BOOST-3 Protocol Version 3

SIREN

Study Protocol

Brain Oxygen Optimization in Severe Traumatic Brain Injury—Phase 3 (BOOST-3)
A multicenter, randomized, blinded-endpoint, comparative effectiveness study of goal-directed critical care based upon monitoring of brain tissue oxygen and intracranial pressure versus monitoring of intracranial pressure alone in patients with severe traumatic brain injury.

Study Chair: Ramon Diaz-Arrastia, MD, PhD

Supported by: The National Institute of Neurological Disorders and Stroke (NINDS) U01 NS099046

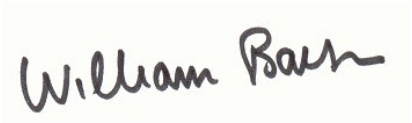
ClinicalTrials.gov ID: NCT03754114

Version: Version 3

IRB approval:

PROTOCOL SIGNATURE PAGE

I have read the attached clinical protocol titled Brain Oxygen Optimization in Severe Traumatic Brain Injury—Phase 3 (BOOST-3) Version 1, dated 12 December 2018. My signature assures that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality.



Contact Trial PI Signature Date of Signature

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

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

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

Investigator's Signature Date of Signature

PROTOCOL CHANGES

If amended versions of this protocol are required, this page will be populated with a specific log of all changes.

	Version 1		Version 2		Version 3	
Section	Page	Previous text	Page	New text	Page	Text
			2	Protocol signature page added		
5.1	22	A single head CT will be obtained after placement of the monitors to confirm location and assess for any placement associated adverse events.	30	A head CT will be obtained after placement of the monitors to confirm location and assess for any placement associated adverse events.		
5.1	23	Each participant will have an FiO_2 challenge close to 1 hour after placement of catheter, according to detailed instructions included in the BOOST-3 MOP. Recorded measurements will be initiated 60 minutes after placement of monitor. Results of the FiO_2 challenge will be blind to the treatment staff.	31	Each participant will have an FiO_2 challenge within 2 hours after placement of catheter, according to detailed instructions included in the BOOST-3 MOP. Results of the FiO_2 challenge will be blind to the treatment staff.		
5.1	26	These participants will have both monitors removed 48 hours after insertion.	34	These participants will have both monitors removed 72 hours after insertion.		
5.1	26	**Type B: Tier 1 interventions** **Tier 1 therapies must be started within 15 minutes of the start of the episode, as detected by the continuous ICP**	34	**Type B: Tier 1 interventions** **Tier 1 therapies must be started within 15 minutes of the start of the episode, as detected by the continuous ICP**		

		recordings. These are listed in no particular order. • Adjust head of the bed to lower ICP. • Ensure Temperature < 38 ◦C. • Adjust pharmacological analgesia and sedation: Titrate to effect. • CSF drainage (if EVD available). Titrate to effect. Either continuous or intermittent CSF drainage is allowed per site protocol. • Standard dose Mannitol (0.25 – 1.0 g/kg), Titrate to ICP control and maintain Sosm < 320 mOsm or Ogap <20. • Hypertonic saline. Titrate to ICP control and maintain serum Na^+ 150-160. • Consider anti-seizure medications (AEDs), either Phenytoin or Levetiracetam, to be used prophylactically for 1 week only.		**recordings**. These are listed in no particular order, more details, and other options may be found in the MOP. • Adjust head of the bed to lower ICP. • Ensure Temperature < 38 ◦C. • Adjust pharmacological analgesia and sedation: Titrate to effect. • CSF drainage (if EVD available). Titrate to effect. Either continuous or intermittent CSF drainage is allowed per site protocol. • Low dose Mannitol (0.25 – 0.5 g/kg), Titrate to ICP control and maintain Sosm < 320 mOsm or Ogap <20. • Hypertonic saline. Titrate to ICP control and maintain serum Na^+ 150-160. • Consider anti-seizure medications (AEDs), either Phenytoin or Levetiracetam, to be used prophylactically for 1 week only.		
5.1	26	**Type B: Tier 2 interventions** **Move to Tier 2 interventions if ICP is > 22 mm Hg for > 60 minutes despite Tier 1**	34	**Type B: Tier 2 interventions** **Providers may move to Tier 2 interventions at any point if ICP is > 22 mm Hg and at least one**		

		therapies. These are listed in no particular order. • Adjust ventilatory rate to lower $paCO_2$ to 32 – 35 mm Hg. • High dose Mannitol >1 g/kg, or higher frequency of standard dose mannitol (if Sosm < 320 mOsm. • Repeat CT to determine if increased size of intracranial mass lesions. • Treat surgically remediable lesions with craniotomy according to guidelines. • Adjust temperature to 35 – 37 ◦C, using active cooling measures.		**intervention from Tier 1 has been used. Providers must move to Tier 2 interventions if ICP is > 22 mm Hg for > 60 minutes despite Tier 1 therapies.** Tier 2 interventions are listed in no particular order and other options may be found in the MOP. • Adjust ventilatory rate to lower $paCO_2$ to 32 – 35 mm Hg. • High dose Mannitol 1.0-1.5 g/kg, or higher frequency of standard dose mannitol (if Sosm < 320 mOsm. • Repeat CT to determine if increased size of intracranial mass lesions. • Treat surgically remediable lesions with craniotomy according to guidelines. • Adjust temperature to 35 – 37 ◦C, using active cooling measures.		
5.1	27	**Type C: Tier 1 interventions** **Tier 1 therapies must be started within 15 minutes of the start of the episode, as detected by the continuous $PbtO_2$ recordings.** These are listed in no particular order.	35	**Type C: Tier 1 interventions** **Tier 1 therapies must be started within 15 minutes of the start of the episode, as detected by the continuous $PbtO_2$ recordings.** These are listed in no particular order and other options may be found in the MOP.		

5.1	27	**Type C: Tier 2 interventions** **Must move on to Tier 2 interventions if $PbtO_2$ < 20 mm Hg for > 60 minutes despite Tier 1 therapies.** These are listed in no particular order. • Adjust ventilator parameters to increase PaO_2 by increasing F_iO_2 to 100% • Increase PaO_2 by adjusting PEEP. • Increase CPP above 70 mm Hg with fluid boluses or vasopressors. • Adjust ventilatory rate to increase $PaCO_2$ to 45 – 50 mm Hg. • Transfuse pRBCs to Hgb ≥ 10 g/dL. • Decrease ICP to < 10 mm Hg. • CSF drainage. • Increased sedation	35	**Type C: Tier 2 interventions** Providers may move to Tier 2 interventions at any point if PbtO2 is < 20 mm Hg and at least one intervention from Tier 1 has been used. **Providers must move on to Tier 2 interventions if $PbtO_2$ < 20 mm Hg for > 60 minutes despite Tier 1 therapies.** These are listed in no particular order and other options may be found in the MOP. • Adjust ventilator parameters to increase PaO_2 by increasing F_iO_2 to 100% • Increase PaO_2 by adjusting PEEP. • Increase CPP above 70 mm Hg with fluid boluses or vasopressors. • Adjust ventilatory rate to increase $PaCO_2$ to 45 – 50 mm Hg. • Transfuse pRBCs to Hgb ≥ 10 g/dL. • Decrease ICP to < 15 mm Hg. • CSF drainage. • Increased sedation		
5.1	28		36	**Type C: Tier 3 interventions** **Tier 3 therapies are optional**, and may be used at any point after at least one option from both Tier 1 and Tier 2 have been attempted and are ineffective**.** If/when Tier 3		

				therapies are utilized, as well as the time when they are utilized, will be recorded in the CRFs. Other options can be found in the MOP.		
5.1	28	**Type D: Tier 1 interventions** **Tier 1 therapies must be started within 15 minutes of the start of the episode, as detected by the continuous ICP and $PbtO_2$ recordings**. These are listed in no particular order. • Adjust head of the bed to lower ICP (ICP protocol dominant for HOB). • Ensure Temperature < 38 °C. • Pharmacologic analgesia and sedation—titrate to effect. • CSF drainage (if EVD available). • Increase CPP up to a maximum of 70 mm Hg with fluid boluses or vasopressors. Standard dose Mannitol (0.25 – 1.0 mg/kg), Titrate to ICP control and maintain Sosm < 320 mOsm or Ogap <20. • Hypertonic saline. Titrate to effect and maintain sNa^+ 150-160.	36	**Type D: Tier 1 interventions** **Tier 1 therapies must be started within 15 minutes of the start of the episode, as detected by the continuous ICP and $PbtO_2$ recordings**. These are listed in no particular order and other options may be found in the MOP. • Adjust head of the bed to lower ICP (ICP protocol dominant for HOB). • Ensure Temperature < 38 °C. • Pharmacologic analgesia and sedation—titrate to effect. • CSF drainage (if EVD available). • Increase CPP up to a maximum of 70 mm Hg with fluid boluses or vasopressors. Low dose Mannitol (0.25 – 0.5 mg/kg), Titrate to ICP control and maintain Sosm < 320 mOsm or Ogap <20. • Hypertonic saline. Titrate to effect and maintain sNa^+ 150-160. • Obtain arterial blood gas to confirm		

		• Obtain arterial blood gas to confirm oxygenation is in desired range before treating with PaO_2 adjustment. 9. Increase PaO_2 by increasing FiO_2 to 60%. • Increase FiO_2 by increasing PEE(Hyperventilation to $PaCO_2$ below 35 mm Hg is not recommended for Type D events). • Consider EEG monitoring. • Consider AEDs, either Phenytoin or Levetiracetam, to be used prophylactically for 1 week only.		oxygenation is in desired range before treating with PaO_2 adjustment. 9. Increase PaO_2 by increasing FiO_2 to 60%. • Increase FiO_2 by increasing PEE(Hyperventilation to $PaCO_2$ below 35 mm Hg is not recommended for Type D events). • Consider EEG monitoring. • Consider AEDs, either Phenytoin or Levetiracetam, to be used prophylactically for 1 week only.		
5.1	28	**Type D: Tier 2 interventions.** **Must move on to Tier 2 interventions if ICP ≥ 22 mm Hg and $PbtO_2$ < 20 mm Hg for > 60 minutes despite Tier 1 therapies.** These are listed in no particular order. • High dose Mannitol >1 g/kg, or frequent boluses standard dose Mannitol (if Sosm < 320 mOsm or Ogap < 20). • Increase CPP above 70 mm Hg with fluid boluses or vasopressors.	36	**Type D: Tier 2 interventions.** **Providers may move to Tier 2 interventions at any point if ICP is > 22 mmHg and $PbtO_2$ is < 20 mm Hg and at least one intervention from Tier 1 has been used. Providers must move on to Tier 2 interventions if ICP ≥ 22 mm Hg and $PbtO_2$ < 20 mm Hg for > 60 minutes despite Tier 1 therapies.** These are listed in no particular order and other options may be found in the MOP. • High dose Mannitol 1.0-1.5 g/kg, or		

		• Increase PaO_2 by increasing FiO_2 to 100%. • Increase PaO_2 by increasing PEEP. • Transfuse pRBCs to Hgb ≥ 10 g/dL. • Repeat CT to determine if increased size of intracranial mass lesions. • Treat surgically remediable lesions with craniotomy according to guidelines. • Induced hypothermia to 35 - 37◦C, using active cooling measures.		frequent boluses standard dose Mannitol (if Sosm < 320 mOsm or Ogap < 20). • Increase CPP above 70 mm Hg with fluid boluses or vasopressors. • Increase PaO_2 by increasing FiO_2 to 100%. • Increase PaO_2 by increasing PEEP. • Transfuse pRBCs to Hgb ≥ 10 g/dL. • Repeat CT to determine if increased size of intracranial mass lesions. • Treat surgically remediable lesions with craniotomy according to guidelines. • Induced hypothermia to 35 - 36◦C, using active cooling measures.		
5.1	29	**Type D: Tier 3 interventions.** **Tier 3 therapies are optional.** If/when Tier 3 therapies are utilized, as well as the time when they are utilized, will be recorded in the CRFs. These are listed in no particular order. • Pentobarbital coma, according to local protocol. • Decompressive craniectomy.	37	**Type D: Tier 3 interventions.** **Tier 3 therapies are optional.** If/when Tier 3 therapies are utilized, as well as the time when they are utilized, will be recorded in the CRFs. These are listed in no particular order and other options may be found in the MOP. • Pentobarbital coma, according to local protocol.		

<table>
<tr><td></td><td></td><td>• Induced hypothermia to 32 – 34.5◦C, using active cooling measures
• Neuromuscular paralysis.</td><td></td><td>• Decompressive craniectomy.
• Induced hypothermia to 32 – 34.5◦C, using active cooling measures
• Neuromuscular paralysis.</td><td></td><td></td></tr>
<tr><td>6.1</td><td>33</td><td></td><td>41</td><td>Removed physical exam from Day 180.</td><td></td><td></td></tr>
<tr><td>6.2</td><td>33</td><td></td><td>41</td><td>Removed Word Reading subtest of WRAT-4 from Formal Measures of Cognition.</td><td></td><td></td></tr>
<tr><td>7</td><td>34</td><td>The potentially associated adverse events and the expected incidence rates are detailed in the table below.

<table><tr><th>Table 6. Specific Anticipated Adverse Events</th><th>Expec Incide</th></tr><tr><td>ARDS / Acute Lung Injury</td><td>5%</td></tr><tr><td>Pneumonia</td><td>25%</td></tr><tr><td>Sepsis / SIRS</td><td>5%</td></tr><tr><td>Septic Shock</td><td>3%</td></tr><tr><td>Hematoma requiring craniotomy for evacuation</td><td>0.5%</td></tr><tr><td>CNS Infection</td><td><0.5</td></tr></table></td><td>43</td><td>Removed.</td><td></td><td></td></tr>
<tr><td>9.3</td><td>38</td><td>The EC, on a regular basis, will review a summary of the data entered in the BOOST3 WebDCU™ database by the participating clinical sites to identify deficiencies in data collection and/or entry. This summary will be the result of the ongoing</td><td>47</td><td>The study leadership, on a regular basis, will review a summary of the data entered in the BOOST3 WebDCU™ database by the participating clinical sites to identify deficiencies in data collection and/or entry. This summary will be the result of the ongoing review by</td><td></td><td></td></tr>
</table>

		review by the DCC Data Manager (DM) and IMSM of data entered by all participating clinical sites.		the DCC Data Manager (DM) and IMSM of data entered by all participating clinical sites.		

Table of Contents

PRECIS

Study Title: Brain Oxygen Optimization in Severe TBI Phase 3 (BOOST-3)

Objectives
BOOST3 is a comparative effectiveness study to test the efficacy of a prescribed treatment protocol based on monitoring the partial pressure of brain tissue oxygen $PbtO_2$.

Primary Objective: To determine whether the prescribed treatment protocol, informed by $PbtO_2$ monitoring, results in improved neurologic outcome measured by the Glasgow Outcome Scale-Extended (GOS-E) 6 months after injury compared to treatment based on intracranial pressure (ICP) monitoring only.

