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Brain Oxygen Optimization in Severe Traumatic Brain Injury (BOOST-3): A multicenter, randomized, blinded-endpoint, comparative effectiveness study of brain tissue oxygen and intracranial pressure monitoring versus intracranial pressure alone.

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Brain Oxygen Optimization in Severe Traumatic Brain Injury (BOOST-3): A multicenter, randomized, blinded-endpoint, comparative effectiveness study of brain tissue oxygen and intracranial pressure monitoring versus intracranial pressure alone.

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Abstract

Introduction: Management of traumatic brain injury (TBI) includes invasive monitoring to prevent secondary brain injuries. Intracranial pressure (ICP) monitor is the main measurement used to that intent but cerebral hypoxia can occur despite normal ICP. This study will assess whether the addition of a brain oxygenation monitor (PbtO₂) prevents more secondary injuries that will translate into improved functional outcome.

Methods and analysis: Multicenter, randomized, blinded-endpoint comparative effectiveness study enrolling 1094 severe TBI patients monitored with both ICP and PbtO₂. Patients will be randomized to medical management guided by ICP alone (treating team blinded to PbtO₂ values) or both ICP and PbtO₂. Management is protocolized according to international guidelines in a tiered approach fashion to maintain ICP < 22mmHg and PbtO₂ > 20 mmHg. ICP and PbtO₂ will be continuously recorded for a minimum of 5 days. The primary outcome measure is the Glasgow Outcome Scale-Extended performed at 180 (+/- 30) days by a blinded central examiner. Favorable outcome is defined according to a sliding dichotomy 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. A large battery of secondary outcomes including granular neuropsychologic and quality of life measures will be performed.

Ethics and dissemination: This has been approved by Advarra ethics committee (Pro00030585). Results will be presented at scientific meetings and published in peer-reviewed publications. The trial is registered at clinicaltrials.gov: NCT03754114

Strengths and limitations of this study (3 to 5 bullet points)

- BOOST-3, a blinded outcome RCT, will determine whether a treatment protocol, informed by PbtO₂ plus ICP monitoring, results in improved neurologic outcome measured by the Glasgow Outcome Scale-Extended (GOS-E) 6 months after injury compared to treatment guided by ICP monitoring alone.
- BOOST-3 is adequately powered to detect a clinically meaningful difference in outcome that remains achievable (10% absolute difference). Sliding dichotomy outcome based on initial injury should reduce heterogeneity bias.
- BOOST-3 includes 47 level 1 trauma centers experienced with active clinical use of PbtO₂ guided management across the United States and Canada. A multifaceted, tiered, physiologically based protocol will allow individualized care. Algorithm options reflect numerous physiological manipulations to correct anomalies.
- The relatively short time window from TBI to randomization (less than 12 hours after injury and 6 hours after presentation at enrolling hospital) will likely reduce generalizability of the findings to underserved communities. This timeframe was chosen to appropriately test the impact of PbtO₂ monitoring and treatment in the acute phase of brain injury to minimize secondary injuries.
- Extensive secondary outcome tests (12 in total) exploring functional and emotional outcome will be performed by blinded centralized examiners.

Introduction

TBI is a major cause of death and disability in modern industrialized societies[1]. The most recent estimates from the Centers for Disease Control and Prevention (CDC) indicate that in the United States alone, 3.5 million individuals experience a TBI annually, of which 300,000 are hospitalized and discharged alive[2]. Among the 300,000 hospitalized survivors, over 40% experience long-term disability[3].

Historically, monitoring of patients with severe TBI focused on intracranial pressure (ICP) and cerebral perfusion pressure (CPP) to prevent secondary injury[4-6]. Although limiting elevation of ICP is an important part of TBI management, the only randomized controlled trial comparing an ICP driven management versus clinical management based on imaging and physical examination did not show improvement in outcome with invasive monitoring[7]. The management of elevated ICP (eICP) is complex and heterogeneous, this likely reflects the difficulty of applying a one size fits all protocol to a heterogeneous population of patients who require individualized care[8,9].

The physiological rationale underlying ICP management is to preserve oxygen delivery to the brain, using CPP as a surrogate for cerebral blood flow (CBF). There are numerous reasons why brain oxygen delivery can be affected despite ICP or CPP being normal [10-12]. In fact, oxygen diffusion in the brain parenchyma is the rate limiting step of delivery[13] and is affected by the presence of edema or microcirculatory failure[14]. Devices that measure brain tissue oxygen (PbtO₂) are now readily available at bedside. Numerous studies have shown that cerebral hypoxia is common, reversible, may be able to measure cerebral ischemic burden, and independently associated with functional outcome [11,15-18]. The use of PbtO₂ was recently the subject of a consensus statement guideline, highlighting the fact that multimodal monitoring allows for management refinement compared to ICP management alone [19].

