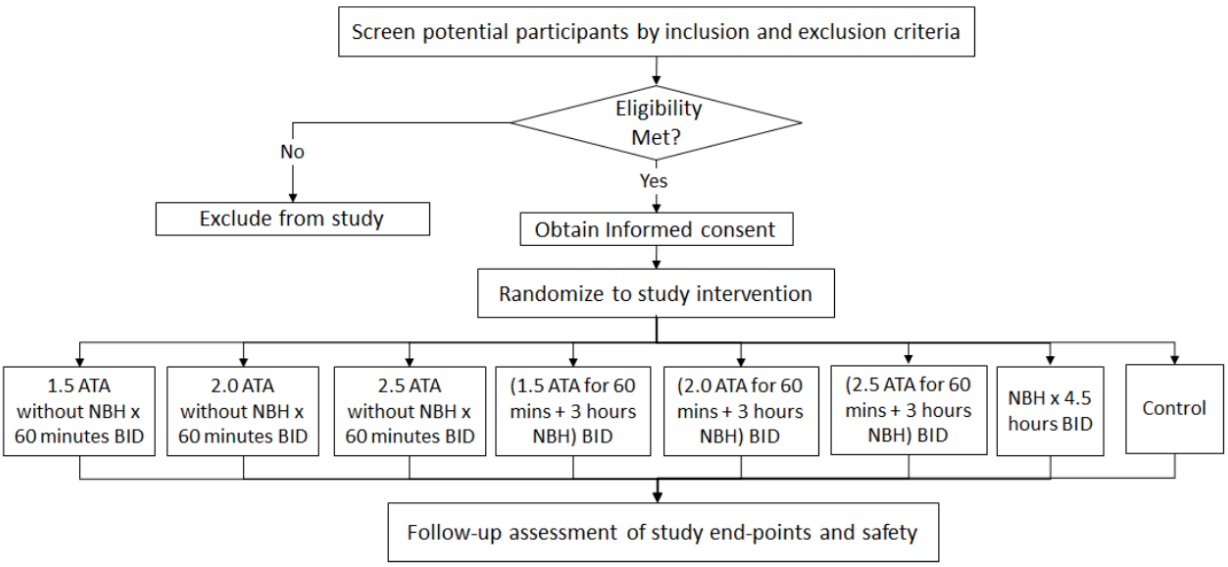
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Hyperbaric Oxygen Brain Injury Treatment (HOBIT) Trial: A Multicenter, Randomized, Prospective Phase II Adaptive Clinical Trial Evaluating the Most Effective *Hyperbaric Oxygen* Treatment Paradigm for Severe Traumatic Brain Injury
Study Description:	There continues to be an overarching problem of high mortality and poor outcome for victims of severe traumatic brain injury (TBI). Preclinical and clinical investigations indicate that hyperbaric oxygen (HBO) has a positive impact on reducing brain injury and improving outcomes in severe TBI. By markedly increasing oxygen (O2) delivery to the traumatized brain, HBO can reverse the lack of O2 that precipitates cellular energy failure and subsequent brain cell death. However, prior to a formal phase III definitive efficacy study, important information is required regarding optimizing the HBO treatment schedule to be instituted in terms of pressure, frequency and other parameters. The lungs in severe TBI subjects have frequently been compromised by direct lung injury and/or acquired ventilator pneumonia and are susceptible to O2 toxicity. It is essential to determine the most effective HBO dose schedule without producing O2 toxicity and clinical complications. This proposed adaptive clinical trial is designed to answer these questions and to provide important data to plan a definitive phase III efficacy trial.
Objectives:	**Objective 1**: (Signal of efficacy) To determine, in subjects with severe TBI, whether there is a >50% probability of hyperoxia treatment demonstrating improvement in the rate of good neurological outcome versus control in a subsequent confirmatory trial. **Objective 2**: (Dose selection) To select, in subjects with severe TBI, the combination of treatment parameters (pressure +/- intervening normobaric hyperoxia [NBH]) that is most likely to demonstrate improvement in the rate of good neurological outcome versus control in a subsequent confirmatory trial.
Endpoints:	**Primary Endpoint:** The primary analysis will use the intention to treat (ITT) sample to compare the proportion of favorable outcomes in the 6-month dichotomized, severity adjusted, GOS-E (section 11.1 of the SAP) in each treatment arm to control dose regimen. Favorable outcome for an individual subject is defined according to a sliding dichotomy (Murray, 2005), where the definition of favorable outcome varies according to baseline prognosis. Prognosis will be defined according to the probability of poor outcome predicted by the IMPACT Core Model (Steyerberg EW, 2008); see section 11.1.2.1 of the SAP). The favorable outcome definition is more stringent for subjects predicted to do well (i.e. a low probability of poor outcome), as outlined in the Table in Section 9.1. The IMPACT core score will be based on the covariate as known at randomization. The primary endpoint will analyze the GOS-E at 26 weeks; intermediate measurements will be taken at 4, 13 weeks.