Secondary Objectives:

- To determine whether treatment informed by $PbtO_2$ monitoring improves functional, cognitive, and behavioral outcome at 6 months
- Safety objective: To determine whether adverse events and serious adverse events associated with $PbtO_2$ and ICP directed therapy are different from adverse events and serious adverse events for therapy directed only at ICP
- To determine whether treatment informed by $PbtO_2$ monitoring improves survival at discharge
- To determine whether treatment informed by $PbtO_2$ monitoring reduces total brain hypoxia exposure, measured by the area under the $PbtO_2$ curve below 20 mmHg
- To determine whether total brain hypoxia exposure is correlated with worse neurological outcome as measured with the GOS-E
- To determine whether total brain hypoxia time is independently correlated with worse neurological outcome as measured by the GOS-E, mortality, as quantified by a composite outcome measure based on functional, cognitive, and behavioral assessments.

Design and Outcomes
This study is a two-arm, single-blind, randomized, controlled, phase III, multi-center trial of the efficacy of $PbtO_2$ monitoring, and is designed to obtain data regarding the efficacy of physiologic maneuvers aimed at normalizing $PbtO_2$ in the first 5 days after injury. Patients with severe TBI who require ICP monitoring will be enrolled into this study within 6 hours of arrival at the enrolling hospital (but no later than 12 hours after injury). All participants in this study will have both ICP monitors and $PbtO_2$ monitors. Half of the participants will be randomized to an arm that includes treatment informed by $PbtO_2$ and ICP, and half will be randomized to an arm that treats only ICP. The study intervention will last for 5 days unless the monitors are removed prior to that.

The $PbtO_2$ values of the ICP only arm will be masked, so that the treating physicians will not be able to read the $PbtO_2$ information. Participants in the active treatment arm will have $PbtO_2$ monitored and hypoxic episodes treated according to the physiologic intervention protocol (PIP). The probe will remain in place for the duration of the study intervention (5 days) and will be removed after that at the discretion of the treatment team.

After the intervention is completed at 5 days, participants will be followed for 6 months and occurrence of serious adverse events or death will be recorded. Participants will have a follow-up interview to assess their level of recovery approximately 6 months post injury.

Interventions and Duration

Participants randomized to the control group will have the $PbtO_2$ monitor implanted in a similar fashion as the participants in the active treatment group, but after calibration of the device, the display will be masked and will not be visible to the medical providers. Participants in the control group will be treated based on ICP monitoring, according to the physiological intervention protocol.

The study intervention group will be treated with both the ICP and $PbtO_2$ values visible to inform care. Participants in the active treatment arm with hypoxic episodes will be treated according to the physiological intervention protocol. The probe will remain in place for the duration of the study intervention.

Treatments for $PbtO_2$ include ventilator adjustments, CPP adjustments with fluid bolus or vasopressors, and transfusion. These treatments may be done even without $PbtO_2$ monitoring if needed for management of ICP or other physiologic parameters. Treatment guidelines will be distributed by the Clinical Standardization Team to reduce variability across enrollment centers.

Sample Size and Population

We plan to enroll a maximum of 1094 male and female subjects, ages 14 years and older among multiple clinical sites. Only subjects who have severe TBI and require ICP monitoring, according to Brain Trauma Foundation (BTF) and American College of Surgeons-Trauma Quality Improvement (ACS TQIP) guidelines, will be enrolled. Management strategies are based on these guidelines.

To reduce the likelihood of imbalance of important prognostic factors between groups, a covariate-adjusted randomization scheme will be used in this study. Adjustment variables are clinical site and probability of a poor outcome as defined by the IMPACT core model.

1 STUDY OBJECTIVES

To test the efficacy of a prescribed treatment protocol based on $PbtO_2$ monitoring.

1.1 Primary Objective:

To determine whether the prescribed treatment protocol, informed by $PbtO_2$ monitoring, results in improved neurologic outcome measured by the Glasgow Outcome Scale-Extended (GOS-E) 6 months after injury compared to treatment based on intracranial pressure (ICP) monitoring only.

1.2 Secondary Objective:

- To demonstrate whether treatment informed by $PbtO_2$ monitoring improves functional, cognitive, and behavioral outcome at 6 months
- Safety objective: To determine whether adverse events and serious adverse events associated with $PbtO_2$ and ICP directed therapy are different from adverse events and serious adverse events for therapy directed only at ICP
- To demonstrate that treatment informed by $PbtO_2$ monitoring improves survival at discharge
- To demonstrate that treatment informed by $PbtO_2$ monitoring reduces total brain hypoxia exposure, measured by the area under the $PbtO_2$ curve below 20 mmHg
- To demonstrate that total brain hypoxia exposure~~time~~ is independently correlated with worse neurological outcome as measured with the GOS-E
- To demonstrate that total brain hypoxia exposure~~time~~ is independently correlated with worse neurological outcome/mortality as quantified by a composite outcome measure based on functional, cognitive, and behavioral assessments

2 BACKGROUND

2.1 Rationale

Magnitude of the problem. TBI is a major cause of death and disability in modern industrialized societies. The most recent estimates from the Centers for Disease Control and Prevention (CDC) indicate that in the United States 3.5 million individuals experience a TBI annually, of which 300,000 are hospitalized and discharged alive, and 52,000 died as a consequence of the TBI.[1] Among the 300,000 hospitalized survivors, over 40% experience long-term disability,[2] which limits their activities of daily living, such as grooming, eating, or walking. Because TBI often affects young people who survive for many years with serious functional limitations, the prevalence of TBI-related disability is high, and it is estimated that 3.3 million people, or 1% of the US population, is living with long-term disabilities from TBI.[3] The annual cost to society resulting from TBI has been estimated to range from $83 billion[4] to $244 billion[5] (in 2014 dollars). The magnitude of this problem has led to numerous clinical trials aimed at improving survival or functional outcome after TBI, yet no effective therapies have been identified to date.

This proposal focuses on the most severely injured victims of TBI, those with prolonged unresponsiveness and extensive intracranial pathology, such as contusions, hemorrhages, edema, and diffuse axonal injury. Since surveillance databases do not typically include data elements commonly used to assess severity,[6] epidemiologic studies specific to severe TBI are sparse. One detailed studied in Aquitaine, France, which included reviews of hospital records of all patients admitted to one of 5 trauma centers over one calendar year concluded that the incidence of severe TBI was 17.3/100,000 population,[7] and the incidence of traumatic coma (severe TBI which resulted in coma lasting longer than 24 hours) was 8.5/100,000.[8] Extrapolating the latter number to the US population, a reasonable estimate of the annual number of cases of traumatic coma in the US is 27,000. These patients experience high mortality and morbidity rates, and less than 20% make a good recovery.[8] They require sophisticated care in intensive care units (ICUs), and the burden to society in direct and indirect costs is very high. Average lifetime costs per TBI survivor in the US has been estimated to be $533,000 in 2014 dollars,[5] but since this estimate is not specific to those with prolonged traumatic coma, the per patient costs for patients who are the target of this proposed study is likely to be significantly higher. Thus, the potential payoff to society from improved care of these most severely injured TBI patients is potentially very high.

Rationale for brain tissue oxygen monitoring. The primary goal of ICU management of severe head injury is to minimize secondary neuronal injury. Historically, ICU monitoring of patients with severe TBI has focused on ICP and cerebral perfusion pressure (CPP), in the hope that lowering ICP when it reaches a critical value (generally > 22 mm Hg) will prevent secondary injury. Although this approach has never been validated in a randomized clinical trial, and recent studies have questioned the benefit of ICP-directed therapies, most clinicians believe that the use of interventions designed to lower ICP when it becomes elevated improves outcome after TBI. This consensus is reflected in the general acceptance of the *Guidelines for the Management of Severe Brain* Injury[9] as well as the American College of Surgeons-Trauma

Quality Improvement Program (ACS TQIP).[10] However, it is unclear how closely these guidelines are followed in routine clinical practice[11].

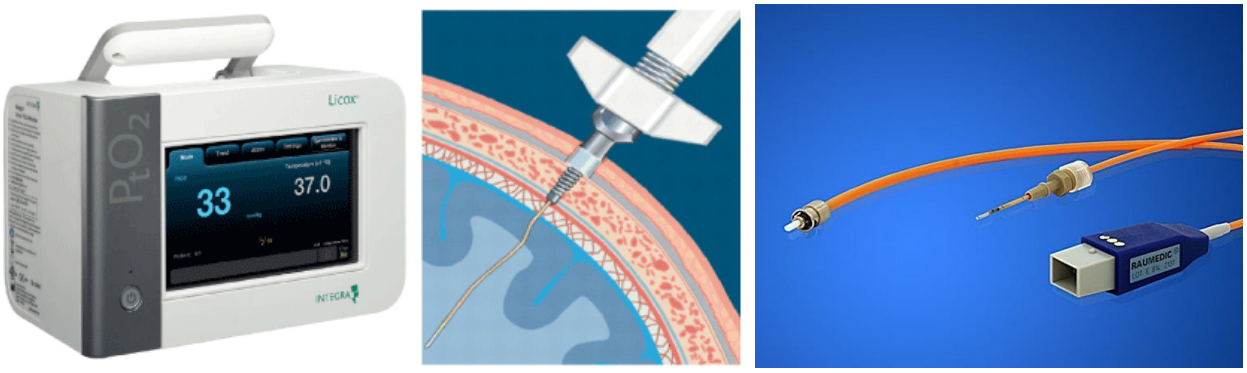


Figure 1. $PbtO_2$ monitoring devices. A:. Licox® System, Integra Neurosciences. B: Neurovent® system, Raumedics.

Another view holds that ICP elevations are insensitive and a late indicator of secondary neural injury. Since the brain depends on an uninterrupted supply of oxygen and glucose to maintain cellular metabolism and viability, several investigators have suggested that monitoring $PbtO_2$ provides a useful marker of tissue metabolism, and that interventions based on $PbtO_2$ may improve patient's outcome. Recently, it has become feasible to continuously monitor $PbtO_2$ using devices from several manufacturers (Fig. 1) that have been approved by the US Food and Drug Administration (FDA). This technology theoretically enables clinicians to detect decreases in brain tissue oxygenation, and to institute therapies to optimize tissue oxygenation, potentially minimizing secondary ischemic injury.

Although several observational studies have shown that low $PbtO_2$ is associated with a poor outcome,[12-14] this technology has not been widely adopted in neurosurgical ICUs, as it is expensive, time consuming, and there is a paucity of well-controlled studies that support its use. While interventions such as increasing inhaled fraction of oxygen (FiO_2), increasing central venous pressure or pulmonary capillary wedge pressure (CVP/PCWP), increasing systemic $PaCO_2$, or transfusion to increase hemoglobin (Hgb) concentration are effective in improving $PbtO_2$ in many clinical situations,[15] no randomized controlled trials have been carried out to determine whether monitoring $PbtO_2$ and intervening to reverse episodes of tissue hypoxia result in improved outcome after severe TBI. Thus, there is equipoise on whether $PbtO_2$ is useful in the management of acute TBI. As part of the development of this study, we conducted a practice survey among lead neurosurgeons at each of the 8 clinical sites of the NIH TBI Clinical Trials Network. In this group of experienced academic neurosurgeons specializing in TBI care, the utilization of $PbtO_2$ monitoring in patients with severe TBI varied from < 2% to > 90%, and all neurosurgeons expressed uncertainty about the usefulness of this device in the management of TBI.

2.2 Supporting Data

Brain tissue hypoxia is common after TBI. One of the guiding principles of neurocritical care is that ischemia is a major cause of secondary brain injury after TBI.[16] This tenet is based on over 30 years of pathologic observations documenting that brain infarction is almost universally

noted in fatal TBI and in the persistent vegetative state.[17-19] More recent data using $PbtO_2$ monitors support this doctrine. Previous work from several investigators indicates that normal $PbtO_2$ is in the range of 25 – 35 mm Hg[12]. In addition, available data indicate that a decline in $PbtO_2$ after TBI is common. Observational studies find that between 70 – 86% of monitored subjects had $PbtO_2$ measurements below 20 mm Hg within the first few days after injury.[12-20] Van den Brink et al. reported that 57% of subjects had $PbtO_2$ lower than 15 mm Hg, 42% had values lower than 10 mm Hg, and values lower than 5 mm Hg were noted in 22%.[21] Artru et al. found episodes of tissue hypoxia in 14 of 16 subjects (87%), that the mean duration of hypoxic episodes was 16 hours, and 86% of episodes lasted longer than 6 hours.[14] In this study, hypoxia ($PbtO_2$ < 15 mm Hg) was identified in 10% of monitoring time. These studies do not specify the inclusion criteria through which subjects were selected, and it is unclear whether subjects studied constituted a representative sample of patients with severe TBI. More recently, Longhi et al. studied 17 subjects with $PbtO_2$ monitors placed in normal appearing brain and reported moderate hypoxia ($PbtO_2$ 10 - 19 mm Hg) 23% of the time and severe hypoxia ($PbtO_2$ < 10 mm Hg) another 11% of the time.[22] The median episode of moderate hypoxia lasted 50 minutes, and the median episode of severe hypoxia lasted 39 minutes. A prospective observational study published in 2004 reported that 14/20 (70%) consecutive patients with severe TBI had episodes of regional cerebral hypoxia, defined as periods of $PbtO_2$ falling below 20 mm Hg.[23] In this study, only 3% of the episodes of regional cerebral hypoxia were associated with elevated ICP, and only 33% were associated with CPP < 65 mm Hg. In another recently reported prospective study, Rosenfeld et al. reported that in a group of patients who underwent PbtO2 monitoring but were not treated, 10% of total monitoring time was < 15 mmHg.[24] Thus, there is good agreement between research centers in different continents on the prevalence of tissue hypoxia detected by $PbtO_2$ monitoring.

Some investigators using ^{15}O PET and other measures of cerebral metabolism have argued that while brain tissue hypoxia and low cerebral blood flow (CBF) are common, they are not associated with increased oxygen extraction fraction (OEF) and are thus a consequence rather than a cause of tissue injury and decreased cerebral metabolic demand (cerebral metabolic rate of oxygen, $CMRO_2$).[25;26] While this may be true in some cases, multiple lines of evidence indicate that, in most cases, tissue hypoxia as measured by $PbtO_2$ monitors is an early sign of incipient tissue injury, while the insult may still be reversible. First, ^{15}O PET studies are inherently limited because they rely on one cross-sectional imaging measurement, whereas continuous measurements using $PbtO_2$ monitoring and cerebral microdialysis find that episodes of hypoxia are usually paroxysmal and transient.[22] Thus, the reversible episodes of hypoxia are likely to be missed by “snapshot” imaging methods. Second, other recent ^{15}O PET studies show that when the $PbtO_2$ monitor is placed in normal appearing brain tissue, interventions such as hyperoxia and augmentation of CPP result in increased $PbtO_2$, decreased OEF, and increased $CMRO_2$, consistent with improving tissue metabolism.[27;28] Thirdly, there is a robust association between tissue hypoxia measured by $PbtO_2$ monitoring and increased lactate/pyruvate ratio measured by microdialysis, indicating that hypoxic episodes result in worsened tissue metabolism.[27-30] In these studies, decline in $PbtO_2$ precedes the increase in lactate/pyruvate ratio, and correction of tissue hypoxia by normobaric hyperoxia[27;30], and/or treatments that elevate CPP,[28] results in normalization of the $PbtO_2$ values and lactate/pyruvate ratios.[27] These studies indicate that correction of tissue hypoxia in the early stages can affect brain metabolism by increasing oxidative metabolism and potentially salvaging tissue at risk.[27] The strong association (rationale below) between duration of hypoxia and functional outcome also supports the hypothesis that tissue hypoxia leads to tissue infarction. Ultimately this important question

will only be settled by a randomized controlled trial of treatments aimed at reversing tissue hypoxia. That is the long-term goal of this study.

