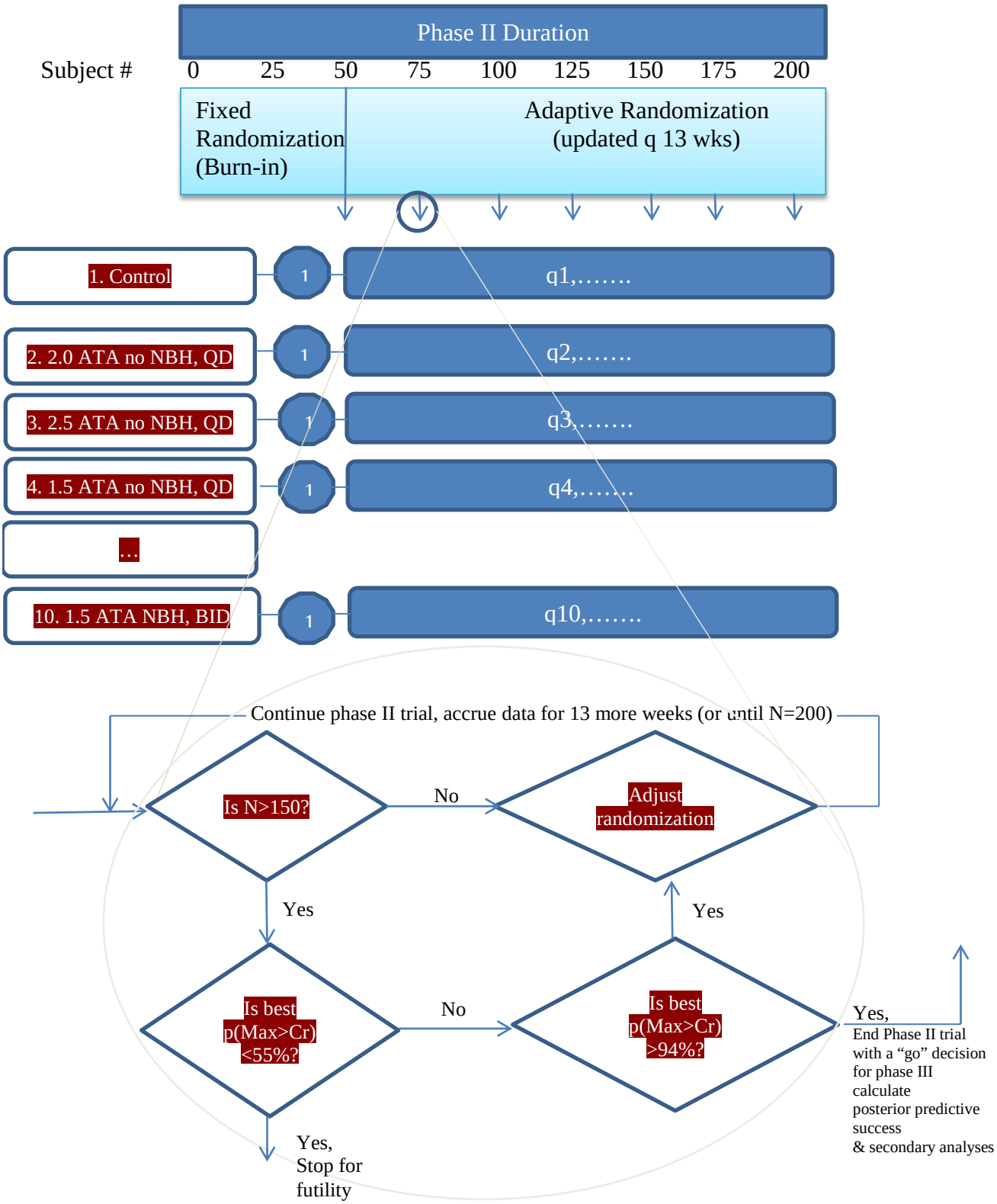
where patients will be classified by the group in which they are randomized, regardless of the treatment received.

13.1.5
The design is a novel Phase II adaptive design (see Figure 1). The purpose of the trial is to explore the different active treatment arms for relative efficacy and comparison to the control arm. The trial will utilize response adaptive randomization to favor the better performing experimental arms. If there is at least one experimental treatment arm promising enough it will advance to a Phase III trial and be compared for superiority to the control arm.

1. Burn-in Phase: An initial burn-in period of 50 subjects is used in which these patients are enrolled in a fixed randomization to the control and each of the experimental arms. A ratio of 1:1:1:1:1:1:1:1:1 will be used for the burn-in period.
2. Adaptive Randomization Phase: After the initial burn-in period adaptive randomization will be utilized. A vector of probabilities, $\boldsymbol{q}=(q_2, q_3, q_4, q_5, q_6, q_7, q_8, q_9, q_{10})$, is created for randomizing to the experimental arms. A constant proportion of 20% of patients will be enrolled to the control arm through Phase II. Interim analyses will take place quarterly to adjust the randomization probabilities based on the current data. The probabilities will be set to be proportional to the probability each experimental arm is the maximally effective treatment arm.
3. Advancing to Phase III: Possibility of early advance to Phase III.
4. Futility During Phase II: The trial can stop for futility if the probability of Phase II success drops below 55% for all experimental treatment arms.
5. The final analysis will be conducted after all subjects have completed 6-month GOS-E response.

Phase II information will be used to predict the probability of a successful Phase III clinical trial (equally randomized to usual care or novel treatment) to confirm the efficacy of novel treatment to increase response and confirm the safety of treating severe TBI with optimal HBO2 compared to usual care. The primary outcome for the Phase III trial will be the same as in Phase II (sliding dichotomized GOS-E at 6 months). The primary analysis in Phase III investigates, with two sample proportions test (chi-square test), whether there is a simple difference between usual care and novel treatment. The sample size for Phase III is assumed to be 500 in control and 500 in the novel treatment (total n=1000), and alpha =.05 2-tailed).

Figure 1: Trial design, and stopping (go/no go) rules.



13.2.0
This section describes the statistical modeling used in the adaptive design and the primary analysis. The modeling is Bayesian in nature.

13.2.1
The primary outcome is 6-month GOS-E response. We label the observations of the 6-month GOS-E response for subject *i*, at the 6-month visit as $Y_{i,6}$. We model the 6-smonth primary outcomes as Bernoulli distributed. The model is

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

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

We label the 6-month GOS-E response for arm *a* as θ_a. Based on prior studies, it is expected GOS-E response for control group and novel treatment have the following prior distributions:

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

and

$$\text{logit}(\theta_a)\sim N(0,1.75^2), \text{ novel treatments } a=2,3,4,\ldots,10.$$

The control prior is equivalent to eight observations worth of weight the novel treatment's prior is equivalent to two observations.

13.2.1.1
The main effects model is

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

for subject *i*.

We construct a main effects model for the GOS-E response rate that is a function of pressure, NBH, and duration. The logit transformation of P_i is modeled with a linear equation. By assuming no interaction among the main factors, this model has a lower number of parameters and is designed to increase ability to predict phase III success. The structure is

$$\begin{gathered} logit(\mathrm{P_i}) = X_{i1}\mu + \\ + X_{i2}\alpha_{1.5ATA} + X_{i3}\alpha_{2.0ATA} + X_{i4}\alpha_{2.5ATA} \\ + X_{i5}\gamma_{NBH} + X_{i6}\gamma_{no\ NBH} \\ + X_{i7}\beta_{BID} + X_{i8}\beta_{QD}. \end{gathered}$$

The *X*s are 0 or 1 depending on the treatment combination subject *i* is assigned. μ represents the effect of control. The α's represent the additional effect of pressure relative to control. The γ's and β's represent the additional effect of NBH and BID respectively. Note: to identify, set $\gamma_{no\ NBH} = 0$ and β_{QD}=0. The main effects model relates to the control and treatment arms in the following way:

1. control (no HBO2 treatment) μ

2. 2.0 ATA no NBH everyday	$\mu + \alpha_{2.0ATA} + \beta_{BID}$
3. 2.5 ATA no NBH everyday	$\mu + \alpha_{2.5ATA} + \beta_{BID}$
4. 1.5 ATA with NBH everyday	$\mu + \alpha_{1.5ATA} + \gamma_{NBH}$
5. 2.0 ATA with NBH everyday	$\mu + \alpha_{2.0ATA} + \gamma_{NBH}$
6. 2.5 ATA with NBH everyday	$\mu + \alpha_{2.5ATA} + \gamma_{NBH}$
7. 1.5 ATA no NBH twice a day	$\mu + \alpha_{1.5ATA} + \beta_{BID}$
8. 2.0 ATA no NBH twice a day	$\mu + \alpha_{2.0ATA} + \beta_{BID}$
9. 2.5 ATA no NBH twice a day	$\mu + \alpha_{2.5ATA} + \beta_{BID}$
10. 1.5 ATA with NBH twice a day	$\mu + \alpha_{1.5ATA} + \gamma_{NBH} + \beta_{BID}$

Based on prior studies, it is expected GOS-E response for control group and novel treatment have the following prior distributions:

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

and

$$\text{logit}(\textit{all other parameters}) \sim N(0, 10^2).$$

The control prior is equivalent to eight observations worth of weight the novel treatment's prior is equivalent to close to 0 observations.

13.2.2
At each interim analysis there will be subjects who could have complete or incomplete information. Some subjects will have complete information on their six-month observation, $Y_{i,6}$. These subjects may also have their interim value, $Y_{i,1}$. There will be subjects with interim observations response, but no six-month value. There will be subjects with no observations.

We utilize the information from subjects with incomplete information to the extent that the interim values are predictive of the final six-month values. A Bayesian model is built to learn from the accruing information (those subjects with complete six-month data) in the early response values to the final endpoint of six-month response.

Estimate transition probabilities from outcome at early time point to final outcome. The number of transitions to final outcome given early outcome is distributed as Binomial. Let p21 and p22 be conditional on a patient showing early response, the respective final probabilities of response and not responsive. For these we use a Beta prior on transition probabilities, (p21,p22)~Beta(20,5). Similarly for a patient that shows no response early, the final prior probabilities are (p31,p32)~Beta(5,20). These are fairly diffuse, each having a prior sample size equivalent to 25 patients.

13.2.3
The following Bayesian quantities are calculated at each interim analysis. These quantities are used in the adaptive design.

13.2.3.1 *Most Likely Maximum Effective Duration*
From the joint posterior distribution the posterior probability that each arm, *a*=2,3,4,…,10 is the maximally effective arm, $P_a^{\max}$, is calculated. The arm with the largest $P_a^{\max}$ is labeled the *most likely maximum effective novel treatment.*

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

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

$$\Pr(\theta_a > \theta_1 | \text{data}), \text{ where } a=2,3,4,\ldots,10.$$

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

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

13.2.4
During the defined burn-in period (50 subjects) the allocation is set at 1:1:1:1:1:1:1:1:1:1 for arms 1,2,3,….,10, respectively. During the adaptive allocation in Phase II randomization will be used in which the allocation probabilities are updated monthly to favor those durations most likely to be the maximum effective treatment arm.

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

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

A *component,* V_a, is constructed for each arm. Set V_1=1, assuring 1/5 probability for control arm throughout the trial. The component for arms *a*=2,3,4,…,10 is

$$V_a = P_a^{\max} \text{ for } a=2,3,4,\ldots,10.$$

The randomization vector, $\boldsymbol{q}$, is set as

$$q_a = V_a/10 \text{ for } a=1,2,3.$$

13.3
Computations were performed using three types of software: Fixed and Adaptive Clinical Trial Simulator (FACTS) (Berry 2010), R (R Core Team 2013), and WinBUGS (Lunn 2000). The main effects model with the longitudinal modeling and RAR was performed in FACTS. The main effects model was performed in R2WinBUGS with custom coding.

First, 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 but accessed through an interactive graphical user interface and does not require programming knowledge to use. While FACTS is very powerful and flexible it does not currently have the capability to implement a main effects model. It was decided to use the flexibility and speed to simulate the cells model in FACTS and then use the data output to call a program in R2WinBUGS that was written specifically for making Phase III predictions. The posterior simulated draws in FACTS were 1,000 burn-in and then 2,500 draws for inference. In WinBUGS the burn-in was 1,000 and 1,000 draws for inference.

13.4

In this section we summarize the results of several simulation cases and an additional scenario of a null scenario in order to ensure type I error control of the design. For each of the cases 1,000 trials are simulated. We present the results as a function of the final 6-month GOS-E response for each of the arms.

For all simulations in this section we assume an accrual rate of 1.75 subjects per week. No drop outs are assumed.

The study is classified as a success if a target duration arm is identified and recommended to be carried to Phase III. In the simulations if a trial enters the possible success or futility stage the trial is stopped in the simulation.

Several cases are presented in Table 1. The value in each cell is the GOS-E response at 6-months. The first case is referred to as the *null hypothesis* as each of the arms have identical GOS-E responses—the novel treatment has no effect on GOS-E response relative to the control arm. The remaining six cases explore scenarios with different GOS-E responses for the experimental arms, including one case where harm is exhibited. The six cases involved are small, medium, and large. Also investigated is a case where the GOS-E response is the factor pressure both as medium and large effects.

Case	Control	1.5, NBH, QD	2.0, NBH, QD	2.5, NBH, QD	1.5, no NBH, BID	2.0, no NBH, BID	2.5, no NBH, BID	1.5, NBH, BID	2.0, no NBH, QD	2.5, no NBH, QD
1. None	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
2. Small Main	0.4	0.45	0.5	0.43	0.45	0.5	0.43	0.48	0.48	0.4
3. Medium Main	0.4	0.5	0.55	0.48	0.5	0.5	0.48	0.55	0.5	0.43
4. Large Main	0.4	0.57	0.7	0.52	0.57	0.7	0.52	0.65	0.63	0.45
5. Harm	0.4	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35

Table 1: The seven cases used to evaluate the trial design. For each treatment arm, the 6-month GOS-E response is reported.

13.4.1

For the purposes of this investigation power for this phase II trial, futility probability, sample size, time (duration), and subject allocation is calculated for the several different cases. We

performed five sets of trial simulations based on the various cases of response shown in Table 2. Each set involved 1000 trial simulations. We highlight four cases. The first uses a medium case . If there is a medium effect, we estimated (identified) that 65% power, 6% futility, the sample size of this trial scenario was on average 187 (36% of these in one of the three 2.0 ATA treatments), and probability greater than 50% probability of Phase III success 71%. The average length of this trial scenario was 131 weeks. The second uses a large case . If there is a large effect, we estimated (identified) that 96% power, 1% futility, the sample size of this trial scenario was on average 174 (45% of these in one of the three 2.0 ATA treatments), and probability greater than 50% probability of Phase III success 98%. The average length of this trial scenario was 125 weeks. The third is the highly unlikely scenario that serves as our null hypothesis). In this scenario there is no difference between the treatments. Therefore, the extent to which this scenario is "successful" actually reflects our Type I error rate. Thus this trial scenario produced an appropriate expected Type I error (α=20%). The sample size of this scenario on average was 186 subjects (equally allocated across groups). The average length of the trials under this scenario was 119 weeks. The futility probability is 34%. The probability greater than 50% probability of Phase III success is 20%.