	Secondary Endpoints: 1. To analyze the level and duration of intracranial hypertension (> 22 mmHg) in hyperoxia-treated versus control groups. 2. To analyze the therapeutic intensity level (TIL) scores for controlling intracranial pressure (ICP) in hyperoxia-treated subjects compared to controls. 3. At sites utilizing brain tissue PO2 monitoring, analyze the level and duration of brain tissue hypoxia (brain tissue PO2 < 20 mmHg) in HBO-treated groups versus control (van den Brink 2000). 4. To compare the type and rate of serious adverse events (SAEs) between hyperoxia treatment arms and control. 5. To examine the association between peak brain tissue PO2 during hyperbaric treatment and favorable outcome at 6-months (measured by the GOS-E). 6. Determine the most effective *hyperbaric oxygen* therapy paradigm using an alternative scoring of the GOS-E (approximately continuous severity adjusted scoring of the GOS-E).
Study Population:	All individuals, aged 16 to 65, presenting to a collaborating institution with a severe TBI defined as a GCS score 3 to 8 are potential candidates for inclusion. Subjects with a GCS score of 7 or 8 with a Marshall CT score = 1 are excluded. Subjects with a GCS score of 3 AND bilateral mid-position, nonreactive pupils are excluded because of their grim prognosis and the fact that it is doubtful any treatment could have a neuroprotective effect.
Phase:	**II**
Description of Study Intervention:	There are eight treatment arms. Participants will be randomized to one of six hyperbaric oxygen (HBO) treatment groups, one normobaric hyperoxia (NBH) treatment group, or one control (no hyperoxia treatment) group. The six hyperbaric oxygen treatment groups are: 1.5 Atmospheres Absolute (ATA) for 60 minutes twice a day; 2.0 ATA for 60 minutes twice a day; 2.5 ATA for 60 minute twice a day; 1.5 ATA for 60 minutes followed by NBH for 3 hours twice a day; 2.0 ATA for 60 minutes with NBH for 3 hours twice a day; 2.5 ATA for 60 minutes with NBH for 3 hours twice a day, and NBH for 4.5 hours twice a day.
Study Duration:	Anticipated 60 months
Participant Duration:	6 months

1.2 SCHEMA


Screen potential participants by inclusion and exclusion criteria
Eligibility Met?
No
Yes
Exclude from study
Obtain Informed consent
Randomize to study intervention
1.5 ATA without NBH x 60 minutes BID
2.0 ATA without NBH x 60 minutes BID
2.5 ATA without NBH x 60 minutes BID
(1.5 ATA for 60 mins + 3 hours NBH) BID
(2.0 ATA for 60 mins + 3 hours NBH) BID
(2.5 ATA for 60 mins + 3 hours NBH) BID
NBH x 4.5 hours BID
Control
Follow-up assessment of study end-points and safety