Hypoxia is prevalent several days after injury. An important issue directly relevant to the proposed study is the time after injury when hypoxia occurs. Given the practical issues related to $PbtO_2$ probe placement, most human studies of $PbtO_2$ monitoring start recording 4 - 24 hours after injury. There is often a period of several hours after probe insertion when readings are below the normal range; it is generally believed that these initial lower values result from localized trauma related to probe insertion, and that within 1 hour of probe insertion accurate measurements are obtained.[12;31] Although significant tissue hypoxia occurs within the first few hours after injury,[32] a large body of observational evidence indicates that brain tissue hypoxia is also common > 12 - 24 hours after injury. In the study by Artru et al., $PbtO_2$ monitors were placed on average 70 hours after injury, and only 7/22 hypoxic episodes occurred within 12 hours of catheter placement.[14] Valadka et al. placed $PbtO_2$ monitors an average of 16 hours after admission, and found that 92% of patients had some measurements lower than 20 mm Hg, 76% had some measurements < 15 mm Hg, and 67% had some measurements < 10 mm Hg.[13] The only study that reported the prevalence of tissue hypoxia by day after injury found that the peak of brain tissue hypoxia was in days 4 and 5 after injury.[24]

Brain tissue hypoxia is associated with poor outcome. Available data indicate that $PbtO_2$ values below a critical threshold are associated with unfavorable neurologic outcome. Bardt et al. found that the odds ratio (OR) of severe disability or death was 10.8 (95% CI 2.09 – 55.7, p = 0.004) for patients with > 30 minutes of $PbtO_2$ under 10 mm Hg.[34] Van den Brink reached similar conclusions, reporting an OR of 3.8 (95% CI 1.6 – 8.4, p = 0.002) for death for patients with > 30 minutes of hypoxia ($PbtO_2$ < 10 mm Hg).[21] Valadka et al. carried out a Tobit regression analysis and concluded that mortality increased linearly with the duration of time that $PbtO_2$ was below 15 mm Hg.[13] Unpublished data from the University of Pennsylvania (included in section C.4) further supports the 20 mm Hg cutoff. Further, physiological studies suggest that mitochondria need an intracellular oxygen concentration of 1.5 mm Hg to support ATP synthesis, a level corresponding to tissue O_2 concentrations between 15 – 20 mm Hg.[36] Our choice of 20 mm Hg is further supported by a recent review which summarized results from various laboratories and concluded that in order to provide a meaningful margin of safety, the consensus of the field is that 20 mm Hg is the threshold value that should trigger interventions to raise $PbtO_2$.[37]

Brain tissue hypoxia is associated with variables known to be related to poor outcome. Low $PbtO_2$ is associated with poor GCS and poor CT score.[38] Low $PbtO_2$ correlates well with CT perfusion measures of mean transit time,[39] with PET scan measures of cerebral blood flow (CBF),[40] and with focal (thermal diffusion, Qflow, Hemedex) measures of regional CBF.[41] Further, although $PbtO_2$ monitoring provides only regional assessments of tissue hypoxia, it correlates well with measures of global brain hypoxia, such as measures of oxygenation obtained using jugular venous oximetry (S_jO_2).[42;43] Finally, $PbtO_2$ measures of hypoxia correlate well with increased tissue glutamate and lactate measured by cerebral microdialysis.[20;29]

ICU interventions are effective in improving brain tissue oxygenation. Although no randomized controlled Phase 3 trials have been carried out, substantial observational evidence indicates that interventions such as ventilator adjustments that raise PaO_2 (increasing FiO_2 or

positive end expiratory pressure (PEEP)), raising CPP, raising $PaCO_2$, or transfusion to raise Hgb concentration are usually effective in reversing brain tissue hypoxia.[15] Stiefel et al. reported that medical management successfully reversed 72.8% of cerebral hypoxia episodes, usually through ventilator adjustments, CPP augmentation, and sedation.[44]

Rosenfeld and colleagues in Melbourne, Australia[24] carried out a controlled (but non-randomized) study, in which the control group consisted of the initial 10 subjects enrolled, who were monitored with $PbtO_2$ probes, but for whom the $PbtO_2$ values were not used to guide treatment. The treatment group consisted of 20 subsequently treated subjects, for whom $PbtO_2$ values were used to guide therapy using a treatment protocol similar to what we propose to use in this proposed study. The investigators found that the control group was hypoxic ($PbtO_2$< 15 mm Hg) for a total of 63 episodes, with a mean duration of 106 minutes, with 10% of total monitoring time being hypoxic. These results give us confidence that the treatment protocol we propose will be effective in reducing the duration of hypoxia.

Two prospective controlled (but non-randomized) studies address the issue of outcome. Investigators from the Medical College of Virginia treated 52 subjects with normobaric hyperoxia (F_IO_2 of 100% for 24 hours, a therapy that is commonly used for lowered $PbtO_2$), which resulted in higher $PbtO_2$, lower ICP, improvement in biochemical parameters such as glutamate, lactate, lactate/pyruvate ratio, and a trend towards improved outcome at 3 and 6 months, when compared to 112 historical controls.[30] Investigators from the University of Pennsylvania recently published the results of a non-randomized trial (using historical controls) which concluded that $PbtO_2$ directed management lowered mortality from 44% to 25% ($p < 0.05$).[33]

These studies, while relatively small and preliminary, do provide proof of the principle that regional brain hypoxia is common in severe TBI, that it is associated with poor outcome, and that several therapeutic modalities are effective in correcting low $PbtO_2$. A dramatic improvement in mortality reported from a single non-randomized study provides stimulus for the proposed randomized controlled study. However, as these studies have serious flaws, there is also the danger that an expensive but ineffective therapy may be widely adapted without rigorous testing.

Results of BOOST-Phase 2 Study. These variable results led us to conduct a Phase II randomized clinical trial of Brain Oxygen Optimization in Severe TBI (BOOST). The primary hypothesis of the study was that a neurocritical care management strategy informed by $PbtO_2$ values as well as ICP values would reduce the total burden on hypoxia. Secondary hypotheses related to safety, feasibility, and non-futility. The target sample size of the study was 182 participants, and the trial was stopped early by the DSMB for efficacy in the primary outcome.

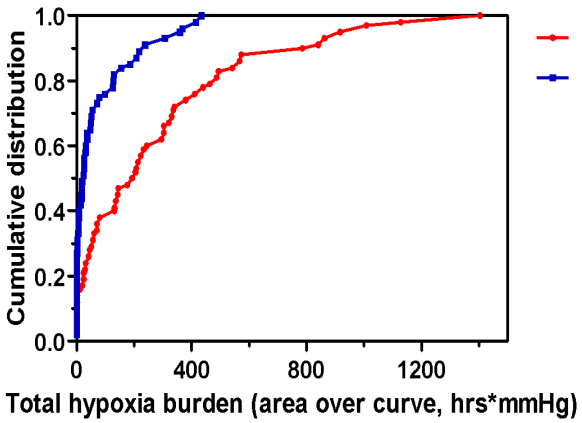


Fig 2. Cumulative distribution of total hypoxia burden (area over the curve in hrs * mm Hg) for each participants in BOOST-2. Mean hypoxia burden in 55 patients in PbtO2 and ICP treatment arm was 74.9 (95% CI 43.9 – 105.9) while for the 58 patients in the ICP only treatment arm mean hypoxia burden was 285.8 (95% CI 202.0 – 369.7) $p < 0.0001$)

Figure 2 summarizes the primary outcome of BOOST-2. There was a substantial and highly statistically significant reduction in total hypoxia burden.[57] More than 20% of the IOCP-only treated subjects experienced a hypoxia burden of > 400 hrs*mm Hg. No subjects in the $PbtO_2$+ ICP treatment group experienced such a high hypoxia burden.

As expected, there was no difference in total intracranial hypertension burden between the two groups (Figure 3), as ICP was treated equivalently.

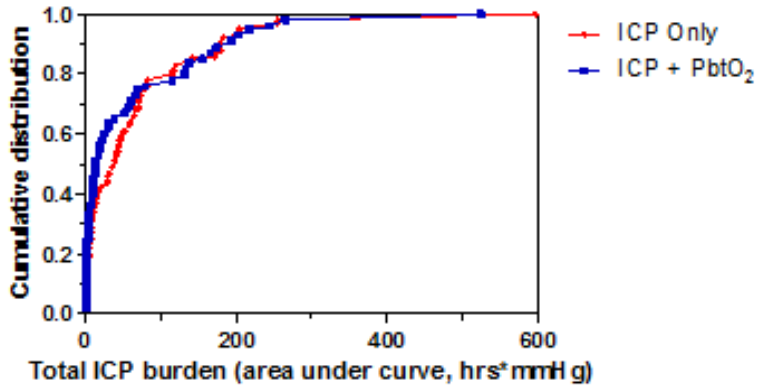


Fig 3. Cumulative distribution of total intracranial hypertension burden (area under the curve in hrs * mm Hg) for each participants in BOOST-2. Mean hypertension burden in 55 patients in PbtO2 and ICP treatment arm was 61.1 (95% CI 35.0 – 87.9) while for the 59 patients in the ICP only treatment arm mean hypertension burden was 67.9 (95% CI 42.5 – 93.4) p = 0.21)

For the non-futility hypothesis, functional outcome was assessed in BOOST-2 participants using the GOS-E administered during a telephone interview 6 months after injury. These results are summarized in Figure 4. There was a trend towards reduced mortality (GOS-E 1) and increased good outcome (GOS-E 7-8) in the $PbtO_2$+ ICP treatment group, compared to the ICP-only treatment grouThe mean (SD) GOS-E was 3.4 (2.2) in the ICP only group and 4.2 (2.5) in the $PbtO_2$+ ICP group (p = 0.111). In the pre-specified analysis dichotomizing the GOS-E at 4, the Odds Ratio favoring good recovery in the $PbtO_2$ + ICP treatment group was 1.8 (p = 0.221, Fisher's exact test). These findings were supportive of the pre-determined non-futility hypothesis.

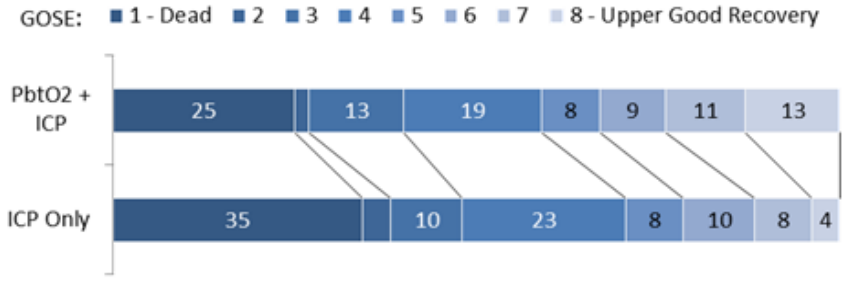


Fig 4. Glasgow Outcome Score-Extended distribution between ICP only and PbtO2 + ICP groups.

Justification for placement of $PbtO_2$ monitor in normal appearing cortex. There is controversy regarding the optimal placement of the $PbtO_2$ probe. In some studies, investigators favor placing the probe ipsilateral to side of maximal injury,[23;33;39;40;43;45] in the hope of monitoring

the pericontusional penumbra, while others favor placing the probe in normal appearing tissue contralateral to visible contusions[12-15;20;21;24;29;30;34;41;46] in the hope of obtaining a measure that reflects global oxygenation status. While there are positive and negative aspects to each, we believe that the only practical approach for a randomized clinical trial is to place the probe in uninvolved cortex, for the following reasons. First, it is the most feasible and reproducible, as $PbtO_2$ probe placement in the pericontusional area typically requires direct observation during craniotomy, or the use of stereotaxic guidance. Second, many patients with severe TBI at risk for tissue hypoxia do not have isolated contusions. In the study by Longhi et al., only 46% of patients had focal lesions that allowed placement of the $PbtO_2$ monitor in the pericontusional region.[22] These investigators found significant differences in $PbtO_2$ depending on the site of insertion. Third, probes placed in the pericontusional region frequently fail to show reactivity to hyperoxia[27] or to augmentation of cerebral perfusion pressure,[28] indicating that they may be monitoring poorly perfused and irreversibly-damaged tissue. Because of these reasons, the majority of the most recent and best available data favors probe placement in normal appearing cortex, contralateral to visible lesions.[12-15;20;21;24;29;30;34;41;46] This was the approach used in our preliminary pilot study, which was used to inform the design of this trial.

Justification for timing of insertion of ICP and PbtO2 monitors. Severe TBI is a neurological emergency, and it is an axiom of neurocritical care that monitoring of secondary brain injury, and interventions to limit such injury, should be instituted as early as is practical. Elevated ICP and brain tissue hypoxia are likely prevalent within minutes of injury in many patients, while in others they arise hours or days later. In an observational study carried out in preparation for BOOST-2,[58] 57% of the initial readings of $PbtO_2$ were below 20 mm Hg. Thus, a strategy to minimize brain tissue hypoxia should commence as soon as possible after injury, in order to have the best chance of saving brain tissue. This is the justification for allowing enrollment under Exemption from Informed Consent (EFIC).

However, it often takes several hours before it is practical to safely insert the ICP and $PbtO_2$ monitors and commence guided therapy. Patients are often initially taken to the nearest emergency department and transported to a Neurotrauma Center capable of performing multimodality monitoring only when the severity of the injury is recognized. In these cases the delay can be several hours. Patients with severe TBI often have to be resuscitated, and systemic injuries have to be evaluated and stabilized. A significant fraction of patients with severe TBI require an emergency craniectomy to evacuate an extra-axial hematoma. Coagulation parameters (platelet count, prothrombin time (PT), partial thromboplastin time (PTT)) have to be assessed to ensure that monitors can be safely inserted. Our experience is that, even in efficient, aggressive, and experienced neurotrauma centers, it takes a minimum of 3 hours for monitors to be inserted, and frequently more.