1. None	0.20	0.34	176	118	33%	0.20
2. Small Main	0.48	0.13	186	129	38%	0.51
3. Medium Main	0.65	0.06	187	131	36%	0.71
4. Large Main	0.96	0.01	174	125	45%	0.98
5. Harm	0.09	0.57	158	102	33%	0.08

*New calculation based on main effects model (S=1000).

Table 2: Simulated trial operating characteristics.

13.4.2

This study, in addition to identifying the optimal dose, offers the opportunity to explore the treatment effect in other important outcome domains using the 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. It is anticipated that the AUC for ICP in patients with novel treatment will drop on average between 75 and 100 mmHg* hour relative to control to determine power, use type I error or 0.2, a standard deviation of 150 mmHg* hour and a *main effects model* for continuous response. With the average allocation of patients dictated from the response adaptive randomization, we have between 75 and 92% power to detect a shift in patients receiving novel treatment relative to control. Note that 75 mmHg* hour is equal to reducing ICP from 25 to 20 mmHg for 15 hours (25-20 = 5 x 15 = 75). Additionally, (1) the TIL scores for controlling ICP in HBO2-treated patients will be compared to controls; and (2) utilizing Licox brain tissue PO2 monitoring, the level and duration of brain tissue hypoxia (brain tissue

PO2 < 15 mmHg) using AUC methodology in HBO2-treated groups versus control will be analyzed. Both of these analyses will be modeled using two continuous versions of the main effects model. The power for these two models is anticipated to be no less than the power for the ICP model (Rockswold 2010, Rockswold 2013).

13.5.0

13.5.1

For the final analysis of the primary safety outcome, Bayesian survival curves will be generated for deaths from any cause within 28 days and at 3 and 6 months.

13.5.3.2

The review of safety data will focus on the following potentially associated AEs:

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

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

13.5.2

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

methods will yield similar inferences, particularly if the missing data are minimal (<5%). We plan to implement the multiple imputation method using the Bayesian longitudinal model.

13.6 _____

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

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

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

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

At regular intervals, the EC will review the material and discuss, among other items, any concerns regarding the principles and intensity of the overall care at particular sites and

aggregations of protocol violations/deviations at particular sites. The EC may recommend that individual sites be contacted to discuss the issues identified at those sites and potential remedial measures. As a result of these reviews, the EC may make recommendations for protocol changes if serious safety concerns arise or there is an overarching issue with implementation of the protocol.

14.1

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

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

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

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

14.2

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

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

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

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

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

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

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

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

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

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

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

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

14.3 _____

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

EC-requested source data reviews based on the per-subject evaluation of safety parameters defined in the protocol. All data monitored on site are verified for accuracy and thoroughness using the most appropriate source documents for all subjects.

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

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

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

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

14.4 _____

Safety assessments will consist of monitoring and reporting AEs and SEAs, both anticipated and unanticipated. Clinical performance sites are instructed to report all fatal events, SAEs, and other unanticipated problems in the WebDCU™ database system within 24 hours of first knowledge of the event. Additionally, all current study data for that particular subject must be entered to allow for timely review by the internal and external MSMs. Upon entry of a SAE, the WebDCU™ system triggers notification of the SAE to the PM and the IMM. When the SAE report has been reviewed and deemed to be adequate, the SAE is forwarded to the MSM.

The MSM conducts independent blinded reviews of all SAEs entered into WebDCU™. Should the IMM or MSM need additional subject data to conduct the review, those data may be accessed on the WebDCU™. The MSM also may contact the site personnel for more information or discussion. The MSM submits her opinion on whether the AE was a) serious, b) unexpected, and c) related to the study treatment within 72 hours of notification of the SAE.

When there is disagreement between the Investigator and the MSM on one or more of these criteria, the SAE will be reviewed by the second MSM, the MSM not conducting the original review, who will act as the arbiter. If the investigator and the MSM believe the AE is serious, study related (possibly, probably or definitely), and unexpected, the SAE will be sent immediately to the HOBIT Trial sponsor/investigator and PM. The determination of a probable or possible relationship to the HBO2 treatment will be discussed with the EC and the NINDS

liaison to the DSMB to determine what, if any, action should be taken with regard to continuation of the trial.

Following the determinations made by the EC and DSMB, the PM will distribute all appropriate information to the clinical site PIs and SCs. Each clinical site PI is then responsible for reporting to their individual clinical site IRB per local requirements.

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

15.1 _____

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

15.2 _____

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

15.3 _____

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

Publication of the results of this trial will be governed by the policies and procedures developed by the EC. The Publication Policy will be fully compliant with the voluntary NIH Public Access Policy mandated by the Consolidated Appropriations Act of 2008 (Division G, Title

II, Section 218 of PL 110-161). The EC will follow NIH policies on data-sharing (as described at the site: http://grants2.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm and any updates thereto).

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

1	Minor
2	Moderate
3	Serious
4	Severe
5	Critical
6	Un-survivable

	Cerebral contusion	3	9
	No injury	0	
	Flail chest	4	16
	Minor contusion of liver Complex rupture spleen	2 5	25
	Fractured femur	3	
	No injury	0	

13-15	> 89	10-29	4
9-12	76-89	> 29	3
6-8	50-75	6-9	2
4-5	1-49	1-5	1
3	0	0	0

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

	TILBasic = TIL Basic; Global summary measure of therapy intensity level for control of intracranial pressure (ICP).
	This summary measure captures a global categorization of therapy intensity over a given period. This may be assessed on a daily basis or represent a single summary measure over the entire ICU period.
	Chart review by investigator or trained research assistant.
	Categorical measure; unique entry
	_____ No specific ICP directed therapy _____ - Sedation for ventilator/endotracheal tube tolerance - Volume/vasopressors for non-CNS cause (e.g. sepsis, myocardial injury) - Head up positioning (ventilator bundle) - Normocapnia (PaCO2 ≥ 40mmHg) _____ - Higher levels of sedation - Vasopressors/volume for CPP support - Low dose osmotic therapy - Mild hypocapnia (PaCO2 4.6-5.3 kPa; 35-40 mmHg) - CSF drainage < 120 ml/day (<5 ml/hour) _____ - Higher doses of osmotic therapy - Moderate hypocapnia (PaCO2 4.0-4.5 kPa; 30-35 mmHg) - Mild hypothermia (> 35oC) - CSF drainage ≥ 120 ml/day (>5 ml/hour) - Profound hypocapnia (PaCO2 < 4.0 kPa; < 30 mmHg) - Hypothermia < 35 oC - Metabolic suppression for control of ICP - Surgery for refractory ICP (decompression, lobectomy)
	Basic
	A judgement of the basic TIL for a given period should be recorded by the investigator or a trained research assistant and entered as a single data entry for that period.

Interpretation of data on ICP is difficult without some reference to the intensity of therapy directed at control of ICP. Therapy Intensity Level can be documented in great detail. The aim of the basic-TIL classification scheme is to broadly categorize treatments into different levels.
Level 0: no specific ICP directed therapy
Level 1: this category includes any intervention required for general ICU care. This can include sedation. The dose of sedation is not specified, since sedation requirements and specific drug use are known to vary between centers and patients; the requirement is that sedative use in this category is not targeted to control ICP. Similarly, the use of vasoactive drugs (e.g. for sepsis) may vary between centers, but at this level they would not be used to support CPP. The underlying implication is that ICP and compliance are a concern in this group of patients.

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

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

TIL 1	0-3
TIL 2	4-6
TIL 3	8-10
TIL 4	≥ 11

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

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

Treatment # _____
Date _____

This checklist is required for each treatment.
Please involve ALL staff working with the patient as you work through this checklist. HBO Staff must initial each item and signature on last page with final check.

Prior to treatment:

_____ Notify HBO nurse (336-0633) that there is a head trauma study patient. _____

_____ Bilateral myringotomies performed by neurosurgery team. _____

_____ Chest x-ray: If pt has had any new invasive chest procedure since last chest x-ray _____

Patient Preparation:

_____ Remove all patient clothing, except patient gown. _____

_____ Remove all jewelry; cover any sharp equipment to prevent scratching inside of chamber, such as fixators. _____

_____ Cover all wounds or lacerations completely with dry dressings. If large wounds with copious amount of medications/ointments, or solution other than NS, notify HBO RN. _____

_____ Remove any petroleum or alcohol products. _____

_____ Remove all medication patches and get orders for substitute IV medications if needed. If this is not possible, notify the HBO RN prior to transporting the patient to the HBO suite. _____

_____ Bring medications with patient (the chamber stocks only emergency drugs). _____

_____ Bring any medications that are scheduled during next 2-3 hours. _____

_____ Bring any prn medication that the patient may require. _____

_____ Hep-lock all non-essential IV fluids (remember that there are only passthroughs on the chamber for IV lines, and lines cannot be piggybacked). _____

_____ Bring enough IV fluids, drips, and medications to last 2-3 hours. _____

Adapt equipment before leaving SICU

_____ If patient has chest tubes- verify that Vaseline gauze at insertion sites are completely covered with dry dressings _____

_____ Remove Sierra suction and apply Heimlich valve to chest tube _____

_____ Place Heimlich valves to foley bag to collect drainage, or to sterile glove if minimal drainage _____

_____ NG tubes to sputum trap,drainage bag or glove during treatment. _____

_____ Feeding tubes should be turned off, flushed and clamped for HBO treatment. _____

_____ If patient has internal pacemaker/defibrillator, notify HBO RN. _____

_____ External pacemakers _____

_____ Empty foley and ostomy bags if monitoring is required or bags full. _____

30 minutes prior to treatment:

_____ Check patients blood sugar, titrate insulin accordingly to keep blood sugar greater than 100. _____
BS = _____ Time _____

_____ Assess lungs. Administer nebs and suction accordingly. _____

_____ Remember that suction for patient while in chamber. _____

_____ Monitor patient temperature. If temperature greater than 100.5 or 38.0 administer Tylenol/Ibuprofen per MD orders. If patient not responsive To medication, notify HBO RN that patient is febrile. _____

_____ Adequately sedate/paralyze for HBO treatment. Pt should be well sedated _____

During transport to Hyperbaric Suite:

_____ Manage airway. Call RT to bag pt to HBO. HBO has a ventilator _____

_____ Manage ventriculostomy and drains. _____

_____ Monitor patient using transport monitors. HBO has M90 monitor equipment _____

At Hyperbaric Suite:

_____ HBO RN to notify HBO MD that tx is underway _____

_____ Place Wedge under head to elevate patient if needed. _____

_____ Air removed from ETT cuff and replaced with NS per RT or RN _____

_____ Patient applied to Magellan Vent. _____

_____ Apply HBO tubing to IV tubing and passthrough chamber hull. (Max of running lines). _____

_____ Apply “Hyperbaric Tubing” label to extension tubing. _____

_____ Change pressure occlusion limit on pumps from 300mmHg to 750mmHg. _____

Connect monitoring equipment:

_____ EKG _____

_____ BP cuff (CAS monitor) _____

_____ Arterial Line _____

_____ ICP (ventriculostomy closed to drain throughout HBO treatment unless Neurosurg team determines ICP too high to remain closed) _____

_____ Cerebral tissue oxygenation done by Research staff _____

_____ Calibrate Arterial Line if needed _____

_____ Calibrate ICP if needed _____

_____ Apply bilateral wrist restraints. _____

_____ Apply ground strap _____

_____ Open JP drains to air. _____

_____ Close Ventric for continuous monitoring unless otherwise directed _____

_____ Apply NBP cuff via CAS monitor and check functionality _____

_____ Check that all lines and drains are secure and positioned correctly for treatment. _____

_____ Suction patient if needed/ check breath sounds _____

During Treatment:

- Administer medications as needed. Monitor sedation needs.
- Monitor patient per ICU protocol.

Post Treatment:

_____ Remove ETT cuff NS and replace with air. _____

_____ Assess breath sounds bilaterally. _____

_____ Keep hyperbaric tubing attached to running lines, unless otherwise Indicated per IV policy. To be re-used for complete HBO series _____

_____ Change IV pump occlusion pressure limit back to 300mmHg _____

- Return patient to SICU with RT in attendance

_____ _____

SICU RN signature HBO RN signature

Others in attendance:

_____ HBO Tech

_____ RT

_____ Head Study Researcher

_____

Date

Additional comments or issues:

☐ Plug in Alarm box for gas in Gas Room
☐ Turn On Gas Room Tanks / bottles

☐ In Use	HP O2 at psi (min. 700psi)
☐ Reserve	HP O2 at psi (min. 1500psi)
☐ O2 Regulator at	psi
☐ In Use	HP Air at psi (min. 700psi)
☐ Reserve	HP Air at psi (min. 1500psi)
☐ Air Regulator at	psi
☐ Mixed Gas Type	
☐ In Use	HP mix at psi (min. 700psi)
☐ Reserve	HP mix at psi (min. 1500psi)
☐ Mixed Gas Regulator at	psi

☐ IMV/CPAP Flow knob on ventilator turned off
☐ Open shut-off valve to Ventilator Drive gas hose
☐ Disconnect Ohmeda Charger adapter (Run monitor on battery only)
☐ Verify sensor clip is labeled as “Heat Resistors Disconnected”
☐ Verify Current limiting fuses (150mA) on supply and return of sensor clip circuit.
☐ Turn On Ohmeda Volume Monitor
☐ Ohmeda sensor on patient exhaust side
☐ Wright Respirometer visible and connected to exhaust
☐ Set ventilator to approx.
☐ Set and test Ohmeda Hi/Low and Apnea alarms
☐ Exhalation valve working properly
☐ Test Pressure both Pop-off valves (55 – 65 cmH2O)
☐ Check valve in place
☐ Safety breathing valve with proper flow direction
☐ Both Pressure manometers working
☐ PEEP valve in upright position
☐ All patient circuit connections secure
☐ Pre-run 15 – 30 min.
☐ Volume and rate stable after warm-up?