In our study we will enroll patients who have monitors placed within 6 hours of arrival at the treating hospital, and no more than 12 hours from injury.. The 6-hour time window was chosen as it most closely corresponds to standard practice regarding the timing of ICP and $PbtO_2$ monitor insertion in efficient and high-quality neuro-ICUs. At Parkland Memorial Hospital, the timing of monitor insertion for 2006 – 2007 was 7.2 ± 5.8 hours after admission (mean ± SD, median 6.2 hours, unpublished observations). At the University of Washington, monitors are placed within 6 hours of admission by protocol (RM Chesnut, personal communication). In Dr. Bullock's study, monitors were placed within 6 hours;[30] in Dr. Le Roux's pilot study, all monitors were placed within 6 hours.[33] The Rotterdam group, which is very experienced with this

technique, placed ICP and $PbtO_2$ monitors 7.0 ± 3.5 hours (mean ± SD) after injury.[21] Thus, although brain tissue hypoxia is prevalent for several days after injury (section B.2.2), limiting enrollment to those patients whose monitors are placed within 6 hours of admission to the treating hospital will most closely mirror clinical practice, increasing the likelihood that our results will be accepted by neuro-ICU practitioners and generalizable to their practice, and will exclude only a few patients at our centers. We limit enrollment to patients who can be randomized within 12 hours of injury, as that represents standard practice in leading neurotrauma centers.

3 STUDY DESIGN

Patients with severe TBI who meet eligibility criteria and are appropriate for ICP monitoring according to Brain Trauma Foundation (BTF) guidelines will be implanted with ICP monitors and $PbtO_2$ monitors. ICP and $PbtO_2$ monitors will be placed following local standard practice patterns. In general, these monitors are placed through a single burr hole using a multi-lumen bolt system, so an additional burr hole or prolonged procedure times are not necessary. Participants will be randomized to a treatment protocol based on ICP values alone (control group) or a treatment protocol based on ICP and $PbtO_2$ values (intervention group). A maximum of 1094 participants will be randomized in the study. All participants will be treated according to a standard protocol which will be triggered when the ICU / ED staff identify a rise in ICP > 22 mm Hg or and/or a fall in $PbtO_2$ < 20 mm Hg.

The treatment protocol is a set of physiologic interventions which vary depending on whether the problem is isolated intracranial hypertension, isolated cerebral hypoxia, or the simultaneous occurrence of elevated ICP and low $PbtO_2$. The treatment protocol is tiered in a hierarchical fashion, with less aggressive interventions attempted before more aggressive maneuvers. Monitoring with $PbtO_2$ will continue until the participant awakens from coma or until it is no longer indicated, according to standardized treatment protocol. Functional outcome will be assessed 6 months after injury using the Glasgow Outcome Scale-Extended (GOS-E). Additionally, a battery of psychometric tests and structured questionnaires will be administered to assess functional, cognitive, and behavioral function at 6 months after injury. If the participant is unable to come to the clinic for in-person follow-up, appropriate questionnaires may be administered by telephone.

In this study, the control group will receive standard care based on ICP monitoring alone, while the treatment group will receive standard care using information from the ICP monitors as well as from the $PbtO_2$ monitors. Participants randomized to the control group will have a $PbtO_2$ monitor implanted in a similar fashion as participants in the active treatment group, but after calibration of the device the display of $PbtO_2$ values will be masked, making the display accessible only to study staff who will check the accuracy of the device function. The oxygen data will be continuously saved by digital data recorders for both groups.

The control group will receive standard therapy targeted at ICP control, as compared with the active treatment group who will receive therapies aimed at both ICP and $PbtO_2$ regulation. Variables collected will include when the episode of intracranial hypertension or tissue hypoxia was recognized, when each of the therapies were initiated for each episode, and the treatment utilized. Additionally, data regarding efficacy of each intervention will be collected, as well as the timing of subsequent tiers of therapies, when less invasive treatments are ineffective. Physiologic and laboratory data will be collected and reviewed within the context of the clinical standardization guideline and physiological intervention protocol with compliance feedback provided directly to each site from the Clinical Standardization Team to reduce clinical management variability across sites. Up to the first five days after randomization, measured physiological data will include: ~~cerebral perfusion pressure (CPP)~~, ICP and~~,~~ $PbtO_2$ ~~(in the treatment arm), systemic and brain temperature, systolic blood pressure (SBP), mean arterial pressure (MAP), paO_2, $paCO_2$, INR, platelet count, and hematocrit~~.

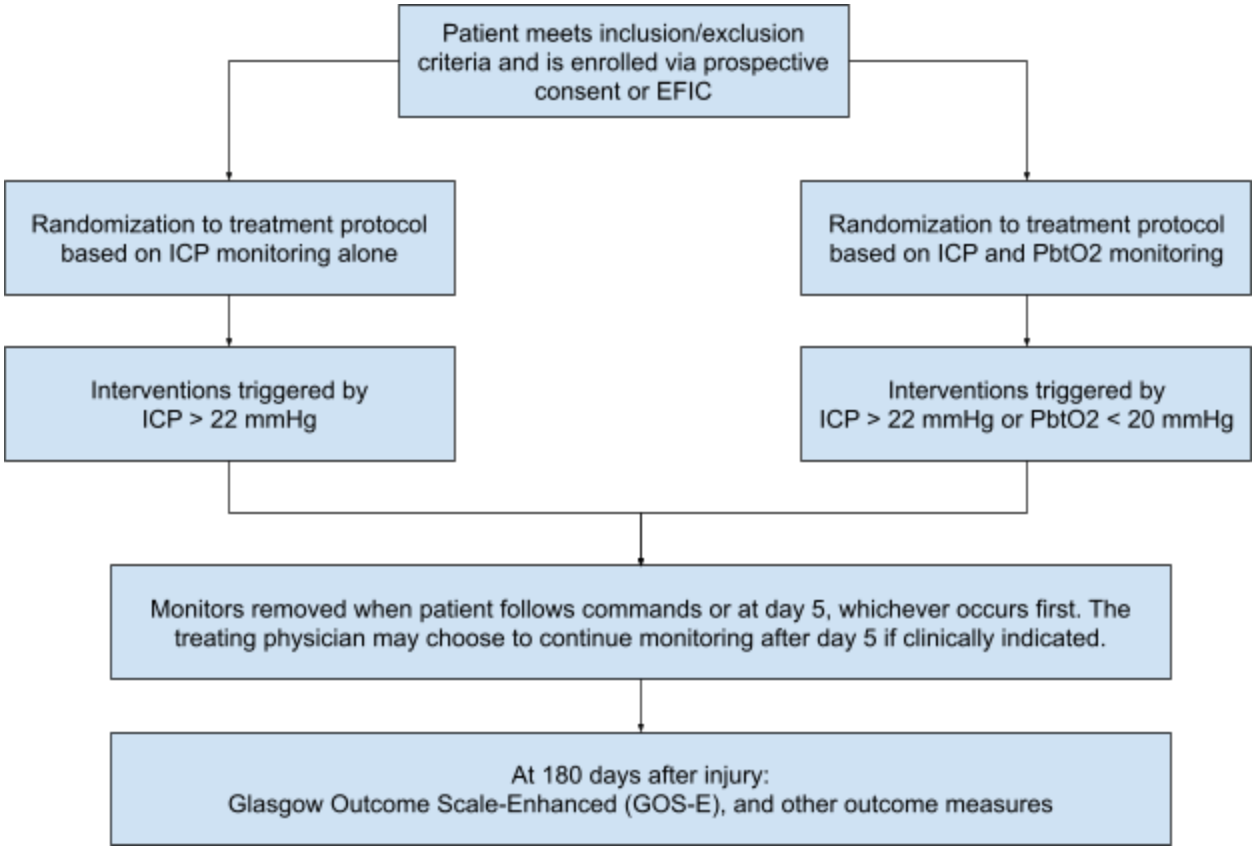


Fig 5. Study Schematic

4 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

Criteria	Rationale	Metric
Non-penetrating traumatic brain injury (TBI)	Primarily focal mechanism of injury; study focuses on diffuse injury	CT scan
Requirement for intracranial pressure monitoring, based on BTF / ACS TQIP Guidelines for the Management of Severe TBI, as operationalized below:	Sufficiently severe TBI to warrant invasive intracranial monitoring	GCS / CT scan
A. GCS 3-8 (measured off paralytics) (In intubated patients, GCS Motor score < 6)		GCS
B. Evidence of intracranial trauma on CT scan.		CT scan. Corresponds to Marshall Score > 1
C. If patient has a witnessed seizure, wait 30 min to evaluate GCS	Post-ictal period may mimic severe TBI but be rapidly reversible	Pre-hospital, ED, and ICU chart
Decision~~Able~~ to place intracranial monitors and ability to randomize within 6 hours of arrival at enrolling hospital, but no later than 12 hours from injury	Treatment of brain tissue hypoxia in first several hours after injury likely influence outcome	Pre-hospital, ED, and ICU chart
Males and females ages ≥14	Cerebral autoregulation different prior to puberty	Demographic history

4.2 Exclusion Criteria

Criteria	Rationale	Metric
Bilaterally absent pupillary response in the absence of paralytic medication in subject with GCS=3	Excessively high risk of unfavorable outcome. Bilaterally absent pupillary response with a GCS > 3 is not uniformly unsalvageable	Physical exam
Contraindication to the placement of intracranial monitors, such as uncorrectable coagulopathy	Need to safely insert intracranial monitors	INR; Platelet count
Treatment of brain tissue oxygen values prior to randomization (monitor can be placed prior to randomization, but readings must be masked to clinical team)	Contamination of group assigned to ICP-only treatment	ICU chart
Planned use of devices which may unblind treating physicians as to brain tissue hypoxia (such devices are listed in the Clinical Standardization Guideline or Physiological Intervention Protocol)	High correlation between information from CBF monitors and $PbtO_2$ monitor	ICU chart; Physical exam
Clinical, demographic, or other characteristic that precludes appropriate diagnosis, treatment, or follow-up		
A. Systemic sepsis at screening	High risk of infection of intracranial monitors	ICU chart
B. Refractory hypotension (SBP < 90 mmHg for two consecutive readings at least 15 minutes apart any time prior to randomization)	High risk of irreversible hypoxic/ischemic brain injury	Pre-hospital, ED, and ICU chart

C. Refractory systemic hypoxia (SaO2 < 90% on FiO2 > 0.5 for two consecutive readings at least 15 minutes apart any time prior to randomization)	High risk of irreversible hypoxic/ischemic brain injury	Pre-hospital, ED, and ICU chart
D. PaO2/FiO2 ratio < 150~~200~~	Severe pulmonary injury making it difficult to sustain systemic and brain oxygenation	ICU chart, arterial blood gas results if done
E. Known pre-existing neurologic disease (e.g. TBI, stroke, or neurodegenerative disorder) with confounding residual neurologic deficits	Minimize confounding effect of neurologic disability prior to index TBI	Medical history
F. Know inability to perform activities of daily living (ADL) without assistance prior to injury	Minimize confounding effect of neurologic disability prior to index TBI	Medical history
G. Known active drug or alcohol dependence that, in the opinion of site investigator, would interfere with physiological response to PbtO2 treatments	Withdrawal from alcohol or other psychoactive drugs may interfere with treatment interventions	Medical history, physical exam
H. Non-survivable injury (e.g. withdrawal of care prior to randomization, no intention for aggressive intervention, on hospice or DNR order etc.)	Excessively high risk of unfavorable outcome	Physical exam
I. Pregnancy	Unknown effects of $PbtO_2$ directed interventions on fetus	Medical history; pregnancy test
J. Prisoner or ward of the state	Inability to provide consent	History
Patient listed on EFIC opt-out registry for study	To be respectful of the wishes of those who learn about the study and	Indicated by the presence of “BOOST trial declined” on any medical alert tag

	declare a desire to not be enrolled in the event of a future injury	or a silicone medical alert bracelet provided by the study to those listed

4.3 Study Enrollment Procedures

4.3.1 Identification and screening process

Subjects will be recruited from patients admitted to the emergency department (ED), trauma, or neurosurgical services at participating clinical sites. Study coordinators will be notified by ED and ICU staff of potentially eligible patients and may also attend daily rounds with the clinical ICU services to further identify eligible participants. Each site will have a system for identification and early notification of potential participants who qualify for the trial. The early notification system will result in timely arrival of the study coordinator or other trained study personnel, who will evaluate participant eligibility. Once notified, study personnel will review the potential participant's information and screen the patient according to the inclusion and exclusion criteria.

A Screen Failure Log will be used for documenting reasons for ineligibility and for nonparticipation of eligible subjects. Data collected for Screen Failures include date screened, gender, race, ethnicity, and reason for non-participation.

4.3.2. Recruitment and informed consent

All patients meeting eligibility criteria for this trial will be obtunded or comatose and unable to give informed consent to participate. Intracranial monitors are emergently placed as part of routine clinical care for all patients with severe TBI who are potentially eligible for this trial. Participants will be enrolled in this trial either with the informed consent of a legally authorized representative (LAR) or with exception from informed consent (EFIC) for emergency research under 21 CFR 50.24. Upon hospital arrival of a potentially eligible subject, study teams will diligently try to determine the availability of an LAR. If an LAR is available prior to the successful placement of intracranial monitoring, the patient will only be enrolled with the written informed consent of the LAR. If an LAR is not available prior to the successful placement of intracranial monitoring, eligible patients will be enrolled with EFIC immediately after intracranial monitor placement, as BTF and ACS guidelines recommend starting intracranial monitoring as promptly as practically possible. Subsequent to an EFIC enrollment, efforts to contact an LAR will continue. An LAR will be notified of an EFIC enrollment and consent to continue in the study will be sought at the earliest opportunity. Complete justification for the use of EFIC and further discussion of human subjects protections are found in section 10 of this protocol.

4.3.3. Randomization procedure for obtaining intervention group assignment

The objective of randomization is to produce study groups comparable with respect to known and unknown risk factors, to remove investigator bias in the recruitment and allocation of participants, and to guarantee that statistical tests have valid significance levels. To reduce the likelihood of imbalance of important prognostic factors between groups, a covariate-adjusted randomization scheme will be used. To receive a treatment assignment, site personnel will enter participant and covariate information into WebDCU™, the electronic Clinical Trial Management System run by the SIREN Data Coordinating Center (DCC) at the Medical University of South Carolina. The variables included in the BOOST-3 covariate adaptive randomization scheme are (1) Clinical site, and (2) probability of poor outcome as defined by the IMPACT core model.

5 STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Overview: Patients with severe TBI who require ICP monitoring according to Brain Trauma Foundation (BTF) guidelines will be implanted with parenchymal ICP monitors and $PbtO_2$ monitors and randomized to a treatment protocol based on ICP values alone (control group) or a treatment protocol based on ICP and $PbtO_2$ values for 5 days. Monitors will be placed in either the ICU or operating room (OR) according to local practice patterns. In general, these monitors are placed through a single burr hole using a multi-lumen bolt system, so an additional burr hole or prolonged procedure times are not necessary. A maximum of 1094 participants will be enrolled in the study. All participants will be treated according to the clinical standardization guideline for the trial. Management of ICP and $PbtO_2$ is directed by the physiological intervention protocol. Specific tier based therapy, as outlined in this protocol, will be triggered when the ICU staff identifies a rise in ICP > 22 mmHg or a fall in $PbtO_2$ < 20 mmHg.