☐ Turn on power to chamber.
☐ Chamber “Supply Open” valve on
☐ Select chamber wall supply: Air____ / Oxygen ____
☐ Hospital wall pressure at 50 – 65 psi
☐ Turn on and calibrate Oxygen monitor (20.8%)
☐ O2 sensor connected to sample line and monitor alarms set for 23% O2
☐ Log on to computer and Select Dive Profile
☐ Inspect Acrylic for scratches, cracks, crazing
☐ Inspect door gaskets & O-ring

- ☐ Inspect penetrations, IV's, secure and ready
- ☐ Inspect cables and tubes for kinks, etc.
- ☐ Manual Vent Control off on chamber
- ☐ Manual Pressure Control off on chamber
- ☐ Inside clean and no contraband items
- ☐ Oxygen delivery device ready for patient
- ☐ Gurney and litter ready for patient
- ☐ Ground strap ready
- ☐ Patient monitor on and ready
- ☐ Cass Monitor ready
- ☐ Entry in Chamber Daily & Monthly PM logs
- ☐ Dive / Pt TX log ready

Comments:_____
Date/Time_____
CHT sign_____

- ☐ Enter patient info in chamber computer
- ☐ Proper clothing
- ☐ No contraband, plastic sheets, etc.
- ☐ Ground strap on
- ☐ Log book ready with patient info and run info
- ☐ NG tube clamped or in glove if needed for drainage.
- ☐ Foley bag ready
- ☐ NS or water in ET cuff
- ☐ Vent circuits secure
- ☐ VT_____ RR_____
- ☐ PIP's_____ PEEP_____
- ☐ BS equal
- ☐ Suction ET tube Yes / No
- ☐ Verify Vent Alarms (MV & Apnea) set and working
- ☐ Patient circuit connections secure
- ☐ Wrist restraints on
- ☐ CASS monitor on and approx. with art line
- ☐ O2 monitor alarms set at 23% and sample line ready
- ☐ Ventric drain open
- ☐ JP line open
- ☐ ECG, IV's, pressure lines, and monitors all working
- ☐ ENSURE OHMEDA CHARGER IS DISCONNECTED (Battery power only during treatment)
- ☐ Current limiting fuses (150mA) on supply and return of Sensor Clip circuit.
- ☐ Sensor Clip labeled as "Heat resistors Disconnected"
- ☐ Wright Respirometer visible and working on exhaust tubing of ventilator.

Comments_____

_____

Date/Time_____
CHT sign_____

_____

- ☐ Chambers, monitors, vent, etc, all off
- ☐ Treatment log completed
- ☐ Chamber Maintenance log completed
- ☐ Clean all patient care equipment
- ☐ Wipe down wires, tubing, etc. and wind up
- ☐ Clean and disinfect chamber inside and out
- ☐ Restock and order supplies
- ☐ Set up chamber and ventilator for next TX
- ☐ Turn off all gases in gas room
- ☐ Unplug gas alarms in gas room
- ☐ Bleed gas room pressures to zero and silence alarm
- ☐ Turn off “Shut Off” valve in vent supply line
- ☐ Order replacement “H” cylinders as needed
- ☐ Turn chamber wall supply gas to OFF
- ☐ Test vent circuit for volume with Ohmeda monitor
- ☐ Test popoff valve and set to 60 cmH2O
- ☐ Plug in Ohmeda monitor to battery charger
- ☐ Only use sensor clip labeled as “Heat Resistors Disconnected”
- ☐ Ensure the current limiting fuses (150mA) are on the supply and return current path of Ohemda sensor clip circuit
- ☐ Put Wright Respirometer on Exhaust side

Supplies needed:

1._____ 6._____
2._____ 7._____
3._____ 8._____
4._____ 9._____
5._____ 10._____

Comments_____

CHRN/CHT_____ Date/Time _____

1. In general, TBI patients who have also suffered injuries to organ systems in addition to the central nervous system should be admitted to and managed by the trauma service or trauma critical care service, with neurosurgeons and neurointensivists providing consultation for management of the brain injury. Other shared arrangements are acceptable but must be consistently applied.
2. Neurosurgery consultation should occur in any patient with suspected brain injury at the earliest time possible, ideally soon after patient arrives in the emergency department. If neurosurgical representation is not available for the initial trauma resuscitation, CT scan imaging and subsequent consultation should occur within 2 hours of arrival of the patient to the emergency department/hospital.

Care of patients with brain injuries can be admitted to or transferred to the neurosurgical service/neurointensivist service once other injuries are ruled out, or the patient is sufficiently stabilized. Those patients with an isolated brain injury may be admitted directly to the neurosurgical service/neurointensivist service.

For the purpose of all patients enrolled in the HOBIT trial, the following physiological parameters should be maintained as part of the goal-directed TBI treatment.

□ Pulse Ox ≥ 90%	□ ICP < 20 mmHg	□ Physiologic Na+ 135-145*
□ PaO_2 ≥ 100 mmHg	□ $PbtO_2$ ≥ 15 mmHg	□ INR ≤ 1.4
□ $PaCO_2$ 35-45 mmHg	□ ≥	□ PLTS ≥ 75 x 10^3 / mm^3
□ SBP ≥ 100 mmHg	□ Temp 36.0-38.3°C	□ Hgb ≥ 8 gm/dl
□ pH 7.35-7.45	□ Glucose 80-180 mg/dL	

**Hypertonic saline therapy: Na+ range: 145 mmol/L (minimum) to 160 mmol/L (maximum)*

1. – Patients should undergo endotracheal intubation with inline cervical spine immobilization. Rapid sequence intubation is the preferred method.
2. through the initial resuscitation, as temporal assessment of neurological status is critical. The selection of specific agents is left up to the site. However, in general we recommend the following agents:

   - - sedation/induction
   - , - paralytic

- - maintenance of sedation, prevention of agitation. Propofol is strongly recommended as the choice for sedation, as it allows for rapid titration and has a short half life, allowing for frequent reassessment of the neurological exam.

≥ 100 mmHg and O Sat ≥

Oxygen saturation should be monitored continuously, both in the pre-hospital and hospital setting. End-tidal CO_2 ($ETCO_2$) should be monitored both in the pre-hospital and ED setting.

1. - Efforts should be made to avoid hypoxia at all times.

   - Intubated patients **should be maintained at ≥ 100 mmHg,** except during weaning.
   - Pulse oximetry > 90 % remains goal during ventilation wean.
   - Monitoring via arterial line placement and serial arterial blood gas testing should be performed.
2. Hyperventilation should be intensively avoided during the initial resuscitation.

   -
   - A CO_2 monitor and other devices to assist in the prevention of hypocarbia / hypercarbia should be utilized to .
   - EMS services that employ intubation should use $ETCO_2$ monitors or ventilation counters to maintain a eucarbic state and to avoid rapid ventilation during transport and evaluation.
   - Prophylactic hyperventilation ($PaCO_2$ < 35 mmHg) is prohibited.
   - Therapeutic hyperventilation may be necessary for brief periods when there is acute neurological deterioration that coincides with a cerebral herniation syndrome or for refractory elevations in ICP (see Tier II section on management of ICP).

1. – Systolic blood pressure (SBP) and mean arterial pressure (MAP) readings should be recorded from a functioning arterial line.

   -

   - Recognize that lower blood pressures can represent a “relative” hypotensive state in TBI patients (especially with elevated ICP)
   - Normal Saline Fluid should be used as the initial method of maintaining euvolemia to achieve the target blood pressure.
   - Assessment for transfusion and/or implementation of vasoactive drugs should be considered for treatment of hypotension. Such Vasopressors or Inotrops include Phenylephrine (Neosynephrine), Levophed, Epinephrine, Dobutamine, and Vasopressin.
2. – Monitoring euvolemia will be per site protocol. In many cases a central venous pressure (CVP) monitor will be placed. A CVP goal of 5-7 mmHg correlates with euvolemia, but should be assessed in the context of the individual patient’s clinical picture. The specific tools for assessing euvolemia may be determined per site protocols.

   - Brain-injured patients should be maintained in a euvolemic state with volume

replacement of blood products and crystalloid.

- The initial resuscitation fluid should be normal saline. Hypertonic saline should only be used as a secondary osmotic agent in ICP control (see Section IV Tier 2).
- Volume resuscitation to achieve euvolemia should NOT be withheld to prevent concerns with cerebral edema.
- Conversely, hypervolemia should be avoided as it is associated with increased incidence of ARDS in TBI patients.
- Refer to the section on blood pressure management for the list of acceptable vasopressors and inotropic adjuncts.

3. The is to keep hemoglobin concentration at . We recognize this is a highly controversial area with limited data for evidence-based guidelines. The hemoglobin goal of ≥ 8 g/dl should be used to maintain consistency between sites.

   - The hemoglobin concentration (Hgb) of the patient should be maintained at ≥ 8 g/dL
   - Blood should be transfused for Hg < 8 g/dL.

4. – Coagulation panels should be followed closely. It is acceptable to use a stricter transfusion criteria, such as Platelet count of ≥ 100 x 10^3/mm^3.

   - The

   - FFP, Vitamin K, Factor VII, DDAVP, or prothrombin complex concentrate should be administered, as clinically indicated, in order to correct coagulopathy.
   - INR and platelet count should be corrected in anticipation of placement of ventriculostomy, or other intracranial surgery.
   - Platelets should be transfused for a platelet count < 75 x 10^3 / mm^3.

(unless there is a direct contraindication to invasive monitoring, such as INR >1.4 or platelet count of <75 x 10^3 / mm^3, in which case attempts should be made to correct these parameters in order to place a ventriculostomy).

1. ***without*** ***ventriculostomy*** A parenchymal ICP monitor may be added to the ventriculostomy according to local protocol.

2. **defined as ≥ 20 mmHg/** See section IV for treatment of increased ICP guidance on Tier Based therapy. See section V for brain tissue oxygen monitoring recommendations.

3. The preferred method for ICP monitoring and drainage is to leave the ICP device to the transducer for continuous monitoring and to drain only for elevations above the threshold (20 mm/Hg). When ICP is ≥ 20, the drain should be opened and allowed to drain to 10 cmH_2O, then returned to the transducer. Recurrent elevations and the need for multiple repeat ICP drainage actions should prompt additional therapy to lower the ICP.

4. For the determination of CPP, the ventriculostomy (ICP) is zeroed at the Foramen of Monroe using the tragus of the ear as a marker. The art line is zeroed at the left atrium.

5. Routine ventricular catheter changes, prophylactic antibiotic use, and routine surveillance cultures for ventricular catheters are not recommended.

6. **of ≥60** CPP is equal to the mean arterial pressure (MAP) minus the intracranial pressure (ICP).
- may be used to improve the CPP in the euvolemic patient in whom measures to decrease intracranial pressure have not been effective. Do not push the CPP greater than 70 mmHg. Spontaneous elevations of CPP greater than 70 mmHg are acceptable and should not be actively lowered.

- – Keep O_2 Sat >90, and PaO_2>100, and PCO_2 = 35-45.
- - avoid hypotension, Systolic >100 mmHg.
- °C: treat fever with acetaminophen and/or cooling blankets.
- placement if applicable.
- : a repeat CT scan of the brain should be done at 6-12 hours post admission to rule out the evolution or development of a surgical mass or unexpected intracranial lesion.
- : see outline in section IV.

- to be placed at ≥ 30 degrees.
- using recommended agents (propofol, fentanyl, and versed). Pain relief and sedation are appropriate initial modalities for treatment of intracranial hypertension.
- ; drain to 10 cmH_2O for ICP ≥ 20 mmHg sustained for ≥ 5min.*
- – 0.25-1.0g/kg; IV bolus x 1 dose.

*Tier 1 completed within 120 minutes, if ICP ≥ 20 mmHg/*27.2 cm H_20 *mmHg proceed to Tier 2.*

-
  - : intermittent boluses of mannitol (0.25 - 1 gm/kg body weight) should be administered. Attention must be placed upon maintaining a euvolemic state when osmotic diuresis is instituted with mannitol. The serum sodium and osmolality must be assessed frequently (every 6 hr) and additional doses should be held if the serum osmolality exceeds 320 mOsm/L. Maintain a serum OSM <320 mOsm or alternative - Osmolar gap <20. Mannitol may be held if there is evidence of hypovolemia.
  - : boluses of 3% sodium chloride solution (250 cc over ½ hour) or other concentrations (e.g. 23.4% - 30 cc) may be used. Serum sodium and osmolality must be assessed frequently (every 6 hr) and additional doses should be held if the serum sodium exceeds 160 mEq/L.
- 30 - 35 mmHg, as long as brain hypoxia is not encountered
- : pharmacologic paralysis with a continuous infusion of a neuromuscular blocking agent should be employed if the above measures fail to adequately lower the ICP and restore CPP. The infusion should be titrated to maintain at least two twitches (out of a train of four) using a peripheral nerve stimulator. Adequate sedation must be utilized if pharmacologic paralysis is employed.

Tier II completed within 120 minutes, if ICP ≥ 20 cmH_20/mmHg proceed to Tier 3.

(includes potential salvage therapies)

- should only be performed if Tiers 1 and 2 are not sufficient. Procedure per site surgical protocol.
- an induced coma is an option for those patients who have failed to respond to aggressive measures to control malignant intracranial hypertension, however it should only be instituted if a test-dose of barbituates or Propofol results in a decrease in ICP, thereby identifying the patient as a "responder". Hypotension is a frequent side effect of high dose therapy. Therefore, meticulous volume resuscitation (measured with a PA catheter) should be insured. A neosynephrine infusion may also be required.

- : Hypothermia (<36 °C) is not currently recommended as an early TBI treatment. Hypothermia should be reserved for "rescue" or salvage therapy after reasonable attempts at ICP control from the Tier treatments above have failed.
- The preferred management is to leave the monitor to the transducer (ICP readings) and to intermittently drain for ICP ≥ 20 mmHg.

Brain tissue PO2 is optional as part of the HOBIT protocol. The Licox brain tissue probe is inserted according to protocol in the least damaged frontal lobe. To confirm the Licox probe is reading accurately and placed properly, a 100% FiO_2 challenge for 20 minutes approximately 1 hour after insertion is performed. The brain tissue PO2 reading should triple within 20 minutes. If it does not, placement should be confirmed on a CT scan of the head. Readings can be erroneous if the Licox tip is within 1.5 cm of the ventricle, in hemorrhagic contusion, or in the subdural or subarachnoid space. If the catheter is in such a position, it has to be replaced. Therapeutic brain tissue PO2 goal is $\geq$ 15 mmHg. Pulmonary function directly affects brain tissue PO2. FiO_2 challenge should be repeated 2 hours prior to each subsequent HBO_2 treatment to ensure proper functioning prior to the treatment.

Algorithm for Low Brain Oxygen Level

If Hgb < 8 g/dl Transfuse with PRBC's p.r.n.
If CPP < 60 Decrease ICP (refer to section on ICP management) Increase MAP with HTS and/or pressors
Evaluate pulmonary function for pneumonia, atelectasis, pneumothorax, mucous plug, etc. Treat accordingly. Evaluate P:F ratio (PaO_2 over FiO_2) $\geq$ 300 normal $\geq$ 250 severe pneumonia $\geq$ 200 ARDS
Increase FiO_2 to achieve $PtO_2 \geq 15$ only as last resort. Decrease FiO_2 as soon as possible.

Phenytoin has proven efficacy in preventing early post-traumatic seizures in patients with traumatic brain injury.

. Dose to therapeutic level. Stop medication after 7 days if no seizure activity.

Phenytoin (or Fosphenytoin) is the recommended initial drug of choice for seizure prophylaxis in the first seven days, or in any patient demonstrating posttraumatic seizure. Use of Keppra is not recommended for seizure prophylaxis. Multiple drug regimens may be utilized at site discretion for intractable seizure treatment. There is a paucity of data studying the use of Keppra in TBI patients; additionally not all study sites have the Keppra drug on formulary. As such, the recommendation is to use Phenytoin in order to standardize across sites.

is defined as anti-seizure treatment 7 days post trauma in patients who have not had seizure activity. "Prophylactic Therapy" or "Late Therapy" in patients without evidence of prior seizure has not been shown to be effective and may cause harm to the patient, and therefore .

The use of glucocorticoids is not effective at improving outcome or reducing intracranial hypertension, and should ____ be administered.

Patients with significant traumatic brain injury requiring mechanical ventilation as well as those with coagulopathies or a history of gastric or duodenal ulcers should receive stress ulcer prophylaxis with an intravenous H-2 blocking agent, proton pump inhibitor, or sucralfate.

All patients should receive DVT prophylaxis in the form of sequential compression stockings upon admission. Subcutaneous low-dose heparin may also be initiated after 72 hours, at the discretion of the treating physicians.

Tracheostomy is recommended in ventilator dependent patients to reduce total days of ET intubation.

The baseline goal for electrolytes (such as, sodium) will be to maintain within normal range (Na 135-145 mmol/L). Patients with documented or suspected diabetes insipidus (DI) or syndrome of inappropriate antidiuretic hormone (SIADH) should have frequent (every 6 hr) monitoring of serum sodium and osmolality levels. Aggressive attempts should be made to normalize these values. In the treatment of elevated ICP with HTS, Na goal increases to a target of 145 mmol/L (lower threshold) and 160 mmol/L (upper threshold).

Hyper- and hypoglycemia are both detrimental to the outcome of patients with TBI. Therefore, serum glucose levels should be monitored in all TBI patients.

Serum glucose should be monitored frequently following the initiation of nutritional support, particularly in patients with known or suspected diabetes mellitus. Initial treatment with regular insulin for hyperglycemia is recommended, with subsequent transition to other patient specific regimens per team.

1. Frequent assessment of residual volumes of gastric nutrition should be performed, as patients with TBI frequently do not tolerate intragastric feeding, and are at risk for emesis and aspiration. Should this occur, efforts should be made to obtain small bowel feeding access.

2. If TPN use is considered unavoidable, monitoring must be done to insure that the patient remains euglycemic.

3. An immune enhancing enteral formula should be considered.

Non-emergent surgeries that require general anesthesia, such as orthopedic procedures and plastic surgery, should be avoided until it is clear that the brain injury has stabilized or resolved. Single episodes of hypotension induced during surgery can result in rapid deterioration and death.

In the case of emergency surgeries, priority should be given to maintaining target physiological parameters such as systolic blood pressure $\geq$ 100 mmHg (or higher if ICP is elevated), and oxygenation ($PaO_2 \geq 100$ mmHg and Pulse Ox ≥ 90%) in all patients. Continued ICP and $PbtO_2$ monitoring should continue in patients undergoing general anesthesia.

(consistent with Brain Trauma Foundation Guidelines)

An epidural hematoma (EDH) of greater than 30 cm^3 should be surgically removed regardless of GCS. Patients with an acute EDH and anisocoria should undergo emergent EDH evacuation.

Acute subdural hematomas (SDH) with a thickness of greater than 10 mm or 5 mm of midline shift on CT scan should be evacuated emergently. An SDH less than 10 mm thickness and less than 5 mm midline shift should be evacuated emergently if the patient has: GCS decrease by 2 points, asymmetric pupils or fixed pupils, or ICP $\geq$ 20 mmHg.

Intraparenchymal hemorrhage (IPH) causing progressive neurological deterioration, medically refractory ICP elevations, or significant mass effect should be emergently evacuated. Frontal or temporal contusions with IPH >20 cm^3 and >5 mm shift or cistern compression should be evacuated. IPH >50 cm3 should be evacuated. IPH in patients with no evidence of neurological change, and ICP <20 mmHg, and no signs of mass effect can be managed non-operatively with intensive monitoring and serial imaging.

Decompressive craniectomy (unilateral or bilateral) for refractory elevated ICP within 48 hours of injury is an option in TIER 3. Ultra early decompressive craniectomy prior to ICP monitoring is not recommended, unless surgery is performed for a mass occupying lesion (hematoma) and the bone flap is not replaced. The procedure should be applied according to individual center protocol consistently in eligible patients. Other decompressive procedures: subtemporal decompression, temporal lobectomy, and hemispheric decompressive craniectomy are treatment options for refractory increased ICP and diffuse parenchymal injury with signs of impending herniation.

Patients with posterior fossa (PF) lesions that show distortion, dislocation, or obliteration of the 4th ventricle, or compression or loss of visualization of the basal cisterns, or obstructive hydrocephalus on CT should be evacuated. PF lesions that show no evidence of mass effect and no clinical deterioration can be intensively monitored with serial imaging.

Open skull fractures depressed greater than the thickness of the inner and outer table should undergo operative management. Open depressed fractures that are less than 1cm depressed *and* have no dural penetration, no significant intracranial hematomas, no frontal sinus involvement, no gross cosmetic deformity, no pneumocephalus, and/or no gross wound contamination may be managed non-operatively. All open skull factures should be treated with prophylactic IV antibiotics, such as Vancomycin and Ceftriaxone.

It is recommended that brain death be determined per the AAN Guidelines. The following information should be documented for all patients:

- Etiology and irreversibility of condition
- Absence of brainstem reflexes
- Absence of motor response to pain

- Absence of respiration with $PCO_2 \geq 60$ mmHg
- Confirmatory test (if utilized) and result of confirmatory test (angiography, EEG, TCD, Technetium-99 scan, SSEP, etc.)
- Repeat neurologic examination. O*ption:* repeat neurological exam per site protocol (6-hour interval is reasonable).

Time and date of determination of brain death should be recorded. If the patient will serve as organ donor, please record brain death as above. Participation in study will stop at time of brain death and care may proceed as per local ICU protocols. Should the patient's family decide to withdraw care, please continue to document patient progress as per study protocols. Please date and time initial decision to withdraw care. Additionally, on each Daily Checklist CRF, note that patient is Withdrawal of Care.

Please insert name of local site PI

This consent form, a copy of which has been given to you, is only part of the process of informed consent. It should give you the basic idea of what the research is about and what is involved with participation in this trial. If you would like more detail about something mentioned here, or information not included here, you should feel free to ask. Please take the time to read this carefully and to understand any accompanying information.

The person you represent is being asked to take part in a research study. You have been asked to agree to allow the person you represent (the subject) to participate in the research. Before you agree on behalf of the subject, it is important that you read this consent form and know enough about the study's risks and benefits in order to make a decision about whether or not you want the subject to participate in this research study.

This study is being conducted under the direction of ***insert name of site PI*** at the ***insert name of institution***. You are entitled to know about the procedures, hazards, risks, discomforts, and possible benefits of this study. This information will assist you in making an informed decision about whether or not you agree on behalf of the subject to take part in this clinical research study. The person you represent has suffered a traumatic brain injury (TBI) within the past 24 hours. Anyone suffering a TBI faces the possibility of long-term disability and even death, regardless of treatment. If patients survive the initial event, the amount of improvement or recovery of function varies from case to case.

Prior studies strongly indicate that HBO2 is beneficial in improving the injuries occurring to the brain in patients suffering severe TBI. However, the exact amount of O2, including the pressure applied during HBO2 treatments, and the duration have not been determined. This trial, by applying several different HBO2 treatment schedules, is designed to answer these questions. The word hyperbaric means to increase the pressure around the patient. This feels similar to the pressure a person feels when they dive into a body of water. The use of HBO2 therapy is currently not a standard treatment for TBI. Therefore, this treatment has to be considered experimental. There will be about 200 patients at 15 institutions across the United State and

Canada involved in this study. This research study is designed so that no person shall be excluded from participation on the basis of sex, race, or national origin.

PROCEDURES AND TESTS

Some of the procedures and tests that will be performed are part of the routine care given to people with a brain injury; other procedures will be performed as part of this study. The most important procedures and tests are listed below.

The subject will take part in the study for 6 months. He/she will receive the same basic care given to all TBI patients. During the course of this study, the following will occur:

- When the subject is first seen in the emergency department, he/she will be seen by a physician and the following evaluations will be performed, some of which are performed as part of routine clinical care: a medical history will be taken, information about the accident and injury will be gathered, a physical exam, vital signs (pulse, blood pressure, breathing rate, oxygen levels in the blood); and, routine blood samples (about 3 teaspoons). A computed tomography (CT) scan, which is a special type of brain x-ray, will be performed within 15-30 minutes of his/her admission. These scans also are considered routine care.
- Patients in the Intensive Care Unit have their blood pressure, pulse, and temperature measured often. Blood pressure is measured with a small tube inserted into an artery in the wrist. Patients with a severe head injury also have their brain pressure measured through a very small tube placed inside their skull. These procedures are all considered routine care.
- To measure the oxygen and temperature in the brain, a set of miniature probes are inserted. These two probes are approximately the diameter of a mechanical pencil lead. The probe directly measures the temperature and amount of oxygen in the brain. Monitoring the oxygen delivery to the brain is considered routine care.
- If the patient is between 16 and 65 years of age and eligible to enter the study as one of possibly 200 subjects, he or she will be randomly assigned (like flipping a coin) to receive various HBO_2 treatments or a control group (standard treatment).
- If the subject is in the HBO_2 treatment group, he or she will be taken to the HBO_2 chamber. The subject will be placed on a bed inside a hyperbaric chamber which is in a large room with specially trained nurses and technicians who are in the room with the patient during this treatment.
- If the patient receives HBO2 therapy, he or she will have a procedure called a myringotomy. During this procedure, a doctor makes a pinpoint-sized hole in each eardrum. The pressure changes in the chamber can cause discomfort to the patient. Myringotomies usually help to relieve this problem.
- Subjects in the HBO_2 treatment group will breathe 100% O2 while in the HBO_2 chamber. After the first treatment, the subject will be taken to the HBO2 chamber according to the schedule assigned. The treatments will be stopped if the subject recovers enough to follow commands consistently, dies, or any other reason involving safety concerns.
- Approximately ninety (90) days after the subject's first treatment and again at 6 months, they will get a phone call from someone on the study staff who will ask questions about their quality of life, memory, and thinking, as well as if there have been any more hospitalizations or medical problems. This interview will take about 30 minutes. If the subject is unable to give the investigators information, they may contact me for the follow-up interview.

The doctors and nurses will watch the subject closely for any side effects. If the oxygen treatments become harmful, they will be temporarily or permanently stopped. Any complication will get the appropriate care.

Since oxygen is used in the hyperbaric chamber, any treatment in it carries the risk of a fire or possibly an explosion. This is extremely rare and every precaution is taken to guard against it. Also, the staff giving the treatment are all very highly trained. There has never been a fire at this hospital.

The subject will be moved from their bed to be placed in the hyperbaric chamber. The doctors and nurses have done this many times and they are able to do it safely. Also, the myringotomy holes placed in my relative's ears will heal closed with no problem within 1 week.

Sometimes oxygen treatments can cause problems with the lungs. The doctors will check the subject's sputum and chest x-rays every day and will closely observe him or her for any signs of lung changes. If changes occur, the subject will be removed from the study and will receive appropriate treatment. In extensive past experience, the lung changes have always cleared.

If the subject is in the group who receive HBO_2 treatments, the subject will be at slight risk (less than 1% risk) of developing seizures. The doctors will give the subject medications to prevent seizures. If the subject experiences a seizure, the doctors will treat the seizure and the subject will be removed from the study.

There is a possible risk of infection if sterile technique is not maintained during placement of brain probes, drains, or arterial/venous lines. Studies have shown that careful sterile technique can reduce infection rate to near zero. This sterile technique is in use at this hospital in the routine placement of medical equipment.

If the subject is a woman of childbearing potential, she can participate in the study only if she is not pregnant. A pregnancy test will be done to make sure that she is not pregnant before starting the treatment.

If you agree to allow the patient to participate in this study, there may or may not be a direct medical benefit to the subject. His/her condition may be improved during the study but there is no guarantee that this research will help him/her. The information we get from this study may help us to provide better treatments in the future for patients who suffer a TBI.

Currently there is no approved specific treatment for severe TBI patients. Participating in the HOBIT trial will not preclude the patient from getting the standard treatments.

You have been told that you will receive any new information during the course of the study concerning significant findings that may affect your willingness for the subject to continue his/her participation. Your name and address, as well as the subject's, will be retained on file at the hospital under appropriate security to notify you and/or the subject in writing of any significant new findings resulting from this study, and in case future follow-up studies become necessary.

The investigator and his/her collaborators will consider the subject's personal information confidential to the extent permitted by law. "Personal Information" means any information that can be used to identify the subject, including name or initials, date of birth, gender, ethnic origin and medical and health-related information such as blood tests, diagnostic imaging results, the results of physical examinations, medical history and hospital records.

The subject's medical and health records may be reviewed for audit purposes by authorized Hennepin County Medical Center, Clinical Coordinating Center, University of Michigan, Data Coordination Unit - Medical University of South Carolina (DCU), and/or other agents of the study who will be bound by the same provisions of confidentiality. Although every effort will be made to maintain confidentiality of the subject's medical and health records, absolute confidentiality cannot be guaranteed. The subject's personal information such as medical and health information will be used to confirm his/her eligibility for the study, to assess the results of the study for purposes of safety, and to meet applicable legal and regulatory requirements. When the study data and copies of the subject's relevant medical records are provided, they will not include the subject's name.

If the subject is transferred to another facility prior to the end of his/her participation in this study, your signature on this document authorizes the principal investigator (PI)/sub-investigator(s), or members of the Executive Committee of this study to access the subject's medical records at the new facility, if necessary.

The subject's study data and personal information (other than the subject's name and address) will be included in the study results. If the results are presented or published in medical literature, the subject will never be identified by name.

The subject's family doctor may be informed of his/her participation in this study.