The physiological intervention protocol is a set of interventions to reduce secondary brain injury in the first 5 days after injury. The protocol outlines specific tier based therapy to treat isolated intracranial hypertension, isolated cerebral hypoxia, or the simultaneous occurrence of both elevated ICP and low $PbtO_2$. The treatment protocol is tiered in a hierarchical fashion, with less aggressive interventions attempted before more aggressive maneuvers. ICP monitoring will continue until the participant awakens from coma (motor GCS = 6) or as clinically indicated. Brain tissue oxygen monitoring will be discontinued if the patient starts following commands or after the 5 day interventional period, unless continued use is deemed clinically indicated. Functional outcome will be assessed at 6 months after injury using the Glasgow Outcome Scale-Extended (GOS-E), as well as a battery of neuropsychometric tests and structured questionnaires for TBI, designed to assess functional, cognitive, and behavioral outcomes. If study participants are unable to attend in-person evaluations, questionnaires may be administered by telephone.

The control group will receive standard care (based on ICP driven interventions alone), while the treatment group will be managed using information from the ICP monitors as well as from the $PbtO_2$ monitors for 5 days. Participants randomized to the control group will have $PbtO_2$ monitors implanted in a similar fashion to subjects in the active treatment group, but after calibration of the device, the display of $PbtO_2$ values will be masked, making the display accessible only to study coordinators who are checking accuracy of the device function. The oxygen data will be continuously saved by digital data recorders. It is not practical to blind ICU medical and nursing staff to group assignment, but the research staff who obtain the outcome measures will be blinded to group assignment.

Clinical standardization guidelines. A Clinical Standardization Team (CST) will develop clinical guidelines for the BOOST-3 trial. Goal directed management of physiologic parameters, such as systemic oxygenation, blood pressure, cerebral perfusion pressure, electrolytes, osmolality, and anticoagulation independently affect participant outcome in TBI. In accordance with the recommended treatment guidelines published by the BTF and the ACS, the BOOST-3

CST will identify and minimize the effects of practice heterogeneity/potential clinical confounders by implementing clinical standardization guidelines and overseeing treatment variability across study centers. Compliance with the CST guidelines will be monitored. The relationship between these physiologic variables and response to treatment paradigms will be studied within the secondary analyses.

Experimental Treatment. Patients who meet eligibility criteria will be randomized to a treatment protocol based on ICP values alone or ICP in addition to $PbtO_2$ values. Management of ICP and/or $PbtO_2$ will be according to the protocol outlined below:

Placement of $PbtO_2$ monitor.
(1). We recognize that there are different FDA approved $PbtO_2$ and ICP monitoring devices available in clinical practice. It is likely that the currently approved monitors measure *in vivo* $PbtO_2$ accurately, and that any differences among the devices are minor and unlikely to affect the clinical benefit of monitoring. We recognize that there is an advantage to allowing clinicians to use the devices with which they are most familiar. There is also a benefit gained from increased generalizability of the results of this Phase 3 trial, by allowing a variety of FDA-approved monitoring devices to be used. We will further perform and report subgroup analyses restricted to individual monitoring devices.

The Moberg CNS Monitor will be used to integrate these physiologic data. The Moberg collects data from over 30 medical devices via digital interfaces. The data are collected at the resolution (data rate) of the source device providing a high definition and time-synchronized record of the participant's physiology (as opposed to a static electronic medical record). The device is FDA cleared and provides a nurse-friendly display as well as embedded instructional material to streamline setup and reduce errors in data collection. Capability of the Moberg monitor supports the native $PbtO_2$ data rate of one sample per minute as a mean or selected signal timepoint from the devices.

(2). Both ICP and $PbtO_2$ monitors will be placed at the same time. In general, these monitors are placed through a single burr hole in either the ICU or OR using a multi-lumen bolt system. Practice patterns vary across sites, and some sites place both an external ventricular drain (EVD) and multi-lumen bolt system. Local placement practices will be respected. Every effort will be made for insertion of the monitors as soon as possible after injury, and it is expected that most will be placed within 6 hours of arrival at the enrolling hospital. A head CT will be generally obtained after placement of the monitors to confirm location and assess for any placement associated adverse events.

Continuous ICP monitoring either by parenchymal monitor or EVD is required. A ventriculostomy can be used as the ICP monitor, particularly if CSF drainage for treatment of elevated ICP is required. CSF drainage via the ventriculostomy can be either continuous or intermittent. The ICP readings may be from the EVD monitor only if continuous readings can be recorded, as is the case with brief intermittent CSF drainage. If CSF drainage is continuous, ICP readings must come from a parenchymal ICP monitor.

(3). The $PbtO_2$ probe will be introduced at the same time the ICP monitor is placed through a burr hole in the skull using equipment per local institutional practices. The procedure will be performed by a qualified person with credentials to perform this procedure. In most cases, the

device will be inserted by a house officer who has been trained in this procedure by one of the neurosurgical investigators.

(4). The $PbtO_2$ probe will be inserted into the right frontal lobe, unless there is a contraindication such as a craniotomy flap, a compound depressed skull fracture, or an underlying focal parenchymal injury, such as a contusion or intracerebral hematoma. In these cases, the probe will be inserted into the left frontal area. In most cases, this will result in the probe being placed at a substantial distance from a focal contusion.

(5). Procedures to check reliability of $PbtO_2$ measurements[31]:

A. Prior to insertion, calibration of the device will be checked according to manufacturer's instructions.[48]
B. Each participant will have an FiO_2 challenge within 2 hours after placement of catheter, according to detailed instructions included in the BOOST-3 MOP. Results of the FiO_2 challenge will be blind to the treatment staff.
C. The study staff may request a second challenge or another challenge on another day, if they suspect the device is not working without telling treatment staff the reason.

(6). Recording of ICP and $PbtO_2$: Continuous tracings of both ICP and $PbtO_2$ values will be recorded by bedside digital monitors, which will be calibrated and checked for proper functioning by both nursing staff and research staff. These recordings have real time resolution. The precise equipment and software used for the continuous recordings will be developed for each clinical site according to local needs and available equipment. These continuous records will become a source document for this study. The $PbtO_2$ monitors will be outfitted with an alarm that advises the ICU nursing staff whenever ICP rises above 22 mmHg or $PbtO_2$ falls below 20 mmHg. The $PbtO_2$ alarms will be silenced for the control group (ICP driven therapy only).

(7). Removal or replacement of monitors is at the discretion of the attending physician at each clinical site. The reason for removal or replacement will be documented and recorded in the case report forms. Brain tissue oxygen monitors will be removed in 5 days unless clinically indicated to continue monitoring. After 5 days (120 hours), continued recording of ICP and PbtO2 data is at the discretion of the treating physicians. **If the probes are maintained beyond 5 days, study protocols and group assignments must be maintained. Any cross over of groups or unblinding of PbtO2 data in the ICP only (control) group after 5 days is a protocol violation.** If probes are maintained beyond 5 days, continued data recording and collection via the Moberg CNS monitor is encouraged. Replacement of the $PbtO_2$ monitor will only be considered in the active treatment group.

~~Removal of the ICP and $PbtO_2$ monitors.~~ For both the active treatment and control groups, the ICP and $PbtO_2$ monitors may be removed when any of the following conditions are met:

A. The participant awakens from coma (motor GCS score = 6).
B. There is a medical indication for removal of the monitor (such as infection or bleeding associated with the catheter).
C. No abnormalities of ICP and $PbtO_2$ are noted for 72 hours

If the monitors haveto be removed (for technical failure of the device, the development of a complication associated with the device, or for the development of a condition that in the opinion of the attending physician requires removal of the device, such as diffuse intravascular coagulopathy), the participants will be analyzed in the group to which they were assigned.

Physiological Intervention Protocol for severe TBI
These guidelines are adapted from the Brain Trauma Foundation (BTF) *Guidelines for the Management of Severe Traumatic Brain Injury*) and the American College of Surgeons – Trauma Quality Improvement Program (ACS TQIP) 2015 guidelines.

Guidelines for management of elevated ICP and/or low PbtO2

	ICP ≤ 22 mm Hg	ICP > 22 mm Hg
$PbtO_2$ ≥ 20 mm Hg	Type A No interventions directed at $PbtO_2$ or ICP needed	Type B Interventions directed at lowering ICP
$PbtO_2$ < 20 mm Hg	Type C Interventions directed at increasing $PbtO_2$	Type D Interventions directed at lowering ICP and increasing $PbtO_2$

Fig 6. Scenarios

In principle, episodes requiring therapy will fall into one of 4 types (types A, B, C, and D, defined in figure 6), which will require different management strategies. The chosen protocol will depend on which type of episode is being treated.

Treatment is tier based and triggered by abnormalities in either ICP (> 22 mmHg) or $PbtO_2$ (< 20 mmHg). Elevations in ICP above 22 mm Hg, or decline in $PbtO_2$ below 20 mm Hg, for more than 5 minutes will trigger intervention. Treatment is directed to an episode. Participants may start in one type of episode and move to another. Therapy will depend on which type of episode they are in at any given time. For the participants randomized to ICP treatment alone, only Type A and Type B episodes are relevant.

Treatments must be initiated within 15 minutes of the start of the episode, as detected by the continuous ICP and $PbtO_2$ recordings. The Moberg monitor will be programmed to signal the treating team in real time, when an intervention is recommended. It is expected that a treatment intervention will be initiated as soon as possible after the start of the episode.The initial choice of a treatment option from Tier 1 for any particular scenario should be determined based on what may be the most effective for the current clinical situation. At least one treatment in Tier 1 must be tried before moving on to Tier 2. Tier 3 treatments are optional. For any treatment chosen from any tier, a rapid response to that particular treatment is expected. Should the treatment not be effective in a timely fashion, additional interventions within the same tier may be attempted, or a decision may be made to quickly move to the next tier. While there is no maximum number of treatment options that can be attempted from any one tier, no more than 60 minutes should be spent trying interventions within any single tier prior to moving on to the next tier.

The tiers are organized in a hierarchical fashion, with less invasive interventions attempted in the lower tiers before more aggressive maneuvers in the higher tiers. Treatments within each individual tier are considered equivalent and should be chosen by the bedside care providers based on participant characteristics, underlying pathophysiology, and local protocols. Treatment algorithms were developed through in person and telephone discussions between BOOST investigators with expertise in critical care medicine. The protocol represents a distillation of evidence-based data and expert opinion regarding best practices in neurocritical care. To ensure compliance with the protocol, before the trial begins, training will be conducted at each site to train local ICU and nursing staff on the protocol and principles behind the management strategies.

The protocol represents an attempt to minimize center-to-center variability and to facilitate interpretation of the $PbtO_2$ information by attending staff, house staff, and nursing staff at each center, who may have variable expertise in interpreting and managing such information. We recognize that center-to-center variability is a critical problem in multicenter clinical trials, and we believe that the protocol as written represents a compromise between the need to standardize treatment at all sites and the reality that TBI is a complex and heterogeneous disease, and that sites have inherent differences in staffing, resources, and practice styles.

Treatment interventions triggered by elevations in ICP and/or decreases in $PbtO_2$ will be recorded by the ICU nurses in bedside flow sheets, and study coordinators will transfer information about those interventions into WebDCU™. Furthermore, the time the abnormality was noted by nursing staff and the time the intervention started will also be recorded in the

medical record, with the goal of an intervention initiation within 15 minutes of onset of the event. Data to be collected includes information regarding the efficacy of the intervention in reversing the abnormal physiologic parameter. Pertinent information from the ICU flow chart, as well as the continuous record of ICP and $PbtO_2$, will be collected daily by the study coordinators and will become a source document for the study.

Type A (ICP ≤ 22 mm Hg; $PbtO_2$ ≥ 20 mm Hg).
This is the target range. Participants in this type of episode require no further therapy other than what is in Section 3 above. It is expected that 10% of subjects enrolled in this study will have only type A events[23] and never require ICP or $PbtO_2$ directed therapy. These participants will have both monitors removed 72 hours after insertion.

Type B (ICP > 22 mm Hg; $PbtO_2$ ≥ 20 mm Hg).
This group is treated with therapy aimed at lowering ICP. It is expected that 35% of episodes requiring therapy will fall into this category.[23] Therapeutic strategies are divided into three tiers. Generally, therapy in each tier is reasonably equivalent in terms of safety and efficacy and can be attempted in any order or combination with the goal of lowering ICP. It is not necessary to use all treatments in the tier if it is judged by the treating physicians that a particular intervention is contraindicated in an individual participant. It is expected that at least one intervention from each tier will be used before proceeding to the next tier. The time the abnormality was noted, the times at which each treatment was instituted, and the effect of the treatment will be documented. ~~Reasons why, in the judgment of the clinician caring for the participant, a particular treatment was not instituted will also be documented.~~

Targets of osmolality therapy with mannitol or saline: target serum osmolality (Sosm) is < 320 mOsm, osmolar gap (Ogap) < 20, or serum sodium (sNa) 150-160 mEq/L. In practice, most centers use osmolality targets for mannitol treatment and Na target for saline, with values checked every 6 hours.

Type B: Tier 1 interventions
Tier 1 therapies must be started within 15 minutes of the start of the episode, as detected by the continuous ICP recordings. These are listed in no particular order, and additional details ~~more details, and other options~~ may be found in the MOP.

- Adjust head of the bed to lower ICP.
- Ensure Temperature < 38 °C.
- Adjust pharmacological analgesia and sedation: Titrate to effect.
- CSF drainage (if EVD available). Titrate to effect. Either continuous or intermittent CSF drainage is allowed per site protocol.
- Optimize CPP: May increase CPP up to a maximum of 70 mm Hg.
- Low dose Mannitol (0.25 – 0.5 g/kg), ~~Titrate to ICP control and~~ maintain Sosm < 320 mOsm and / or Ogap <20.
- Low dose Hypertonic saline. The concentration of hypertonic saline should be based on local protocol and may include 1.5% to 3% HTS. Maintain sNa ≤ 160 mEq/L. ~~Titrate to ICP control and maintain serum Na^+ 150-160 mEq/L.~~
- Consider initiation or titration of anti-seizure medications (AEDs), ~~either Phenytoin or Levetiracetam, to be used prophylactically for 1 week only~~.
- Adjust ventilator for a target $PaCO_2$ of 35 - 40 mm Hg and target pH of 7.35 - 7.45

Type B: Tier 2 interventions

Providers may move to Tier 2 interventions at any point if ICP is > 22 mm Hg and at least one intervention from Tier 1 has been used. **Providers must move to Tier 2 interventions if ICP is > 22 mm Hg for > 60 minutes despite Tier 1 therapies.** Tier 2 interventions are listed in no particular order and additional details ~~other options~~ may be found in the MOP.