A description of this clinical trial will be available on http:[sol] [sol] www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Funds are not available to cover the costs of any ongoing medical care and the subject remains responsible for the cost of non-research related care. Some of the procedures in this study are part of the standard treatment for the subject's condition and would be performed even if he or she was not in this study. The costs for these procedures will be billed to the subject's insurance company, or, if the subject is uninsured, they will be billed to the subject. The subject will be responsible for any costs his or her insurance does not cover. Tests, procedures, or other costs incurred solely for purposes of this research study, such as the treatments in the HBO_2 chamber, will not be the subject's financial responsibility. If you have questions about the subject's medical bill relative to research participation, you may contact ***insert site Investigator name.***

There will not be any payment for the subject's participation in this study.

In the event that the subject suffers injury as a result of his/her participation in this research study, no compensation will be provided for the subject by the granting agency (National

Institute of Neurological Disorders and Stroke), the *insert your institution name*, or the Researchers. The research subject still has all their legal rights. Nothing said here about treatment or compensation in any way alters their right to recover damages.

The subject's involvement in this study is entirely voluntary. The subject, or you on behalf of the subject, is free to withdraw consent at any time during the study and not participate in this study with no penalty, loss of benefits, or prejudice to his/her further care. The study physician may decide to terminate this study for either medical or other reasons (such as the research is not beneficial or if it appears to be medically harmful to the subject or for administrative reasons). You may ask and will receive answers to any questions during the course of the study. You will be informed of any significant information regarding new findings that may develop during the course of this research study that may relate to your willingness for the subject to continue in this study. If you have any questions regarding this study or if the subject experiences any side effects or medical problems, you should contact *insert site Investigator name and phone number*.

Your signature on this form indicates that you understood to your satisfaction the information regarding participation in the research project and agree to allow the person you represent to participate. In no way does this waive your legal rights nor release the investigators, sponsors, or involved institutions from their legal and professional responsibilities. You are free to withdraw the subject from the study at any time without jeopardizing their health care. If you have further questions concerning matters related to this research please contact:

insert name
insert number
: *insert number*

Subject's Name			
Surrogate's Name	Signature	Date	Time
Investigator/Delegate's Name	Signature	Date	Time
Witness' Name	Signature	Date	Time

A signed copy of this consent form has been given to you to keep for your records and reference.

Your injury made it difficult for the researchers to include you in the informed consent process. The person making medical decisions on your behalf during your illness agreed that you could be in this research study. Now that you are again able to make decisions, you can choose whether or not to remain a subject.

If you decide to stay in the study, you will be asked to review and sign the full consent form for this research.

If you decide to end your participation, your personal and medical information gathered since the start of the research project may still be used for this research.

Please check the appropriate box to indicate your decision:

❑ I wish to stay in the study

❑ I wish to end my participation in the study

_____ _____

_____ _____

_____ _____

A signed copy of this consent form has been given to you for your records and reference.

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The Data Coordination Unit (DCU) at the Medical University of South Carolina is the NETT Statistical and Data Management Center (SDMC) and will be the SDMC for the proposed HOBIT Trial. The SDMC will collaborate with the HOBIT Clinical Coordinating Center (CCC) in all aspects of trial management to ensure the efficient and proper conduct of the HOBIT protocol.

The DCU has experience managing several federally-funded, large multi-center clinical trials, including SHINE (NCT 01369069), POINT (NCT 00991029), ProTECT (NCT 00822900), ALIAS (NCT 00235495), IMS III (NCT00359424), HI-DEF (NCT01662895) and ATACH II (NCT01176565) in the neurological disorders and stroke field, and a several more in other disease areas, such as mental health, digestive diseases, liver failure and diabetes. To facilitate the operations of these trials, DCU has developed a web-based integrated clinical trial management system (CTMS), referred to as WebDCU™, providing a central information support tool for electronic data capture with real-time rule based data quality checking, subject randomization with baseline covariate imbalance control, subject study progress tracking, study drug/device distribution tracking, data monitoring, medical safety monitoring, clinical site monitoring, study outcome central review and adjudication, regulatory document management, study payment management, event/calendar driven emails, real-time secure data accessibility for all authorized study team members, and secure data protection. WebDCU™ not only eliminates burdens associated with paper-based data management practices, but also prevents data discrepancies caused by redundant data capture when several silo-type electronic data systems are used for different management tasks of the same trial. By integrating information management functions for data management and project management, the WebDCU™ enables information collected in the study database to be used immediately for trial operation management, in order to ensure study protocol compliance and timely response to action items during the course of the study. For instance, central medical safety reviewers will receive email alerts when serious adverse events are submitted into the system; the CCC will be notified to issue site payment as soon as all required Case Report Forms for a particular subject are submitted and all associated queries are resolved.

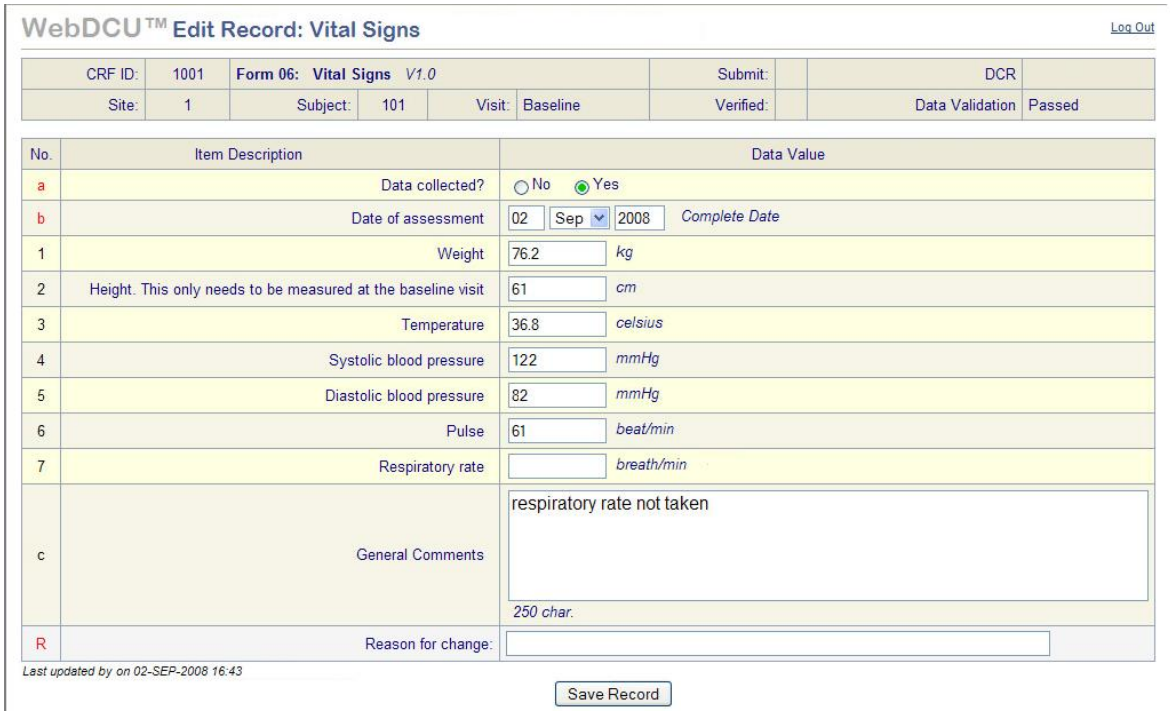
WebDCU™ has demonstrated significant benefits in enhancing both quality and efficiency of large multicenter clinical trial operation and management and has been widely accepted by site investigators as well as central coordinating centers. The study database for this HOBIT trial will be developed in Microsoft SQL Server, and will be implemented in the WebDCU™ system.

DCU's data management team is led by Ms. Dillon, a Certified Clinical Research Professional with over eight years of extensive experience in data management and trial operation management for a wide variety of protocols including multi-site, international, industry and federally funded, acute and exception from informed consent trials. Under the supervision of Ms. Dillon, a designated data manager will be assigned to the proposed HOBIT trial. Based upon the study protocol and in conjunction with the CCC, the data management team will develop the study visit transition matrix, study data collection schedule, case report forms, skip patterns and conditional selection logic for data entry user interfaces, and data validation and protocol violation rule checks. A PDF file matching the web-based eCRF along with detailed CRF Completion Guidelines developed by the data management team will be posted and available for download by the sites on the study website. A project specific Data Management Plan (DMP) will be developed and maintained by the data management team.

The data management team also will be involved in the study database implementation, testing, user end validation, and user training. During the trial operation period, DCU data managers will oversee the quality and efficiency of trial conduct and clinical data collection across all clinical sites, and provide instructions and technical support for WebDCU™ users. Data collected through the WebDCU™ will be reviewed by data managers as it is submitted to ensure data quality. Insight accumulated from such reviews will be used to enhance the study database and rule checks, as well as protocol compliance training.

The WebDCU™ system is comprised of several modules that were developed to facilitate clinical trial management. The following is a description of modules that will be used for the HOBIT trial.

- All CRF data will be entered directly by authorized study team members at participating clinical sites through WebDCU™ user interfaces, which has skip patterns and conditional selections programmed based on basic data logic. Initial data checking will be performed by the system before the data can be saved to prevent low level data errors, such as entering text into a numeric data field. After the data is saved, rule based data validation will be conducted based on common logic and the study protocol. Potential data errors and protocol violations will be flagged on the user interface. The data entry person is expected to confirm or correct the data based on the original source document. Only CRFs without unresolved rule violations are eligible for submission.



WebDCU™ Edit Record: Vital Signs — Log Out

CRF ID:	1001	Form 06: Vital Signs V1.0				Submit:		DCR	
Site:	1	Subject:	101	Visit:	Baseline	Verified:		Data Validation	Passed

No.	Item Description	Data Value
a	Data collected?	○ No ◉ Yes
b	Date of assessment	02 Sep 2008 *Complete Date*
1	Weight	76.2 *kg*
2	Height. This only needs to be measured at the baseline visit	61 *cm*
3	Temperature	36.8 *celsius*
4	Systolic blood pressure	122 *mmHg*
5	Diastolic blood pressure	82 *mmHg*
6	Pulse	61 *beat/min*
7	Respiratory rate	*breath/min*
c	General Comments	respiratory rate not taken *250 char.*
R	Reason for change:	

Last updated by on 02-SEP-2008 16:43

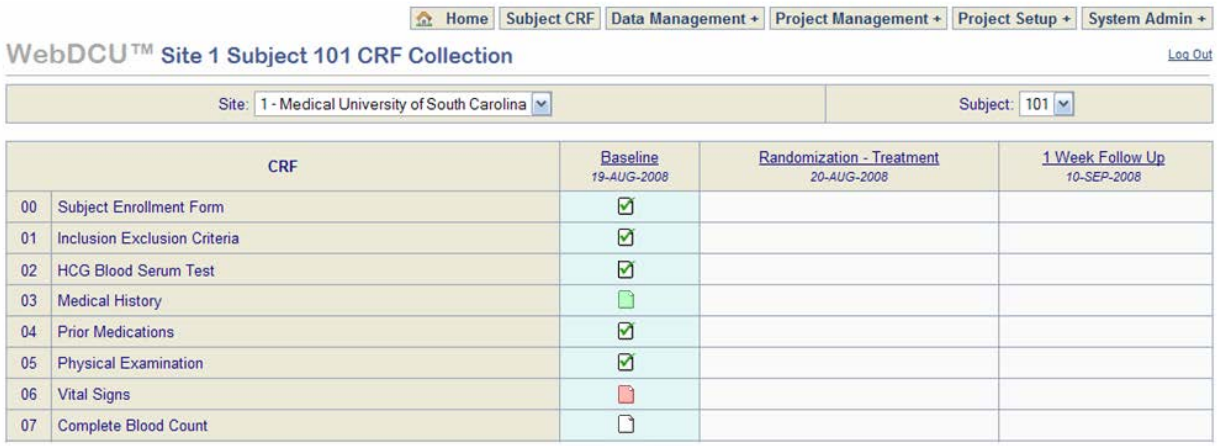
Save Record

- Once submitted, CRFs will be reviewed by DCU data managers. When needed, Data Clarification Requests (DCRs) will be created by the data manager. Site staff are expected to respond to each DCR and edit the CRF data, as needed. DCR responses will be reviewed by the data manager, who can either close the DCR or request further clarification. All DCR processing activities are coordinated by the WebDCU™ with event driven email notifications. All CRF data edits including the reason for the data change and time stamps, are archived in the audit trial.

- Dependent on the requirements of the study, certain data will be monitored by an on-site data monitor against source documents. Should a data discrepancy between the source document and database be identified, a DCR will be generated by the data monitor.

- When CRF data are transferred to the study biostatisticians for analysis and report generation, further data quality checks will be conducted by biostatisticians in SAS. Findings regarding CRF data quality will be transferred to the data management team and resolved though the DCR channel.

One caveat to web-based data management is its dependence on the timeliness of data entry at the clinical sites. WebDCU™ posts CRFs for each subject based on his/her progress in the study. The time-window for sites to submit the CRF is specified based on the nature of the CRF. User intuitive interfaces are provided to the site study coordinator and SDMC data managers, showing the current data processing status of each subject.



Site specific CRF processing summary reports and detailed missing or late CRF lists are also provided by WebDCU™, allowing the data manager at the SDMC to carefully monitor the study data collection activities across all sites and ensure that data collection is proceeding uniformly and efficiently. Should a site become delinquent in this regard, the DM will contact the site coordinator to determine the reasons for delay and suggest means to improve the data entry timeliness at that site. The DM will pay special attention to CRFs associated with subject eligibility, baseline, primary efficacy and safety outcome data.

- WebDCU™ provides a secure central randomization support with 24/7 accessibility through the internet. The central randomization strategy enhances the treatment allocation blinding protection and reduces the likelihood of selection bias associated with local randomization.

- With the integration of the randomization algorithm within the CTMS system, subject randomization information can be seamlessly shared within the study community in real time to optimize the trial operation management.