- Optimize CPP: May increase CPP above 70 mm Hg.
- Adjust ventilatory rate to lower $paCO_2$ to 3~~2~~ – 3~~6~~5 mm Hg and target pH of 7.35 - 7.45.
- High dose Mannitol 1.0-1.5 g/kg, or higher frequency of lower ~~standard~~ dose mannitol. Maintain Sosm < 320 mOsm and / or Ogap <20.
- High dose Hypertonic Saline bolus (7.5% or higher). Maintain sNa ≤ 160 mEq/L. ~~(if Sosm <320 mOsm)~~.
- Repeat CT to determine if increased size of intracranial mass lesions and treat surgically remediable lesions according to guidelines..
- ~~Treat surgically remediable lesions with craniotomy according to guidelines~~.
- Adjust temperature to 35 – 3~~6~~7 ºC, using active cooling measures.
- Neuromuscular blockade with short acting agents.

Type B: Tier 3 interventions

Tier 3 therapies are optional. If/when Tier 3 therapies are utilized, as well as the time when they are utilized, will be recorded in the CRFs. These are listed in no particular order and additional details may be found in the MOP.

- Pentobarbital coma, according to local protocol.
- Decompressive craniectomy.
- Adjust temperature to 32 – 3~~4~~5 ºC, using active cooling measures.
- Adjust ventilatory rate for a target $PaCO_2$ of 30 - 35 mm Hg while maintaining a pH less than 7.5
- Other salvage therapy based on local protocol and practice patterns.~~Neuromuscular paralysis.~~

Type C (ICP ≤ 22 mm Hg, $PbtO_2$ < 20 mm Hg).

It is expected that 35% of episodes requiring therapy will fall into this category.[23] This group will have therapy directed at $PbtO_2$.

Type C: Tier 1 interventions

Tier 1 therapies must be started within 15 minutes of the start of the episode, as detected by the continuous $PbtO_2$ recordings. These are listed in no particular order and additional details ~~other options~~ may be found in the MOP.

- Adjust head of the bed to improve brain oxygen level.
- Ensure Temperature < 38 ºC.
- Optimize ~~Increase~~ CPP: May increase CPP up to a maximum of 70 mm Hg ~~with fluid boluses or vasopressors as clinically appropriate~~.
- Optimize hemodynamics through resuscitation or diuresis.
- Optimize PaO_2 through adjustments to FiO_2 (maximum of 60%), positive end expiratory pressure (PEEP), or pulmonary toileting measures. ~~Obtain arterial blood gas to confirm that oxygenation is in desired range before treating with PaO_2 adjustment. Increase PaO_2 by increasing FiO_2 to 60%.~~

- Adjust ventilatory rate to achieve a $PaCO_2$ of 38 - 42 mm Hg while maintaining a target pH of 7.35 - 7.45. ~~Increase PaO_2 by adjusting positive end expiratory pressure (PEEP).¶~~
- ~~Consider EEG monitoring.~~
- Initiate or titrate ~~Consider~~ anti-seizure medications (AEDs)

Type C: Tier 2 interventions

Providers may move to Tier 2 interventions at any point if $PbtO_2$ is < 20 mm Hg and at least one intervention from Tier 1 has been used. **Providers must move on to Tier 2 interventions if $PbtO_2$ < 20 mm Hg for > 60 minutes despite Tier 1 therapies.** These are listed in no particular order and additional ~~other~~ details~~options~~ may be found in the MOP.

- Optimize PaO_2 through adjustments to FiO_2 (maximum of 100%), PEEP, or pulmonary toileting measures.~~Adjust ventilator parameters to increase PaO2 by increasing FiO2 to 100%.¶~~
- ~~Increase PaO2 by adjusting PEEP~~.
- Optimize ~~Increase~~ CPP: May increase CPP above 70 mm Hg ~~with fluid boluses or vasopressors~~.
- Adjust ventilatory rate to increase $PaCO_2$ to 40 ~~45~~ – 4~~5~~0 mm Hg while maintaining a pH of 7.35 - 7.45.
- Neuromuscular blockade with short acting agents
- Transfusion~~e~~ of pRBCs ~~to Hgb ≥ 10 g/dL~~.
- Decrease ICP to < 15 mm Hg.
- CSF drainage.
- Increased sedation

Type C: Tier 3 interventions

Tier 3 therapies are optional, and may be used at any point after at least one option from both Tier 1 and Tier 2 have been attempted and are ineffective**.** If/when Tier 3 therapies are utilized, as well as the time when they are utilized, will be recorded in the CRFs. These are listed in no particular order and additional details may be found in the MOP.~~Other options can be found in the MOP~~.

- Adjust ventilatory rate to increase $PaCO_2$ to > 45 mm Hg while maintaining a target pH of 7.30 – 7.45.
- Increase cardiac output with inotropes .
- Assess for vasospasm.
- Hyperventilation to address possible 'reverse Robin-Hood syndrome'.
- Other salvage therapy based on local protocol, practice patterns, and presumed causes of low $PbtO_2$ (spreading depolarizations, pulmonary embolism, cerebral venous thrombosis, etc.).

Type D: (ICP > 22 mm Hg; $PbtO_2$ < 20 mm Hg).
It is expected that 20% of episodes requiring therapy will fall into this category.[23] Treatment for this group is primarily aimed at lowering ICP. Thus, it is similar to Type B with some modifications.

Type D: Tier 1 interventions

Tier 1 therapies must be started within 15 minutes of the start of the episode, as detected by the continuous ICP and $PbtO_2$ recordings. These are listed in no particular order and additional details~~other options~~ may be found in the MOP.

- Adjust head of the bed to lower ICP (ICP protocol dominant for HOB).
- Ensure Temperature < 38 °C.
- Adjust p~~P~~harmacologic analgesia and / or~~and~~ sedation — titrate to effect.
- CSF drainage (if EVD available).
- Optimize hemodynamics through resuscitation or diuresis.
- Optimize ~~Increase~~ CPP: May increase CPP up to a maximum of 70 mm Hg ~~with fluid boluses or vasopressors~~.
- Low dose Mannitol (0.25 – 0.5 mg/kg)~~.~~; ~~Titrate to ICP control and m~~Maintain Sosm < 320 mOsm and / or Ogap <20.
- Low dose Hypertonic saline. The concentration of hypertonic saline should be based on local protocol and may include 1.5% to 3% HTS. ~~Titrate to effect and m~~Maintain sNa^+ ~~<150~~ 160 mEq/L.
- Optimize PaO_2 through adjustments to FiO_2 (maximum of 60%), PEEP, or pulmonary toileting measures.
- Adjust ventilatory rate to achieve a $PaCO_2$ of 38 - 42 while maintaining a target pH of 7.35 – 7.45.
- Initiate or titrate AEDs
- ~~Increase PaO_2 by increasing FiO_2 to a maximum of 60%. Obtain arterial blood gas to confirm oxygenation is in desired range before treating with PaO_2 adjustment. 9. Increase PaO_2 by increasing FiO_2 to 60%.¶~~
- ~~Increase FiO_2 by increasing PEEP (Hyperventilation to $PaCO_2$ below 35 mm Hg is not recommended for Type D events).¶~~
- ~~Consider EEG monitoring.¶~~
- ~~Consider AEDs, shouldeither Phenytoin or Levetiracetam, to be used prophylactically for 1 week only. ¶~~

Type D: Tier 2 interventions.

Providers may move to Tier 2 interventions at any point if ICP is > 22 mmHg and PbtO2 is < 20 mm Hg and at least one intervention from Tier 1 has been used. Providers must move on to Tier 2 interventions if ICP ≥ 22 mm Hg and $PbtO_2$ < 20 mm Hg for > 60 minutes despite Tier 1 therapies. These are listed in no particular order and additional details~~other options~~ may be found in the MOP.

- High dose Mannitol 1.0-1.5 g/kg, or frequent boluses standard dose Mannitol. ~~(~~Maintain~~if~~ Sosm < 320 mOsm and / or~~or~~ Ogap < 20).
- High dose Hypertonic saline bolus (7.5% or higher). Maintain sNa levels < 160 meq/l
- Optimize~~Increase~~ CPP: May increase CPP above 70 mm Hg ~~with fluid boluses or vasopressors~~.
- Optimize PaO_2 through adjustments to FiO_2 (maximum of 100%), PEEP, or pulmonary toileting measures.
- ~~Increase PaO_2 by increasing FiO_2 to 100%.¶~~
- ~~Increase PaO_2 by increasing PEEP.~~
- Transfusion of~~e~~ pRBCs ~~to Hgb ≥ 10 g/dL~~.
- Repeat CT to determine if increased size of intracranial mass lesions and ~~.~~¶
- ~~T~~treat surgically remediable lesions ~~with craniotomy~~ according to guidelines.

- Adjust temperature ~~Induced~~ hypothermia ~~-~~ to 35 - 36 °C, using active cooling measures.
- Neuromuscular blockade with short acting agents.

Type D: Tier 3 interventions.
Tier 3 therapies are optional. If/when Tier 3 therapies are utilized, as well as the time when they are utilized, will be recorded in the CRFs. These are listed in no particular order and additional details~~other options~~ may be found in the MOP.

- Pentobarbital coma, according to local protocol.
- Decompressive craniectomy.
- Adjust temperature ~~Induced hypothermia~~ to 32 – 35~~4.5~~ °C, using active cooling measures
- Increase cardiac output with inotropes~~Neuromuscular paralysis~~.
- Assess for vasospasm.
- Hyperventilation to address possible 'reverse Robin-Hood syndrome'.
- Other salvage therapy based on local protocol, practice patterns, and presumed causes of low $PbtO_2$ (spreading depolarizations, pulmonary embolism, cerebral venous thrombosis, etc.).

5.2 Clinical Monitoring

General Intervention Related Monitoring
Blood pressure will be monitored via an arterial line during the treatment period and mean arterial pressure will be recorded (MAP) by the clinical team. Hypotension will be defined as MAP < 70 mm Hg. The extent and duration of hypotension will be recorded. ICP will be monitored, and the duration and extent of intracranial hypertension (ICP > 22 mmHg) will be recorded. Cerebral perfusion pressure (CPP) will be monitored~~, and the duration and extent of cerebral hypoperfusion (CPP < 60 mm Hg) will be recorded~~. Chest x-rays will be obtained as clinically indicated to assess for pneumonia, infiltrates, or changes suggestive of pulmonary oxygen toxicity / Adult Respiratory Distress Syndrome.

EEG Monitoring EEG monitoring data, when performed for clinical purposes, will be collected on study subjects. EEG monitoring is not required for research purposes. Treatment of seizures will be according to clinical protocols at each site, and information about antiepileptic treatments will be recorded in CRFs. More detail is provided in the MOP.

5.3 Potential Risks of Treatment Interventions

In general, a severe TBI puts patients at risk for hospital related complications. There is also the risk that a management strategy based on $PbtO_2$ monitoring produces clinical results worse than standard care, as well as the parallel risk that $PbtO_2$ monitoring is better than standard care. Assessments of those risks are a goal of this study. In addition, there are potential risks directly associated with protocol related treatment interventions.

5.3.1 Risks Associated with Placement of Monitors

Potential risks resulting from placement of the intracranial monitors in this study are low. $PbtO_2$ and ICP monitors are FDA-approved devices for the management of patients with severe TBI

and are recognized to have a low risk of complications. Both are listed as treatments in the Brain Trauma Foundation *Guidelines for the Management of Severe TBI.* All sites for BOOST3 have experience using brain tissue oxygen monitors in patients with TBI

There is a small risk of bleeding at the site of insertion of the $PbtO_2$ and ICP monitors. There is also a small risk of infection related to monitor placement. The frequency of adverse events resulting from monitor placement reported in the literature ranges from zero (101 patients studied by van den Brink et al.[21] and 20 patients studied by Gracias et al.[23]) to 1.7% (2 of 101 patients studied by Dings et al.[45]). Both adverse events were small iatrogenic hematomas that did not require evacuation. There are no reported infectious adverse events in the available literature. There were no adverse events resulting from monitor placement (either infections or hematomas) in the 122 participants in the BOOST-2 study.

5.3.2 Risks Associated with Treatment Interventions to Manage ICP Elevations

Treatment of ICP elevations is considered a standard of care in the TBI literature. The risks of these interventions have been considered acceptable based on the potential for decreased ICP-related mortality and morbidity.

Participants randomized to the ICP only treatment arm may have some of the following interventions from Type B and D scenarios if their ICP increases above 22 mm Hg for more than 5 minutes:

- Placement of an external ventricular drain (EVD) if not previously placed
- Mannitol (standard or high dose)
- Hypertonic saline (bolus or continuous infusions)
- Hyperventilation
- Hypothermia
- Decompressive hemicraniectomy
- Barbiturate coma
- Neuromuscular paralysis

Monitoring for complications related to these interventions will be performed and appropriate management provided as indicated.

5.3.3 Risks Associated with Treatment Interventions to Manage Low $PbtO_2$

There is a risk that the interventions prompted by $PbtO_2$ readings may be associated with specific treatment related complications such as pneumonia or lung injury, which may occur more frequently when treating a participant for oxygen deficiency.

Participants randomized to the $PbtO_2$ treatment group may have some of the following interventions from Type C and D scenarios if their $PbtO_2$ drops below 20 mm Hg for more than 5 minutes:

- Increase cerebral perfusion pressure (CPP) with fluid boluses or vasopressors (such as norepinephrine or phenylephrine)
- Transfusion
- Adjust ventilator parameters to increase PaO_2. (increase FiO_2 and/or increase PEEP)
- Optimize hemodynamics by increasing volume status, which may require assessment of central venous pressure, pulmonary capillary wedge pressure, and/or cardiac output.

Monitoring for complications related to these interventions will be performed and appropriate management provided as indicated.

5.3.4 Safety Monitoring:

All adverse events (AEs) will be recorded through Day 5 (i.e. 120 hours) or Discharge, whichever comes first. All serious adverse events (SAEs) will be recorded through the end of study.
The expected incidence of specific intervention related AEs are listed in Table 6.

Table 6. **Specific Anticipated Adverse Events**	Expected Incidence
ARDS ~~/ Acute Lung Injury~~	5%
Ventilator associated p~~P~~neumonia	25%
Sepsis ~~/ SIRS~~	5%
Septic Shock	3%
Hematoma related to probe placement requiring craniotomy for evacuation	0.5%
CNS Infection related to intracranial monitoring	<0.5%

Safety Monitoring: The study has three levels of protection designed to assess subject safety and adverse events.

First, the PI at each site will review all Serious Adverse Events (SAEs) with the coordinator to determine relatedness of the intervention to the SAE. These individuals are highly experienced in the management of acute traumatic brain injury and with brain tissue oxygen monitoring and are aware of the possible and probable complications of interventions prescribed by the protocol, as well as adverse complications common to traumatically injured participants but unlikely to be related to the treatment protocol.

Second, an independent Medical Safety Monitor (iMSM) will review SAEs in a timely fashion and in aggregate on a quarterly basis. The iMSM will communicate with the NINDS Liaison to the Data and Safety Monitoring Board regarding any safety issues or concerns.

Third, a Data and Safety Monitoring Board will be appointed by NINDS and will meet as often as the DSMB and NINDS decide, to review the safety data in an unblinded fashion. Aggregate results presented to the study investigators will be blinded as to group assignment. The DSMB may recommend to NINDS stopping the study for safety reasons if there is evidence that $PbtO_2$ monitoring or treatment aimed at increasing $PbtO_2$ is harmful. Refer to the Safety Monitoring Plan for more details on the safety monitoring process.

5.3.5 Adequacy of Protection Against Risks.

Training: Given the need for adherence to the treatment protocol, nursing and medical staff at each clinical site will receive extensive training on details of the protocol as well as the rationale behind the treatment strategies.

Within approximately one month prior to study start-up, the PIs at each site will conduct in-service education, which will be attended by neuro-ICU nurses, house staff in neurosurgery, neurology, emergency medicine, and critical care medicine, respiratory therapists, as well as attending physicians in different specialties involved in the management of TBI.

Protection against risk of monitor placement. Every effort will be made to minimize these potential risks. $PbtO_2$ monitors and ICP monitors will be inserted by trained physicians, under the direct supervision of a board certified neurosurgeon. Device placement and possible occurrence of iatrogenic hematomas will be checked by CT scanning as is standard of care in our units. Participant's status will be followed closely, and unexplained fevers will be evaluated by standard clinical protocols. If there is any suspicion that the device has become infected it will be removed.

5.4 Handling of Study Interventions

Blinding: The $PbtO_2$ monitors will be masked for this study in the control group, so that hospital staff will not be able to read the $PbtO_2$ information. Hospital staff are not blinded as to who is in the control or active treatment groups. The 6 Month outcomes will be collected by an assessor blinded to randomization assignment.

5.5 Concomitant Interventions

5.5.1 Required Interventions.

Patients with severe TBI who require ICP monitoring according to Brain Trauma Foundation (BTF) guidelines will be implanted with parenchymal or EVD ICP monitors and $PbtO_2$ monitors and will~~may~~ be randomized to a treatment protocol based on ICP values alone (control group) or a treatment protocol based on ICP and $PbtO_2$ values.

5.5.2 Prohibited Interventions.

Patients who qualify will be randomized and treated per study guidelines, provided they do not already have a $PbtO_2$ monitor in place that is being read and acted on by the medical team.

5.6 Adherence Assessment

Adherence to a complex critical care protocol is critical for success of this study. This will be accomplished in two ways. First, study data for the first 2 participants enrolled at each study site will be reviewed by the trainer assigned to that site.~~a member of the Clinical Standardization Team (CST) after the required de-identified records are uploaded into the database by the study site staff~~. The purpose of this review will be to monitor adherence to the study protocol, identify reasons for protocol deviations, implement changes in clinical procedures, and assess the need for training to improve compliance. Second, a study monitor will visit each of the clinical sites to review study participants' medical and study records and perform source document verification against data submitted in WebDCU™.

6 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations

Table 5 Study Procedures	Screening (0-1 days)	Entry	Day 1-5	Day 6 - Discharge	Day 180
Informed Consent	X				
Documentation of Disease/Disorder	X				
Medical/Treatment History	X	X	X	X	X
Assessment for AEs and SAEs		X	X	X	X
Physiologic Data Collection	X	X	X		
Physical Exam	X				
CT evaluation	X				
Hematology TD	X				
Chemistry TD	X				
Pregnancy Testing	X				
Outcome Measures					X

6.2 Final Evaluation Detail

Assessment of outcome 6 months after injury (180 Days ± 30 days). Trained study personnel who are blinded to the treatment arm will administer the outcome assessments, which will include the measures listed below. The battery includes measures of functional status (GOSE and FSE), cognition, and emotional health**.** The 6-month follow-up interview will be done in person whenever possible. It may be done by telephone or video conference with participants where an in-person interview is not possible.

Table 3. **Outcome Assessments**		
Functional Status	Formal Measures of Cognition	Emotional Health Measures
• Glasgow Outcome Scale-Extended (GOSE) • Structured Interview • Functional Status Examination	• Rey Auditory Verbal Learning Test • Trail Making Test Part A+B • WAIS IV Processing Speed Index	• Rivermead Post-Concussive Symptom Questionnaire • Brief Symptom Inventory • Satisfaction with Life Scale
For explanations, citations, and expected testing durations of each component of the battery please refer to the MOP-Outcomes Manual ~~study protocol~~.		

Assessment of adherence to the outcome protocol: All outcome examiners will be trained to administer and score the 6-month outcome battery. All outcome examiners must be certified prior to their first study test administration. Regular conference calls will be held to discuss any

common errors. Re-certification may also be required as needed (e.g., repeated errors are made).

7 CRITERIA FOR TRIAL ~~INTERVENTION~~ DISCONTINUATION

Plans for stopping the trial for efficacy and futility are discussed in the Statistical Analysis Plan. The trial can be stopped at any time for safety concerns. Potentially associated adverse events will be analyzed for treatment group differences in the semi-annual reports to the DSMB via relative risk and 95% confidence interval. In addition, a 95% confidence interval will be constructed around the event proportion within each treatment arm. The DCC will highlight in the DSMB report events for which the relative risk is significantly greater than 1, or for which the incidence rate is significantly higher than the expected rate, based on these confidence intervals.

8 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

Study Design -- Primary and secondary outcomes:
This is a phase III study of the effectiveness and safety of brain oxygen monitoring and management against standard management for the treatment of severe brain injury. The primary outcome is the Glasgow Outcome Scale-Extended (GOS-E), including disability associated with the overall injury, assessed at 6 months post randomization. Favorable outcome is defined according to a sliding dichotomy[50], where the definition of favorable outcome varies according to baseline severity. Severity will be defined according to the probability of poor outcome predicted by the IMPACT core model.[51] The favorable outcome definition is more stringent for subjects with a low probability of poor outcome, as outlined in the table below.

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

8.2 Hypotheses

8.2.1. Primary Hypothesis:

The prescribed treatment protocol, informed by $PbtO_2$ monitoring, results in improved neurologic outcome measured by the sliding dichotomy of the GOS-E 6 months after injury.

8.2.2 Sample size justification.

The primary endpoint is favorable outcome at 6 months post randomization, where favorable outcome is defined according to the sliding dichotomy of the GOS-E as described above. A clinically relevant effect size of 10% absolute difference in favorable outcome proportions is prespecified. In order to achieve 85% power with a two-sided type I error probability of 0.05, 880 subjects are required. This calculation assumes a 50% favorable outcome proportion in the control arm. Inflation to account for interim analysis, as specified in the Statistical Analysis Plan, and 7% non-adherence, as indicated by Friedman, Furberg and DeMets (1998), results in a maximum sample size of 1094 subjects.

8.3 Statistical Methods to Analyze the Primary Outcome

Favorable outcome will be defined according to a sliding dichotomy of the GOS-E, as defined in the Primary Outcome section above. The primary analysis will be conducted according to the Intention-to-Treat principle. The proportion of subjects with favorable outcome will be compared across treatment arms via generalized linear model, with adjustment for the severity strata

defined according to the probability of a poor outcome resulting from the IMPACT core model as described above.

Details of all planned statistical analyses, including the interim analyses, are provided in the Statistical Analysis Plan (SAP). Two interim analyses are planned. Analyses for overwhelming efficacy and futility will be conducted according to O'Brien-Fleming boundaries. The SAP contains the specific details of the planned boundaries, the timing of which can be altered by the Data and Safety Monitoring Board (DSMB). The Data Coordinating Center (DCC) will conduct these analyses and compile results for the DSMB, who will make recommendations regarding study termination or continuation.

8.4 Data Management and Quality Assurance

Data management will be handled by the BOOST DCC, which is housed in the Data Coordination Unit (DCU) of the Department of Public Health Sciences at the Medical University of South Carolina. All study activities will be conducted in coordination with the study co-PIs, the hubs/spokes, and the CCC and DCC, and will use an electronic data acquisition method where all clinical data on randomized subjects will be entered by site personnel. The latest version of each CRF will be available as a PDF file on the study website for use as worksheets and source documents by study personnel.

The study data will be managed by the DCC using the WebDCU™ system. This user-friendly web-based clinical trial management system, developed by the DCC, will be used for regulatory document management, subject randomization, data entry, data validation, project progress monitoring, subject tracking, user customizable report generation and secure data transfer. Upon entry of CRFs into the study database, quality control procedures will be applied at each stage of data handling in order to ensure compliance with GCP guidelines, integrity of the study data and document processing system reliability.

9 DATA COLLECTION AND ADVERSE EXPERIENCE REPORTING

9.1 Data Collection

Study personnel will collect information to characterize the participant such as demographics, medical history, injury information and vitals. This information describes the participant before starting the experimental treatment. In addition, in the first 24 hours after randomization, information will be collected regarding surgical interventions, severity of injury, and other medical treatments that the participant receives. As part of the baseline data collection, family members will be asked to complete a contact information form with the names, addresses and phone numbers of other people who could assist in locating him/her if the study coordination cannot locate him/her for the scheduled phone interviews.

Information specific to the $PbtO_2$ monitoring study will be collected while the monitors are in place or up to 5 days. This will include continuous digital recordings of ICP and $PbtO_2$ values. In addition hourly measures of the worst ICP and $PbtO_2$ readings, as recorded by nursing staff in the bedside ICU flow sheets will be collected during the first 5 days after placement, in order to assess the time at which nursing staff noted ICP or $PbtO_2$ abnormalities. All changes in ventilator parameters, blood transfusions, the use of mannitol, vasopressors, or fluid boluses instituted in order to correct abnormalities in the physiologic parameters, as well as the time of those interventions, will also be recorded.

Additional information will be collected daily during the acute hospitalization. The amount of information collected will depend upon the participant's location in the hospital and will be greatest for participants in the Intensive Care Unit (ICU) and least for participants on a regular floor, but will include the symptom checklist, concomitant medications, surgical interventions, adverse events, serious adverse events, and death.

CT scans will be read locally to determine eligibility. These CT scans will be available for central review of possible protocol violations, assessment of safety of device implantation, and assessment of the relationship between adverse events and the treatment protocol. Imaging data will be sent to central imaging database for collection and review.¶

9.2 Continuous EEG Data

Many of the hospital centers use continuous EEG monitoring as standard of care with participants who have severe TBI. Continuous EEG data will be collected from sites that provide this information in a central location to be used for future ancillary studies. Analysis of these data is outside the scope of this investigation.

9.3 Quality Assurance/Site Monitoring

The Clinical Core will oversee the Quality Assurance procedures related to the ICU management of episodes of intracranial hypertension and brain tissue hypoxia. Safety and protocol adherence monitoring reports will be submitted and reviewed centrally. Raters are required to pass a certification test. Scoring and coding of the outcome measures will be double-checked by the data quality specialist.

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

The study leadership on a regular basis, will review a summary of the data entered in the BOOST3 WebDCU™ database by the participating clinical sites to identify deficiencies in data collection and/or entry. This summary will be the result of the ongoing review by the DCC Data Manager (DM) and IMSM of data entered by all participating clinical sites.

9.4 Adverse Events and Serious Adverse Events

9.4.1 Definition of Adverse Events (AE)

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

9.4.2 Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions. Important medical events may also be considered serious when they require medical or surgical intervention to prevent death, risk of permanent injury or disability, or prolonged hospitalization. The population being studied has a high rate of clinically expected adverse events related to their underlying condition and standard treatment, independent of any research intervention. 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 approaching ~~of~~ 40%. Examples of common medical events in this population include (but are not limited to): ventilator associated pneumonia, venous thromboembolic disease, or progressive cerebral edema. Examples of common medical or surgical interventions include: evacuation of an intracerebral hematoma secondary to ventriculostomy insertion, or inferior caval filter placement to prevent pulmonary embolism.

Subjects may also incur AE that could be expected to occur at higher rates because of the study intervention. These include medical events such as exacerbated lung injury, transfusion reaction, or other events associated with a treatment directed at low PbtO2. Particular attention will be paid to potential complications from PbtO2 treatment listed in section 9.4.

Pre-existing medical conditions or unchanged, chronic medical conditions. Pre-existing medical conditions or unchanged, chronic medical conditions are NOT considered AEs and should not be recorded on the AE case report form (CRF). These medical conditions should be adequately documented on the medical history and/or other source documents. In the BOOST-3 Trial, any medical condition not present prior to randomization but that emerges after randomization are considered AEs.

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

9.4.3 Classification of an Adverse Event

Severity of Event
For adverse events (AEs) not included in the protocol defined grading system, the severity of adverse events will be determined referencing the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE). The CTCAE provides a grading (severity) scale for AEs with unique clinical descriptions of severity based on this general guidance:

Grade 1: Mild AE
Grade 2: Moderate AE
Grade 3: Severe AE
Grade 4: Life-Threatening or Disabling AE
Grade 5: Death related to AE

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

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

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

Algorithm to Determine Relatedness of Adverse Event to Study Agent	
Unrelated	The temporal relationship between treatment exposure and the adverse event is unreasonable or incompatible and/or adverse event is clearly due to extraneous causes (e.g., underlying disease, environment)
Unlikely	Must have both of the following 2 conditions, but may have reasonable or only tenuous temporal relationship to intervention.
	● Could readily have been produced by the subject’s clinical state, or environmental or other interventions. ● Does not follow known pattern of response to intervention.
Reasonable Possibility	Must have at least 2 of the following 3 conditions
	● Has a reasonable temporal relationship to intervention. ● Could not readily have been produced by the subject’s clinical state or environmental or other interventions. ● Follows a known pattern of response to intervention.
Definitely	Must have all 3 of the following conditions
	● Has a reasonable temporal relationship to intervention. ● Could not possibly have been produced by the subject’s clinical state or have been due to environmental or other interventions. ● Follows a known pattern of response to intervention.

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

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

Certain adverse events will be captured and reported in WebDCU™. Information to be collected includes time of onset, clinician’s assessment of severity, relatedness to study intervention, and time of resolution/stabilization of the event. All AEs occurring through Day 6 (120 hours~~5~~) or Discharge, whichever comes first must be reported in WebDCU™. After Day 5 or Discharge, whichever comes first, only serious adverse events will be reported in WebDCU™. All AEs will be followed to adequate resolution/stabilization or subject end of study.

9.4.5 Adverse Event Reporting

All AEs are reported on the AE case report form (CRF) through the WebDCU™. The site PI or Study Coordinator or designee is responsible for entering all AEs and SAEs and updating the information (e.g., date of resolution, action taken) in a timely manner.

All non-serious AEs must be recorded on the electronic AE CRF within 5 days from the time it was discovered by the site study personnel. For SAEs, the data entry must take place within 24 hours of discovery of the event. The site PI is responsible for the monitoring and follow-up of AEs until resolution (or end of study for that subject) and appropriate documentation in the subject research record.