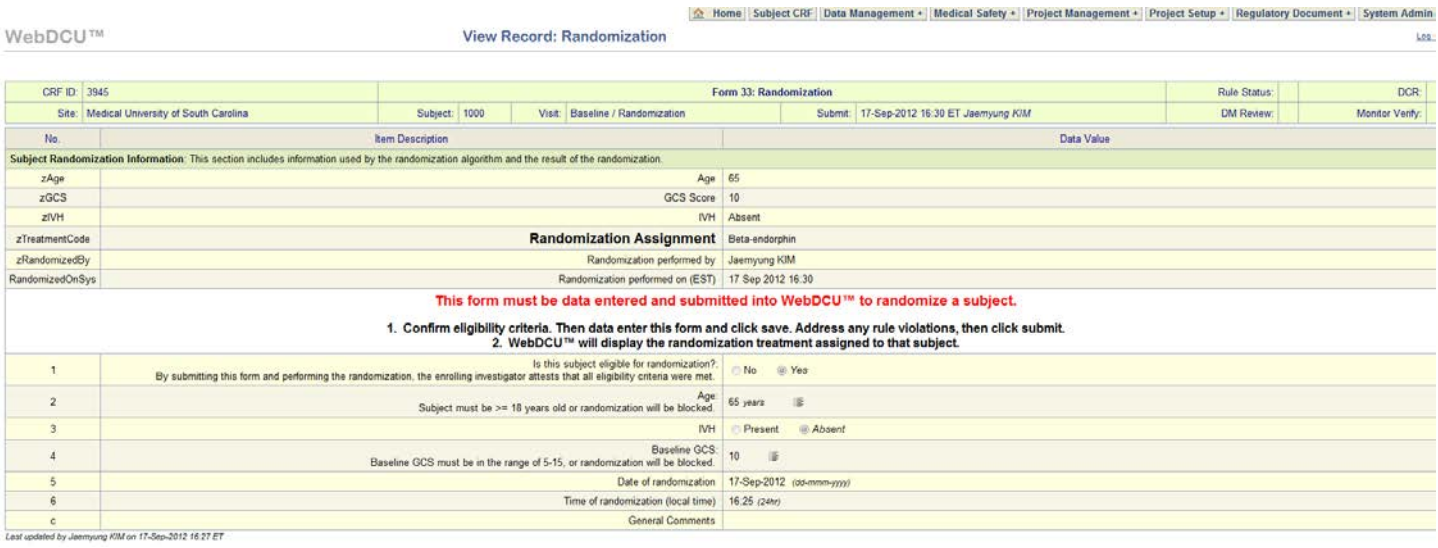
- WebDCU™ central randomization system allows advanced randomization algorithms to be implemented. For the HOBIT Trial, all clinically important baseline covariates will be included in the randomization algorithm, and the Minimal Sufficient Balancing randomization algorithm will be applied in order to prevent serious imbalances in any of the baseline covariates in addition to maintaining of the randomness of the treatment allocation. In

addition, response-adaptive randomization will be incorporated into the randomization algorithm.

- Before performing a subject randomization, WebDCU™ checks the subject's eligibility and baseline covariate information. While these data are captured on relevant CRFs, no redundant data entry is needed for subject randomization. Cross CRF checking ensures that ineligible patients will be blocked from randomization.

- When a new subject is randomized, an automated email will be send to relevant study team members, such as Principal Investigators, study Executive Committee members, and clinical coordination center staff, allowing real-time monitoring of the study recruitment progress.

- The DCU has a contingency plan developed for situations when the web-based randomization system fails for any reason. Study Coordinators will have an emergency contact number for the SDMC which will provide randomization assistance.



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WebDCU™ — View Record: Randomization

CRF ID:	3945	Form 33: Randomization					Rule Status:	DCR:
Site:	Medical University of South Carolina	Subject:	1000	Visit:	Baseline / Randomization	Submit: 17-Sep-2012 16:30 ET *Jaemyung KIM*	DM Review:	Monitor Verify:

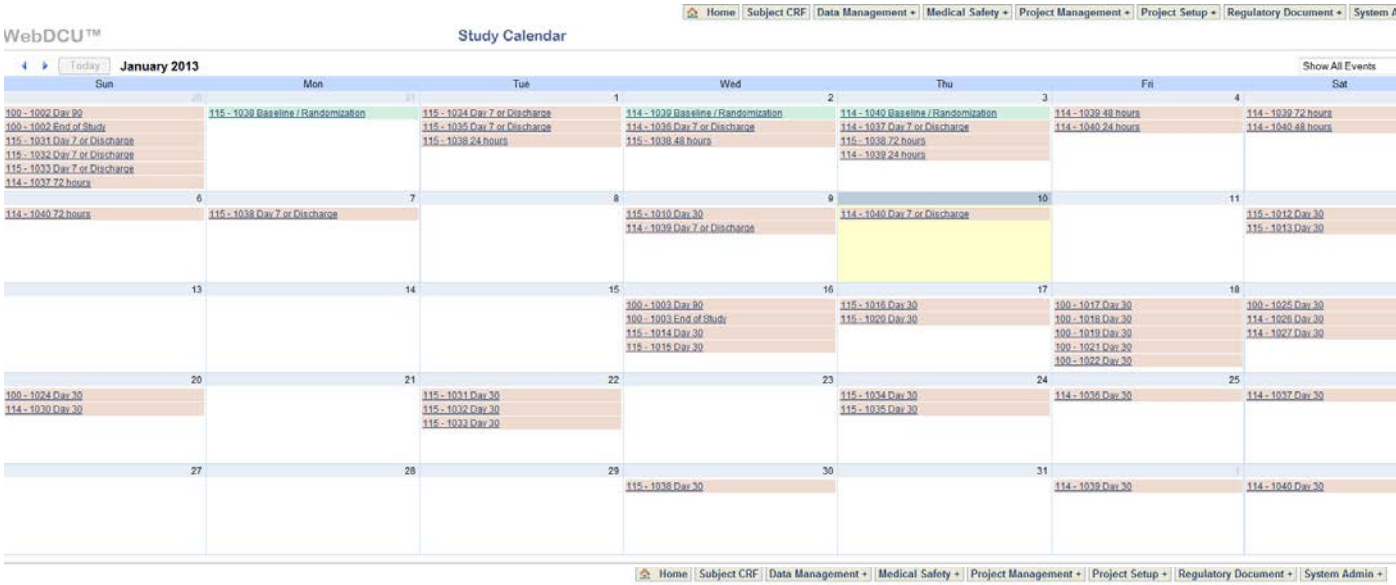
No.	Item Description	Data Value
Subject Randomization Information: This section includes information used by the randomization algorithm and the result of the randomization.		
zAge	Age	65
zGCS	GCS Score	10
zIVH	IVH	Absent
zTreatmentCode	**Randomization Assignment**	Beta-endorphin
zRandomizedBy	Randomization performed by	Jaemyung KIM
RandomizedOnSys	Randomization performed on (EST)	17 Sep 2012 16:30
	This form must be data entered and submitted into WebDCU™ to randomize a subject.	
	1. Confirm eligibility criteria. Then data enter this form and click save. Address any rule violations, then click submit. **2. WebDCU™ will display the randomization treatment assigned to that subject.**	
1	Is this subject eligible for randomization?: By submitting this form and performing the randomization, the enrolling investigator attests that all eligibility criteria were met.	○ No ◉ Yes
2	Age: Subject must be >= 18 years old or randomization will be blocked.	65 years
3	IVH	○ Present ◉ Absent
4	Baseline GCS: Baseline GCS must be in the range of 5-15, or randomization will be blocked.	10
5	Date of randomization	17-Sep-2012 (dd-mmm-yyyy)
6	Time of randomization (local time)	16:25 (24hr)
c	General Comments	

Last updated by Jaemyung KIM on 17-Sep-2012 16:27 ET

WebDCU™ data managers divide the entire study period into several visits, such as baseline, treatment, follow-up and end-of-study. When a new subject is enrolled in the study, a study calendar is generated by the system with an expected date for each study visit. A monthly study calendar is composed by the WebDCU™ with color coded items for completed, pending and overdue subject visits, allowing study coordinators to efficiently manage subject visit scheduling, treatment and assessment.

Based up this, a real-time study progress summary report is provided in WebDCU™, with the number of subjects passed each visit and number of subjects currently within each visit, ensuring that each subject visit is counted while eliminating duplication of information. In addition, a complete subject visit list is accessible to all authorized users.

The study calendar and the study progress report allow trial managers to track the study progress in a real-time with each subject counted. These web-based tools increase the efficiency of clinical trial project management and enhance the protocol compliance for study subjects.



The automated adverse event (AE) processing module coordinates the activities of AE data collection, reporting, medical safety monitoring, and filing of safety reports. In this module, AEs are reported through the study website within a specified timeframe. In order to implement expedited safety review and reporting, all Serious Adverse Event (SAE) reports are required to be submitted into the WebDCU™ system within 24 hours of first knowledge of the SAE. The submission of the SAE report will trigger an automated email notification sent to the project manager at the CCC, the independent medical safety monitor (MSM), and other appropriate trial managers. The MSM will enter into the database his/her agreement or disagreement with the SAE as reported by the site in regards to the event's relatedness to the study treatment and whether the event was expected or unexpected. Should the MSM need additional subject data to conduct the review, those data will be accessible on WebDCU™.

SAE Review

Review Step	Date	Record Version	Q1	Q2	Q3	Comments
PM Review	7/1/2010 11:52:15 AM	65	Report type = *New Event Report*	Requires MSM review = *Yes*		*This is the same subject that has the PE and suspected pneumonia.*
MSM Review	7/1/2010 11:55:55 AM	65	Serious = *Yes*	Unexpected = *No*	Relationship to study drug = *Possibly*	
PM Closing	7/1/2010 2:37:18 PM	65	MedWatch Report needed = *No*			
PM Review	7/8/2010 9:24:01 AM	67	Report type = *Follow-up Report*	Requires MSM review = *No*		

Timely payment to sites for delivered goods is critical for trial morale and optimal enrollment rates. Equally important is ensuring that the site has fulfilled their obligations prior to payment. The WebDCU™ system balances these two needs through the Payment Management Module. Subject payment records are posted at the time of subject enrollment. Conditions for each payment are defined in the WebDCU™ system based on study visit completeness, CRF submission status, query response status, and reason for study termination. Payment readiness is evaluated based on subject's study data that has been entered into the system. Financial managers can access real-time reports indicating which subjects are ready to be paid. All payments are recorded in the database with detailed information on site, subject, payment amount, payment date, etc. This allows both the sites and financial managers to easily manage and track the status of payments for each enrolled subject.

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WebDCU™

List Records: Subject Payment

Hub <> SHINE Ancillary

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#	Subject	Hub	Site	Payment	Status	Invoiced On	Check Issued On	Amou
1	5204	Emory	Grady Memorial Hospital	Payment 1	Invoiced	28-Aug-2012		
2	5204	Emory	Grady Memorial Hospital	Payment 2	Ready			
3	4657	Emory	Grady Memorial Hospital	Payment 1	Invoiced	28-Aug-2012		
4	4657	Emory	Grady Memorial Hospital	Payment 2	Ready			
5	6044	Texas	Memorial Hermann Hospital	Payment 1	Invoiced	19-Sep-2012		
6	6044	Texas	Memorial Hermann Hospital	Payment 2	Ready			
7	3001	Cincinnati	The University Hospital (Cincinnati)	Payment 1	Invoiced	21-Aug-2012		
8	3001	Cincinnati	The University Hospital (Cincinnati)	Payment 2	Ready			
9	3391	Cincinnati	The University Hospital (Cincinnati)	Payment 1	Ready			
10	3391	Cincinnati	The University Hospital (Cincinnati)	Payment 2	Ready			
11	4304	Texas	Memorial Hermann Hospital	Payment 1	Not Ready			
12	4304	Texas	Memorial Hermann Hospital	Payment 2	Not Ready			
13	4662	Kentucky	University of Kentucky	Payment 1	Ready			
14	4662	Kentucky	University of Kentucky	Payment 2	Ready			
15	4994	Maryland	University of Maryland Medical Center	Payment 1	Ready			
16	4994	Maryland	University of Maryland Medical C nter	Payment 2	Ready			
17	6459	Emory	Grady Memorial Hospital	Payment 1	Ready			
18	6459	Emory	Grady Memorial Hospital	Payment 2	Ready			
19	6790	Cincinnati	The University Hospital (Cincinnati)	Payment 1	Ready			
20	6790	Cincinnati	The University Hospital (Cincinnati)	Payment 2	Ready			

Regulatory documents can be divided into two categories: site documents and personnel documents. Site documents must be submitted for each site and are independent of the study team. Personnel related regulatory document requirements depend upon the roles of each member of the study team. As a result, when study teams change, the regulatory documents required for the study team change. Most regulatory documents have a limited lifespan and require renewal prior to the expiration date. In addition, all submitted regulatory documents should be reviewed and approved by a regulatory document manager. WebDCU™'s Paperless Regulatory Document Management module addresses all of these challenges and, like all modules in WebDCU™, utilizes generic data entry and data retrieval user interfaces in order to maintain a high level of performance reliability.

Prior to study initiation at the site, study required regulatory documents must be uploaded into WebDCU™ for CCC review. The CCC will review all required documents for completeness and accuracy and communicate to the sites any corrections or additions that need to be made to the documents prior to enrollment of any subject into the study. Once a site has uploaded all of the necessary regulatory documents and site personnel have undergone the required training, the site will be released to enroll subjects into the study.

Throughout the study periodic review of these regulatory documents will be conducted by CCC and automatic alerts and email notifications from WebDCU™ will remind sites of upcoming

expiration dates. The site will be contacted to request outstanding materials and to remind them of upcoming expirations approximately 1 month in advance of expirations.

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WebDCU™

List Records: Reg Doc Submission

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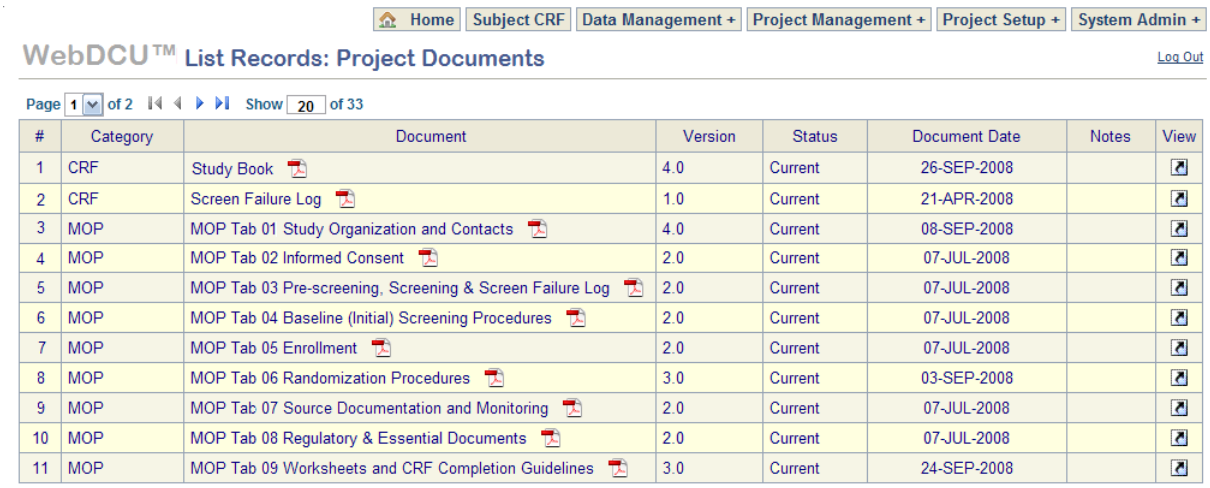
#	Document Type	Site	Document	Waived	Effective Date	Expiration Date	Document File	Submitted On	Status
1	Site	Abington Memorial Hospital	IRB Approval V1	No	08-Sep-2010	07-Sep-2011	F103.pdf	28-Sep-2010 14:17 ET	Accepted
2	Site	Abington Memorial Hospital	Informed Consent Approval V1	No	08-Sep-2010	07-Sep-2011	F104.pdf	28-Sep-2010 14:17 ET	Accepted
3	Site	Research Medical Center	IRB Approval V1	No	18-Aug-2010	17-Aug-2011	F105.pdf	05-Oct-2010 14:26 ET	Accepted
4	Site	Research Medical Center	Informed Consent Approval V1	No	15-Sep-2010	17-Aug-2011	F106.pdf	05-Oct-2010 14:26 ET	Accepted
5	Site	New Jersey Neuroscience Institute, JFK Medical Center	IRB Approval V1	No	13-Aug-2010	13-Aug-2011	F108.pdf	22-Oct-2010 14:36 ET	Accepted
6	Site	New Jersey Neuroscience Institute, JFK Medical Center	Informed Consent Approval V1	No	13-Aug-2010	13-Aug-2011	F107.doc	22-Oct-2010 14:36 ET	Accepted
7	People	Fairview UMMC	Curriculum Vitae	No	18-Nov-2010		F123.pdf	18-Nov-2010 11:02 ET	Accepted
8	People	Fairview UMMC	Medical License	No	01-Jun-2009	31-May-2011	F124.pdf	18-Nov-2010 11:05 ET	Accepted
9	People	Fairview UMMC	Curriculum Vitae	No	11-Jun-2009		F125.pdf	18-Nov-2010 11:06 ET	Accepted
10	People	Fairview UMMC	NIHSS Certification	No	27-Oct-2010	27-Oct-2012	F126.pdf	18-Nov-2010 11:08 ET	Accepted
11	People	Upenn	Curriculum Vitae	No	28-Oct-2010		F127.pdf	23-Nov-2010 14:14 ET	Accepted
12	People	Upenn	Curriculum Vitae	No	28-Oct-2010		F128.pdf	23-Nov-2010 14:18 ET	Accepted
13	People	Upenn	Curriculum Vitae	No	13-Jan-2010		F129.pdf	23-Nov-2010 14:19 ET	Accepted
14	People	Upenn	Curriculum Vitae	No	01-Nov-2010		F130.pdf	23-Nov-2010 14:21 ET	Accepted
15	People	Upenn	Curriculum Vitae	No	14-Jul-2010		F131.pdf	23-Nov-2010 14:22 ET	Accepted
16	People	Upenn	Curriculum Vitae	No	02-Aug-2010		F132.pdf	23-Nov-2010 14:23 ET	Accepted
17	People	Upenn	Medical License	No		31-Dec-2012	F133.pdf	23-Nov-2010 14:37 ET	Accepted
18	People	Upenn	Medical License	Yes				23-Nov-2010 14:38 ET	Accepted
19	People	Upenn	Medical License	Yes				23-Nov-2010 14:38 ET	Accepted
20	Site	Upenn	CAP Certification	No	13-Nov-2009	13-Nov-2011	F134.pdf	23-Nov-2010 14:58 ET	Accepted

WebDCU™ allows for the most current version of all study documents to be housed in one convenient location accessible to all WebDCU™ users. Study documents include, but are not limited to, the protocol, informed consent templates, worksheets for data collection, manual of procedures, and Investigator's brochure. The current version of each study document will be available as a PDF file on the study website and can be printed, as needed, by study personnel. This module facilitates version control of all study related documents, particularly as documents may change through the course of the study.



#	Category	Document	Version	Status	Document Date	Notes	View
1	CRF	Study Book	4.0	Current	26-SEP-2008		
2	CRF	Screen Failure Log	1.0	Current	21-APR-2008		
3	MOP	MOP Tab 01 Study Organization and Contacts	4.0	Current	08-SEP-2008		
4	MOP	MOP Tab 02 Informed Consent	2.0	Current	07-JUL-2008		
5	MOP	MOP Tab 03 Pre-screening, Screening & Screen Failure Log	2.0	Current	07-JUL-2008		
6	MOP	MOP Tab 04 Baseline (Initial) Screening Procedures	2.0	Current	07-JUL-2008		
7	MOP	MOP Tab 05 Enrollment	2.0	Current	07-JUL-2008		
8	MOP	MOP Tab 06 Randomization Procedures	3.0	Current	03-SEP-2008		
9	MOP	MOP Tab 07 Source Documentation and Monitoring	2.0	Current	07-JUL-2008		
10	MOP	MOP Tab 08 Regulatory & Essential Documents	2.0	Current	07-JUL-2008		
11	MOP	MOP Tab 09 Worksheets and CRF Completion Guidelines	3.0	Current	24-SEP-2008		

The Monitor Module represents a centralized effort to ensure that the Trial EC can fulfill their responsibilities related to monitoring trial conduct and data quality overall and at the individual clinical centers. Specifically, the module presents real-time information of subject trial data reviewed and verified by site monitors (based on scheduled site visits) and provides metrics regarding data accuracy by CRF and by clinical center as well as pending data reviews. The module allows for a central location for documentation of monitor findings as well as an interface for sites to enter corrective action preventive action (CAPA) plans. This centralized information allows the Trial EC to efficiently and effectively monitor the trial conduct across all participating clinical centers using a combination of remote and on-site monitoring.

The SDMC will be responsible for training WebDCU™ users. This training can be completed at face-to-face Investigator's meetings, via web-cast conferencing, or by video training. The SDMC has effectively utilized each of these training mechanisms for past studies. Staff responsible for data entry at the clinical site can be certified after successful completion of a training session.

The SDMC will conduct continued data training throughout the course of the study. In addition, an SDMC data manager will be available during business hours to answer user's questions and a step-by-step WebDCU™ User Manual will be posted on the study website.

Rapidly changing computer and communications technology requires that security issues be assessed on a regular basis and modified as indicated. It is important that all personnel involved fully understand the importance of handling data in a proper manner. Specific measures implemented to assure data integrity include the following:

- SDMC complies with regulatory requirements and guidelines, including Code of Federal Regulations Title 21, HIPAA, ICH guidelines, and a complete set of internal SOPs for trial management.
- A personal user account and password will be required to logon to the study website. Passwords will be encrypted in the database and must be updated within a pre-specified time period. All user logon attempts will be tracked. Additionally, after successfully logging on to the study website, all user navigation activities will be tracked by the system. If the user remains idle for a pre-specified amount of time, they will automatically be logged off of the system.
- Users will be granted data access based on their roles in the study. By default, all clinical site personnel access will be limited to information for their site only. Data access permissions will include read, write, delete and summary actions. User privileges will be managed by user group and group members. Access to aggregate information on treatment assignment and primary outcome will be limited to the minimal core personnel, on a need – to-know basis. The CCC will closely monitor the status of site team members. When a person leaves the study team, his/her user account will be deactivated and his/her user group membership will be removed.
- All changes, including edits and deletions, after the generation of a data record in the database will be automatically archived in audit tables, with information on time stamp, user name, and reason for change (if required). Authorized users will be able view complete audit trials for any record with corresponding access permissions.
- WebDCU™ adopts Secure Sockets Layer (SSL) protocol to enable encrypted and authenticated communication across the internet.
- WebDCU™ stores all information in Microsoft SQL Server databases. All data processing functions are running on the server side of the WebDCU™ system. No specific applications need to be installed on a user's computer. High speed internet access is required to access WebDCU™.
- Study data will be transferred from MS SQL Server database to SAS datasets when data analysis is required. All HIPAA defined Protected Health Information (PHI) will be de-identified for analytical SAS datasets.

Data Center Security and Data Back-up Schedule

All SDMC server systems used in the management and storage of clinical trial data are maintained on site at the limited access offices of the MUSC Data Center, where safety issues such as virus, power cut-off, hardware failure, fire, flood, earthquake and theft are professionally addressed. The MUSC Data Center is approximately 4,400 sq.ft. and is manned by the operations staff 24x7x365. These operators monitor all servers, environmental conditions, and notify appropriate personnel as needed. The entire data center is protected by a card access system and 24 hour security cameras are placed at each door of the third floor along with cameras at each door of the internal data center.

Weekly full-verified backup, daily differential verified backup and every 6 hour transaction log backup are captured by IBM® TSM system, so that a new system can be restored using the

backup tapes with minimal data loss in case a catastrophic failure to a web or database server. In addition, DCU utilizes commercial website failure detection services for its WebDCU™ system. Access attempts from the east coast and west coast are made every 15 minutes. DCU IT personnel will be notified immediately whenever a connection to the website cannot be established. When such an event happens, contingency measures will be implemented to minimize its impact on site trial operations, including subject randomization and safety reporting. The SDMC SOPs address prevention plans to be followed in case of emergencies (SOP 04-008 Emergency Operations and Disaster Recovery).

This presents a design for the HOBIT trial. The goal of the trial is to determine if hyperbaric oxygen treatment (HBO2) administered either 1.5, 2.0, or 2.5 ATA are effective every day or once a day and with NBH in the treatment of severe traumatic brain injury.

There are ten treatment arms in the trial;

1. control (no HBO2 treatment)
2. 2.0 ATA no NBH everyday
3. 2.5 ATA no NBH everyday
4. 1.5 ATA with NBH everyday
5. 2.0 ATA with NBH everyday
6. 2.5 ATA with NBH everyday
7. 1.5 ATA no NBH twice a day
8. 2.0 ATA no NBH twice a day
9. 2.5 ATA no NBH twice a day
10. 1.5 ATA with NBH twice a day

We label the control arm as $a = 1$, and the experimental arms as $a = 2, 3, 4, 5, 6, 7, 8, 9$, and 10 respectively.

The primary endpoint is the six-month GOSE response (success or failure). Additionally each patient will have earlier, possibly associated outcome of 1-month prediction of GOSE response.

We label the six-month GOSE response as Y_6. The 1-month prediction response value as Y_1.

The primary analysis is of the six-month GOSE response. The primary analysis will be that a treatment arm is superior to the control arm, meaning that the rate of response with GOSE 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 . 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.
2. End of Enrollment Success: If at the conclusion of accrual of the 200 patients, the most likely arm has at least a 0.94 posterior probability of being better than control.
3. Early Futility: If at any interim analysis the most likely arm has at most a 0.55 posterior probability of being better than control.

Additionally a prediction of Phase III success will be calculated. If recommended novel treatment has a greater than 50% probability of HBO2 treatment demonstrating improvement versus placebo in a subsequent confirmatory trial.

The following subject groups or analysis populations will be used to complete the analysis of data:

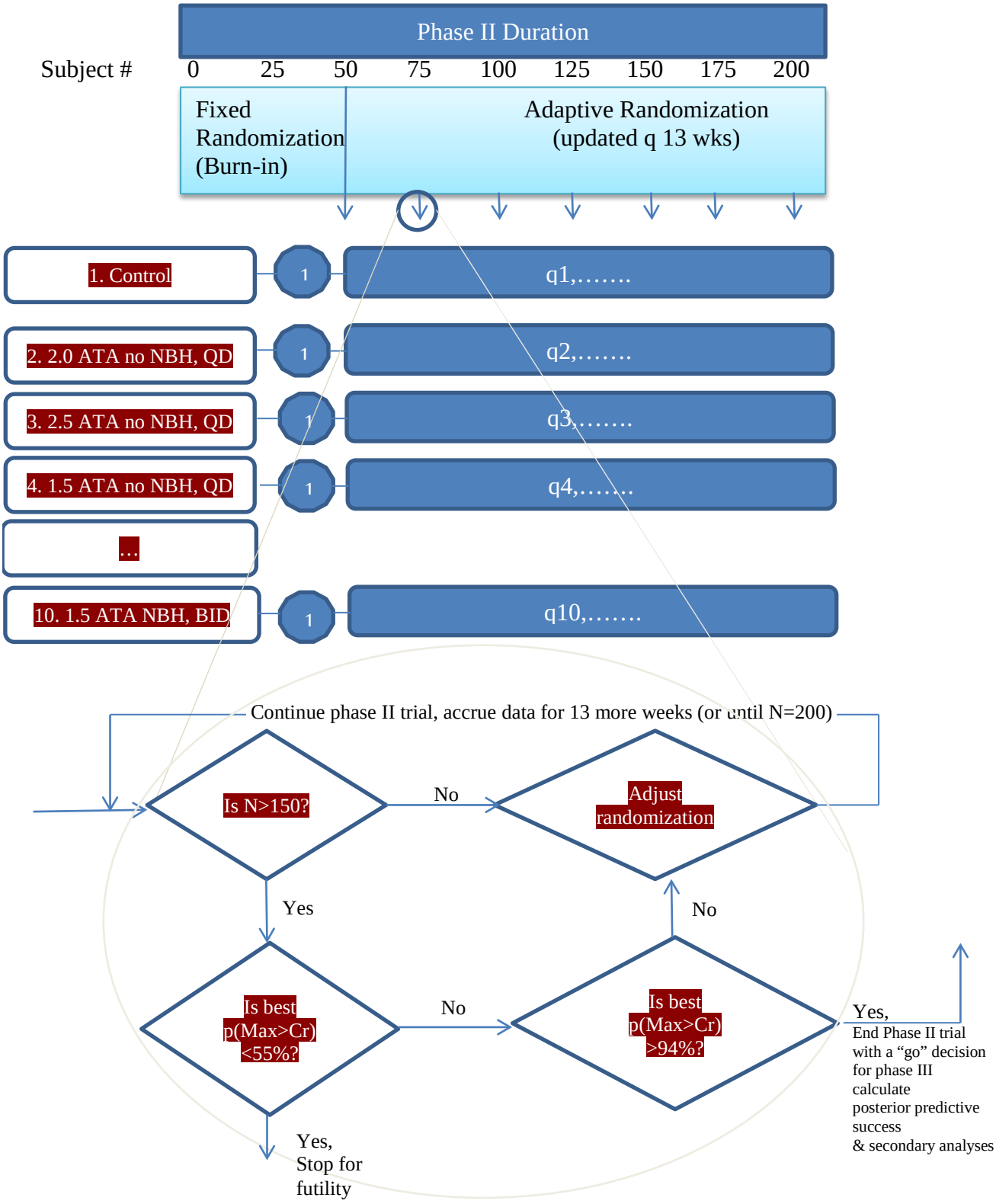
Intent-to-treat patient population (ITT): The ITT patient population will include all patients randomized, where patients will be classified by the group in which they are randomized, regardless of the treatment received.