10. HUMAN SUBJECTS

The protection of human subjects is of primary importance in clinical research and in this comparative-effectiveness clinical trial. Clinical treatment teams must assess and treat patients with TBI rapidly. This trial has been designed to protect human subjects by balancing the goal of finding a legally authorized representative to act as a surrogate decision maker for participation with the goal of avoiding delays of treatment because delays may increase morbidity or mortality.

10.1 Institutional Review Board

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by a single central IRB responsible for oversight of the study. The IRB will also review and approve the inclusion of each enrollment site prior to enrollment at that site.

10.2 Data and safety monitoring board (DSMB)

A Data and Safety Monitoring Board (DSMB) appointed by the NINDS will provide ongoing evaluation of safety data as well as the overall conduct of the trial. The DSMB will operate in accordance with NINDS guidelines. The DCC statisticians will generate Data and Safety Monitoring (DSMB) Reports at a frequency determined by the DSMB. This review will aid in identifying any safety issues that may need to be addressed.

10.3 Consent and Exception to Consent

All patients meeting eligibility criteria for this trial will be obtunded or comatose and unable to give informed consent to participate. Participants will be enrolled in this trial either with the informed consent of a legally authorized representative (LAR) or with exception from informed consent (EFIC) for emergency research under the conditions established at 21CFR50.24 and pursuant to 45CFR46.101(i) and the HHS Secretarial Waiver at FR Doc. 96–24968 . Upon hospital arrival of a potentially eligible subject, study teams will diligently try to determine the availability of an LAR. If an LAR is available prior to the routine emergent placement of intracranial monitors, the patient will only be enrolled with the written informed consent of the LAR. If an LAR is not available prior to the routine emergent placement of intracranial monitors, eligible patients will be enrolled with EFIC after placement of intracranial monitors. Subsequent to an EFIC enrollment, efforts to contact an LAR will continue. An LAR will be notified of an EFIC enrollment and consent to continue in the study will be sought at the earliest opportunity. The study will allow enrollment using foreign language consent forms approved by the Central IRB.

10.3.1 Enrollment with Consent

If an LAR is available prior to the routine emergent placement of intracranial monitors, the patient will only be enrolled with the written informed consent of the LAR. Informed consent is a process involving a meaningful and compassionate exchange of information, questions, and answers between an LAR and a study team member delegated to obtain informed consent. The study team member will discuss the opportunity to participate in a balanced and

noncoercive manner and review the informed consent document with the LAR. The informed consent document provides a record of the process and a place for the LAR to indicate agreement to allow the patient's participation and to provide a signature acknowledging the consent.

The definition of LAR for purposes of clinical research is typically determined by local or state regulations. Further discussion of LAR hierarchies is included in the MOP. Some local or state regulations may require consent from more than one parent when the subject is a child.

10.3.2 Enrollment with EFIC

Upon hospital arrival of a potentially eligible subject, study teams will diligently try to determine the availability of an LAR. Both routine hospital and study team resources and processes should contribute to the determination of the availability of an LAR. The steps undertaken to seek the LAR should be documented and included on the informed consent log case report form. If an LAR is not available prior to the routine emergent placement of intracranial monitors, eligible subjects will be enrolled with EFIC after placement of intracranial monitors. Subsequent to an EFIC enrollment, efforts to contact an LAR will continue. An LAR will be notified of an EFIC enrollment and consent to continue in the study will be sought at the earliest opportunity.

Once located, the LAR will be informed of the subject's enrollment in the study and of the details and risks of the study. At that time, the LAR will be given the option of allowing the subject to continue in the study, or withdrawing the subject's participation then or at anytime throughout the course of the study. If the LAR wants to continue the subject's participation, an informed consent form signed by the LAR for continuation of participation will be obtained at that time.

The informed consent log case report form is also used to document continuing efforts to locate an LAR until notification and a consent process can occur, and the final results of that process. The log will include the types of attempts made, and the number and times of those attempts. If an LAR is never found, then the subject must be notified and approached for consent to continue in the study if and when the subject regains consciousness and decision-making capacity. For subjects who expire prior to identification of an LAR, consent is not obtained. If an LAR is eventually located, they should be notified of the subject's participation. In the rare case where an LAR can not be found and the subject remains incapable of consent at 6 months, attempts to find an LAR will be discontinued, but documentation of the LAR search process until that time, and the subject's decisional capacity will be documented.

10.4 Withdrawal from Participation

Regardless of whether a subject was initially enrolled with informed consent or EFIC, an LAR may withdraw the subject from further participation at any time and for any reason. After regaining consciousness and decision making capacity, subjects may also withdraw themselves from further participation. Whenever possible, the reason for wishing to withdraw should be determined. Those wishing to withdraw the study intervention should be aware that the intervention can be discontinued (i.e. request that the $PbtO_2$ monitors be removed, or that ICU staff be unblinded to $PbtO_2$ values) without withdrawing from the trial and further data collection. Discontinuation of the study intervention itself does not constitute withdrawal from further

participation in the study. After withdrawing from either the intervention or any further participation in the study, the participant's care should revert to standard care at the enrolling site. Consistent with OHRP and FDA guidance, participant data collected prior to withdrawal from the study is maintained in the study database, but no additional participant data will be collected from the participant or their medical record subsequent to withdrawal from the study.

10.5 Confidentiality

To protect against risks related to loss of confidentiality, clinical information will be kept coded, and participant names or other identifying information will be kept separate in a secure database. Records collected will be confidential, unless required to be disclosed to oversight bodies, funders, regulators, or by state or federal law. Subjects will not be personally identified in any publications resulting from this project. Numerous safeguards are maintained at all levels of the trial, including standard data management procedures at the DCC.

10.6 EFIC Plan

Compliance with Criteria and Processes Required for EFIC

FDA regulations identify the specific circumstances in which EFIC is appropriate even when performed under the secretarial waiver rather than an IND or IDE. BOOST fulfills these requirements for emergency research. In the following section, the components of the regulation are reproduced, along with an explanation of how BOOST will comply with each requirement.

TBI is life-threatening and available treatments are unsatisfactory or unproven.

> *21 CFR 50.24(a)(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.*

TBI is a major cause of death and disability in modern industrialized societies, the scope of which is described in section 2.1 of the study protocol. Despite 52,000 deaths from TBI annually in the US, and years of clinical investigation there are still no proven specific treatments available. Although both ICP guided and PbtO2 guided goal-directed are used in standard care of patients with severe TBI, neither is proven to be effective. The Cochrane Library (http://www.cochranelibrary.com/) contains numerous systematic reviews of various unsuccessful or persistently unproven interventions. Further clinical trials are clearly needed.

Obtaining prospective informed consent is often not feasible.

> *21 CFR 50.24(a)(2) Obtaining informed consent is not feasible because: (i) the subjects will not be able to give their informed consent as a result of their medical condition; (ii) the intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and (iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.*

Potential subjects with severe TBI are unconscious and unable to provide informed consent due to their medical condition. Critical care of patients with TBI, however, must be initiated rapidly after hospital arrival. The hypothesized benefit of reducing tissue hypoxia in this trial relies upon early detection and correction. The BOOST II trial demonstrated that brain tissue hypoxia is already present in many patients at the time that their monitoring was initiated.

In ProTECT, a trial which treated 882 participants with moderate to severe TBI within 4 hours of injury, an LAR was available to provide consent within 6 hours for 427 participants (48%). An LAR was not available to provide consent within 6 hours for 52% of participants. When an LAR did not arrive within 6 hours, the time lag until an LAR did become available rapidly increased, with a median value of about 30 hours. In this previous TBI trial, the consent and retention rates were very high. Without EFIC, half of the TBI patients potentially desiring participation may be denied access to the trial, making the trial impracticable. Since TBI is accidental and unpredictable, there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research.

Participation holds prospect of direct benefit to subjects

> *21 CFR 50.24(a)(3) Participation in the research holds out the prospect of direct benefit to the subjects because: (i) subjects are facing a life-threatening situation that necessitates intervention; (ii) appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and (iii) risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.*

Participation in BOOST holds out the prospect of direct benefit to subjects. Subjects may directly benefit from participation because TBI is a life-threatening condition and the PbtO2 goal directed interventions used in this study may be more effective than the ICP goal directed therapies alone. There is also some evidence that participants with TBI may benefit in any arm of a clinical trial because of improved monitoring and adherence to clinical standardization and Brain Trauma Foundation guidelines.

The trial can not be practicably carried out without exception from informed consent

> *21 CFR 50.24(a)(4) The clinical investigation could not practicably be carried out without the waiver.*

This research could not be carried out without EFIC because treatment for TBI needs to begin rapidly after hospital arrival. Since TBI patients are unable to consent for themselves and there often is no LAR available within the therapeutic window, we expect that approximately half of the participants in this trial will be enrolled under EFIC. In TBI, time to treatment is especially critical. Inability to obtain informed consent in the absence of EFIC can limit the ability to discover better treatments for this critical and life-threatening condition.

Need for rapid treatment of TBI often precludes consent from an LAR

> *21 CFR 50.24 (a)(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that*

window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

The narrow therapeutic window described above, the inability of patients with TBI to communicate, and the lack of an LAR available to provide surrogate consent in more than half of subjects precludes the possibility of obtaining informed consent for many potential subjects in BOOST. Attempts to contact LAR for notification and consent to continue participation will be tracked and summarized at continuing reviews.

Provision of an informed consent document

21 CFR 50.24(a)(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sec. 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.

A written informed consent document for this study will be reviewed and approved by the study CIRB. Subjects enrolled in BOOST, or their LAR, are approached for consent prior to enrollment or informed of the subject's inclusion in the clinical investigation at the earliest possible opportunity. The study team is immediately notified of the arrival of potential subjects after arrival. An on call study team member quickly responds to the hospital to enroll subjects or to complete the subject enrollment after EFIC. For the latter, the subject (or LAR or family) is approached, and an informed consent process initiated as soon as possible. The study team notifies the subject or LAR/family about the subject's enrollment, provides information about the study and about the subject's rights and the responsibilities of the investigators, and answers any questions about the study and further participation. A written informed consent document is used to reinforce the information provided verbally and to document a decision to either continue in the study or to not participate any further. A copy of this form is provided to the subject and another copy is placed in the research record.

Community Consultation

21 CFR 50.24(a)(7) Additional protections of the rights and welfare of subjects will be provided, including, at least: (i) consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn

The community will be consulted prior to the initiation of research. With guidance from the CIRB, the community will be asked to give their opinions of the research. A menu of options is included in the detailed EFIC plan in the MoP and includes mechanisms such as community meetings, town hall meetings, focus groups, meetings with established community advisory boards, in-person surveys, and random-digit dialing surveys. The site will choose from this menu and perform sufficient consultations to satisfy the CIRB that it has been satisfactorily completed at each site. Reporting of community consultation results will be standardized across the BOOST sites.

Public Disclosure

> *21 CFR 50.24(a)(7) Additional protections of the rights and welfare of subjects will be provided, including, at least: ….(ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits; (iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results*

Public disclosure is the primary element in making certain that BOOST is conducted in an entirely transparent manner. Methods of announcing information about the trial, and the development of advertising and other materials about the trial, will take place both locally and nationally. Public disclosure will be initiated prior to approval of the trial, may continue during enrollment, and will conclude with dissemination of study results after the trial is completed. A menu and discussion of many public disclosure methods and procedures is detailed in the EFIC plan in the MoP. The CIRB will determine the type and form of public disclosure. Reporting of public disclosure efforts will be standardized. Summaries of public disclosure will be reported to the CIRB, and made publically available.

Data Monitoring Committee

> *21 CFR 50.24(a)(7) Additional protections of the rights and welfare of subjects will be provided, including, at least: ….(iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation;*

A Data and Safety Monitoring Board (DSMB) is appointed by the NINDS to provide ongoing evaluation of safety data as well as the overall conduct of the trial, per institute guidelines. The members will have a meeting with the study team prior to study commencement to discuss the protocol as well as content and format of the DSMB reports. The DCC will prepare requested reports at specified time intervals. Data and safety monitoring will be performed consistent with the guidance provided by the NIH notices 98-084 “Policy for data and safety monitoring” and OD-00-038 “Further guidance on data and safety monitoring for phase I and phase II trials”, and by the NINDS document based on these notices “NINDS Guidelines for Data and Safety Monitoring in Clinical Trials”.

Contacting Other Family

> *21 CFR 50.24(a)(7) Additional protections of the rights and welfare of subjects will be provided, including, at least: …. (v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.*

Whenever possible, informed consent will be used in lieu of EFIC enrollment. EFIC enrollment will also not proceed if an LAR or any other surrogate either at bedside or remotely declines participation on behalf of the potential subject. A provision of the protocol has been made to allow subjects that learn of the trial through public disclosure efforts or other means, and who would not want to participate if treated in the hospital for TBI, to communicate that decision to

the ED without causing any delay in treatment. As part of the primary assessment of any TBI patient, ED providers already check for medical alert jewelry to ascertain emergent medical information about the patient. If the words “BOOST declined,” or alternative designation as defined in the MoP, are listed on the medical alert tag, the patient will not be enrolled in the clinical investigation. A tag or bracelet may also be provided by the study team as needed for this purpose. Use of this enrollment exclusion will be tracked and this information made available to IRBs at the time of continuing review.

Post Enrollment Notification and Consent to Continue

> *21 CFR 50.24(b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.*

Subjects enrolled in BOOST, or their LAR, are informed of the subject’s inclusion in the clinical investigation at the earliest possible opportunity as detailed above and in the MoIt is anticipated that the notification of subjects, or their families or LAR, will most commonly take place in the ED within hours of subject enrollment. Attempts to notify the subject or an LAR are repeated until successful. All notification attempts are logged and recorded in the subjects online case report form in WebDCU™. Reports of these logs will be available for inclusion in annual reports to the respective IRBs.

Record Keeping

> *21 CFR 50.24(c) Like other IRB records, records of the determinations above must be kept for a minimum of three years after the completion of the clinical investigation. Again, like other IRB records, these are subject to inspection and copying by FDA.*

Records documenting the enrollment of participants using EFIC, procedures for notification of enrollment, and informed consent forms will be kept for a minimum of three years after completion of the clinical investigation.

IND Requirement

> *21 CFR 50.24(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for*

investigations under this section may not be submitted as amendments under Secs. 312.30 or 812.35 of this chapter.

This trial has been reviewed by FDA, including intent to enroll with EFIC, and the Agency has determined that an IDE is not required for this trial. The Agency has pointed out that this finding is consistent with their latest guidance on EFIC specifically for device trials.

Communication of IRB Determination

21 CFR 50.24(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRBs that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

Pursuant to the NIH single IRB policy for multicenter clinical trials, BOOST will be reviewed and approved by a single CIRB. If the CIRB does not approve the trial, no subjects will be enrolled at any site, and all stakeholders will be informed. Because of the single IRB of record, there will be no opportunity for discordant IRB findings, and no other reporting of disapprovals.

11. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Executive Committee consistent with the SIREN publication policy . Any presentation, abstract, or manuscript will be made available for review by the Executive Committee prior to submission for publication.

12 REFERENCES

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