The design is a novel Phase II adaptive design (see Figure 1). The purpose of the trial is to explore the different active treatment arms for relative efficacy and comparison to the control arm. The trial will utilize response adaptive randomization to favor the better performing experimental arms. If there is at least one experimental treatment arm promising enough it will advance to a Phase III trial and be compared for superiority to the control arm.

1) Burn-in Phase: An initial burn-in period of 50 subjects is used in which these patients are enrolled in a fixed randomization to the control and each of the experimental arms. A ratio of 1:1:1:1:1:1:1:1:1 will be used for the burn-in period.
2) Adaptive Randomization Phase: After the initial burn-in period adaptive randomization will be utilized. A vector of probabilities, $\boldsymbol{q}=(q_2, q_3, q_4, q_5, q_6, q_7, q_8, q_9, q_{10})$, is created for randomizing to the experimental arms. A constant proportion of 20% of patients will be enrolled to the control arm through Phase II. Interim analyses will take place quarterly to adjust the randomization probabilities based on the current data. The probabilities will be set to be proportional to the probability each experimental arm is the maximally effective treatment arm.
3) Advancing to Phase III: Possibility of early advance to Phase III.
4) Futility During Phase II: The trial can stop for futility if the probability of Phase II success drops below 55% for all experimental treatment arms.
5) The final analysis will be conducted after all subjects have completed six-month GOSE response.

Phase II information will be used to predict the probability of a successful Phase III clinical trial (equally randomized to usual care or novel treatment) to confirm the efficacy of novel treatment to increase response and confirm the safety of treating severe TBI with optimal HBO2 compared to usual care. The primary outcome for the Phase III trial will be the same as in Phase II (sliding dichotomized GOSE at 6 months). The primary analysis in Phase III investigates, with two sample proportions test (chi-square test), whether there is a simple difference between usual care and novel treatment. The sample size for Phase III is assumed to be 500 in control and 500 in the novel treatment (total n=1000), and alpha =.05 2-tailed).

Trial design, and stopping (go/no go) rules.



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

The primary outcome is six-month GOSE response. We label the observations of the six-month GOSE response for subject *i*, at the six-month visit as $Y_{i,6}$. We model the six-month primary outcomes as Bernoulli distributed. The model is

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

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

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

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

and

$$\text{logit}(\theta_a)\sim N(0,1.75^2), \text{ novel treatments } a=2,3,4,\ldots,10.$$

The control prior is equivalent to eight observations worth of weight the novel treatment's prior is equivalent to two observations.

The main effects model is

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

for subject *i*.

We construct a main effects model for the GOSE response rate that is a function of pressure, NBH, and duration. The logit transformation of P_i is modeled with a linear equation. By assuming no interaction among the main factors, this model has a lower number of parameters and is designed to increase ability to predict phase III success. The structure is

$$\begin{aligned} logit(\mathrm{P_i}) &= X_{i1}\mu + \\ &+ X_{i2}\alpha_{1.5ATA} + X_{i3}\alpha_{2.0ATA} + X_{i4}\alpha_{2.5ATA} \\ &+ X_{i5}\gamma_{NBH} + X_{i6}\gamma_{no\ NBH} \\ &+ X_{i7}\beta_{BID} + X_{i8}\beta_{QD}. \end{aligned}$$

The *X*s are 0 or 1 depending on the treatment combination subject *i* is assigned. μ represents the effect of control. The α's represent the additional effect of pressure relative to control. The γ's and β's represent the additional effect of NBH and BID respectively. Note: to identify, set $\gamma_{no\ NBH} = 0$ and β_{QD}=0. The main effects model relates to the control and treatment arms in the following way:

1. control (no HBO2 treatment)	μ
2. 2.0 ATA no NBH everyday	$\mu + \alpha_{2.0ATA} + \beta_{BID}$
3. 2.5 ATA no NBH everyday	$\mu + \alpha_{2.5ATA} + \beta_{BID}$
4. 1.5 ATA with NBH everyday	$\mu + \alpha_{1.5ATA} + \gamma_{NBH}$
5. 2.0 ATA with NBH everyday	$\mu + \alpha_{2.0ATA} + \gamma_{NBH}$
6. 2.5 ATA with NBH everyday	$\mu + \alpha_{2.5ATA} + \gamma_{NBH}$
7. 1.5 ATA no NBH twice a day	$\mu + \alpha_{1.5ATA} + \beta_{BID}$
8. 2.0 ATA no NBH twice a day	$\mu + \alpha_{2.0ATA} + \beta_{BID}$
9. 2.5 ATA no NBH twice a day	$\mu + \alpha_{2.5ATA} + \beta_{BID}$
10. 1.5 ATA with NBH twice a day	$\mu + \alpha_{1.5ATA} + \gamma_{NBH} + \beta_{BID}$

Based on prior studies, it is expected GOSE response for control group and novel treatment have the following prior distributions:

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

and

$$\text{logit}(\textit{all other parameters}) \sim N(0, 10^2).$$

The control prior is equivalent to eight observations worth of weight the novel treatment's prior is equivalent to close to 0 observations.

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

We utilize the information from subjects with incomplete information to the extent that the interim values are predictive of the final six-month values. A Bayesian model is built to learn from the accruing information (those subjects with complete six-month data) in the early response values to the final endpoint of six-month response.

Estimate transition probabilities from outcome at early time point to final outcome. The number of transitions to final outcome given early outcome is distributed as Binomial. Let p21 and p22 be conditional on a patient showing early response, the respective final probabilities of response and not responsive. For these we use a Beta prior on transition probabilities, (p21,p22)~Beta(20,5). Similarly for a patient that shows no response early, the final prior probabilities are (p31,p32)~Beta(5,20). These are fairly diffuse, each having a prior sample size equivalent to 25 patients.

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

2.3.1 *Most Likely Maximum Effective Duration*
From the joint posterior distribution the posterior probability that each arm, a=2,3,4,…,10 is the maximally effective arm, $P_a^{\max}$, is calculated. The arm with the largest $P_a^{\max}$ is labeled the *most likely maximum effective novel treatment.*

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

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

$$\Pr(\theta_a > \theta_1 | \text{data}), \text{ where } a=2,3,4,\ldots,10.$$

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

2.3.3 *Posterior predictive probability phase III success*

Taking the maximum arm from Phase II trial simulations we calculated the posterior predictive probability whether there is a >50% probability of hyperbaric treatment demonstrating improvement in the rate of good neurological outcome versus placebo in a subsequent Phase III confirmatory trial. This is calculated with the main effects model among the successful treatment combinations.

During the defined burn-in period (50 subjects) the allocation is set at 1:1:1:1:1:1:1:1:1:1 for arms 1,2,3,….,10, respectively. During the adaptive allocation in Phase II randomization will be used in which the allocation probabilities are updated monthly to favor those durations most likely to be the maximum effective treatment arm.

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

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

A *component,* V_a, is constructed for each arm. Set V_1=1, assuring 1/5 probability for control arm throughout the trial. The component for arms *a*=2,3,4,…,10 is

$$V_a = P_a^{\max} \text{ for } a=2,3,4,\ldots,10.$$

The randomization vector, $\boldsymbol{q}$, is set as

$$q_a = V_a/10 \text{ for } a=1,2,3.$$

Computations were performed using three types of software: Fixed and Adaptive Clinical Trial Simulator (FACTS) (Berry & Sanil, 2010), R (R Core Team, 2013), and WinBUGS (Lunn et al., 2000). The main effects model with the longitudinal modeling and RAR was performed in FACTS. The main effects model was performed in R2WinBUGS with custom coding.

First, 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 but accessed through an interactive graphical user interface and does not require programming knowledge to use. While FACTS is very powerful and flexible it does not currently have the capability to implement a main effects model. It was decided to use the flexibility and speed to simulate the cells model in FACTS and then use the data output to call a program in R2WinBUGS that was written specifically for making Phase III predictions. The posterior simulated draws in FACTS were 1,000 burn-in and then 2,500 draws for inference. In WinBUGS the burn-in was 1,000 and 1,000 draws for inference.

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

For all simulations in this section we assume an accrual rate of 1.75 subjects per week. No drop outs are assumed.

The study is classified as a success if a target duration arm is identified and recommended to be carried to Phase III. In the simulations if a trial enters the possible success or futility stage the trial is stopped in the simulation.

Several cases are presented in Table 1. The value in each cell is the GOSE response at six-months. The first case is referred to as the *null hypothesis* as each of the arms have identical GOSE responses—the novel treatment has no effect on GOSE response relative to the control arm. The remaining six cases explore scenarios with different GOSE responses for the experimental arms, including one case where harm is exhibited. The six cases involved are small, medium, and large. Also investigated is a case where the GOSE response is the factor pressure both as medium and large effects.

Case	Control	1.5, NBH, QD	2.0, NBH, QD	2.5, NBH, QD	1.5, no NBH, BID	2.0, no NBH, BID	2.5, no NBH, BID	1.5, NBH, BID	2.0, no NBH, QD	2.5, no NBH, QD
1. None	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
2. Small Main	0.4	0.45	0.5	0.43	0.45	0.5	0.43	0.48	0.48	0.4
3. Medium Main	0.4	0.5	0.55	0.48	0.5	0.5	0.48	0.55	0.5	0.43
4. Large Main	0.4	0.57	0.7	0.52	0.57	0.7	0.52	0.65	0.63	0.45
5. Harm	0.4	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35

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

For the purposes of this investigation power for this phase II trial, futility probability, sample size, time (duration), and subject allocation is calculated for the several different cases. We performed five sets of trial simulations based on the various cases of response shown in Table 2. Each set involved 1000 trial simulations. We highlight four cases. The first uses a medium case . If there is a medium effect, we estimated (identified) that 65% power, 6% futility, the sample size of this trial scenario was on average 187 (36% of these in one of the three 2.0 ATA treatments), and probability greater than 50% probability of Phase III success 71%. The average length of this trial scenario was 131 weeks. The second uses a large case . If there is a large effect, we estimated (identified) that 96% power, 1% futility, the sample size of this trial scenario was on average 174 (45% of these in one of the three 2.0 ATA treatments), and probability greater than 50% probability of Phase III success 98%. The average length of this trial scenario was 125 weeks. The third is the highly unlikely scenario that serves as our null hypothesis). In this scenario there is no difference between the treatments. Therefore, the extent to which this scenario is "successful" actually reflects our Type I error rate. Thus this trial scenario produced an appropriate expected Type I error (α=20%). The sample size of this scenario on average was 186 subjects (equally allocated across groups). The average length of the trials under this scenario was 119 weeks. The futility probability is 34%. The probability greater than 50% probability of Phase III success is 20%.

1. None	0.20	0.34	176	118	33%	0.20
2. Small Main	0.48	0.13	186	129	38%	0.51
3. Medium Main	0.65	0.06	187	131	36%	0.71
4. Large Main	0.96	0.01	174	125	45%	0.98
5. Harm	0.09	0.57	158	102	33%	0.08

*New calculation based on main effects model (S=1000).

Table 2: Simulated trial operating characteristics.

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. It is anticipated that the AUC for ICP in patients with novel treatment will drop on average between 75 and 100 mmHg * hour relative to control to determine power, use type I error of 0.2, a standard deviation of 150 mmHg * hour and a *main effects mode*l for continuous response. With the average allocation of patients dictated from the response adaptive randomization, we have between 75 and 92% power to detect a shift in patients receiving novel treatment relative to control. Note that 75 mmHg * hour is equal to reducing ICP from 25 to 20 mmHg for 15 hours (25-20 = 5 x 15 = 75). Based on our previous work, we anticipate brain tissue PO2 AUC would have better power than ICP (Rockswold 2010, Rockswold 2013). Additionally, (1) the therapeutic intensity level (TIL) scores for controlling intracranial pressure (ICP) in HBO2-treated patients will be compared to controls; and (2) utilizing Licox brain tissue PO2 monitoring, the level and duration of brain tissue hypoxia (brain tissue PO2 < 15 mmHg) using AUC methodology in HBO2-treated groups versus control will be analyzed. Both of these analyses will be modeled using two continuous versions of the main effects model. Based on our previous work, we would anticipate brain tissue PO2 AUC would have better power that ICP.

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3. Lunn, D.J., Thomas, A., Best, N., and Spiegelhalter, D. (2000) WinBUGS -- a Bayesian modelling framework: concepts, structure, and extensibility. *Statistics and Computing*, :325—337.

4. Rockswold SB, Rockswold GL, Zaun DA, Liu J: A prospective, randomized phase II clinical trial to evaluate the effect of combined hyperbaric and normobaric hyperoxia on cerebral metabolism, intracranial pressure, oxygen toxicity, and clinical outcome in severe traumatic brain injury. J Neurosurg 2013; 118(6):1317-1328.

5. Rockswold SB, Rockswold GL, Zaun DA, Zhang X, Cerra CE, Bergman TA, Liu J A prospective, randomized clinical trial to compare the effect of hyperbaric to normobaric hyperoxia on cerebral

metabolism, intracranial pressure, and oxygen toxicity in severe traumatic brain injury. Journal of Neurosurgery 2010; 112(5):1080-94.

6. Vik A, Nag T, Fredriksli O, et al: Relationship of “dose” of intracranial hypertension to outcome in severe traumatic brain injury. J Neurosurgery 2008; 109:678-684.

Screening	X									
Inclusion/Exclusion Criteria	X									
Demographics	X									
Medical History	X									
Pre-hospital Events	X									
Informed consent	X									
GCS	X	X	X	X	X	X	X			
AIS	X									
ISS	X									
Revised Trauma Score	X									
Randomization		X								
Enrollment Head CT	X									
ICP Monitor Insertion	X									
Licox Monitor Insertion Option	X									
Check Licox Monitor Function q HBO_2 Rx	X	X X	X X	X X	X X	X X				
Head CT to Check Placement	X									
1st HBO Rx		X								
HBO Rxs		X	X X	X X	X X	X X				
ICP Monitoring		X	X	X	X	X				
Licox Monitoring		X	X	X	X	X				

Option										
TILS Recording		X	X	X	X	X				
Vitals	X	X	X	X	X	X				
Labs		X	X	X	X	X				
Concomitant Medications		X	X	X	X	X				
Hospital Discharge							X			
Surgical Procedures		X	X	X	X	X	X			
GOS-E							X	X	X	
AE (only SAEs after Day 5/Discharge)		X	X	X	X	X	X	X	X	
End of Study										X