TBI management heterogeneity requires that any multicenter clinical trial protocol allows various treatment options based on bedside evaluation of cerebral physiology while maintaining the rigor and clinical standardization necessary to conduct a randomized clinical trial (RCT). BOOST-2, a multicenter RCT, found that treatment of elevated ICP and correction of low PbtO₂ decreased the total cumulative ischemic burden compared to treatment of elevated ICP alone ($p = 0.0000002$) [20]. Furthermore, a trend in improved functional outcome at 6 months was supportive of the pre-determined non-futility hypothesis.

The primary objective of BOOST-3 is to determine whether a treatment protocol, informed by PbtO₂ plus ICP monitoring, results in improved neurologic outcome measured by the Glasgow Outcome Scale-Extended (GOS-E) 6 months after injury compared to treatment guided by ICP monitoring alone.

Methods

Trial design, study setting and study population

BOOST-3 is a two-arm, single-blind, randomized, controlled, phase III, multi-center trial to determine whether treatment algorithms informed by PbtO₂ and ICP monitoring improve subject outcomes more than treatment informed by ICP alone. The trial is registered at clinicaltrials.gov: NCT03754114. The complete study protocol, manual of operating procedures (MOP) and other

documentation can be found on the study website: siren.network/clinical-trials/boost-3. Inclusion and exclusion criteria are summarized in **figure 1**.

BOOST-3 includes 47 level 1 trauma centers that are experienced with active clinical use of PbtO₂ guided patient management across the United States and Canada. These sites place PbtO₂ and ICP monitors according to BTF guidelines as part of their standard of care for severe TBI patients. Monitors will thus be inserted following local standard practice patterns. Of these patients, those who meet eligibility criteria for the study will be randomized. Specifically as per inclusion criteria, randomisation will occur if the decision to place catheters is made within 6 hours from arrival to the enrolling center and no later than 12 hours from injury (**figure 1**).

Both ICP (Codman®, Camino® or EVD) and PbtO₂ monitors (Integra Licox or Raumedic Neurovent) will be used as per local standard practice. Correct catheter placement will be confirmed by a head CT scan within 24 hours of placement. PbtO₂ probe reliability will be assessed performing an FiO₂ challenge (blinded in the ICP only group) with an appropriate response defined by an increase of at least 5 mmHg. In the PbtO₂+ICP group, non-functioning PbtO₂ probes will be replaced.

The trial is being conducted in the SIREN (Strategies to Innovate EmeRgENcy Care Clinical Trials Network) network, which is an emergency care clinical trials network funded by the National Institute for Neurological Disorders and Stroke (NINDS), the National Heart Lung and Blood Institute (NHLBI) and the National Center for Advancing Translational Science (NCATS) to improve outcomes of subjects with acute illness and injury.

Randomization and blinding

Subjects are randomized in a 1:1 ratio to a treatment protocol informed by both ICP and PbtO₂ or by ICP alone, using a covariate-adjusted randomization scheme (**figure 1**). The randomization scheme controls imbalances in the overall treatment distribution, within injury severity category, and within clinical site.

Both arms will have a PbtO₂ probe inserted, but the clinical teams will be blinded to PbtO₂ values in the ICP only group. Daily FiO₂ challenges will be conducted by unblinded study personnel not involved in patient care to assess probe reliability.

The primary outcome assessment will be centrally performed by trained personnel blinded to group assignment (see outcome section).

Intervention

A Clinical Standardization Committee (CST) for the BOOST3 trial developed general targets for physiological variables for both groups (**Table 1**) and finalized the MOP. Arterial blood pressure monitoring for CPP purposes will be standardized to the level of the heart.

The patient's clinical course will fall into 4 different clinical scenarios based on monitoring information, 3 of which (types B, C, and D, defined in **Figure 2**) will require management strategies. Type D combines the treatment options of type B and C scenarios.

Scenarios for type B (**Table 2**) and type C (**Table 3**) are addressed with a set of physiologically based interventions to correct ICP and PbtO₂. The treatment protocol is tiered in a hierarchical fashion, with less aggressive interventions attempted before more aggressive maneuvers.

Interventions in this protocol were adapted from the Brain Trauma Foundation (BTF) 2016 *Guidelines for the Management of Severe Traumatic Brain Injury* [5] and the American College of Surgeons – Trauma Quality Improvement Program (ACS TQIP) 2015 guidelines[6]. Some interventions represent expert opinions. Treatment algorithms were developed through discussions between BOOST investigators with expertise in critical care medicine and neurosurgery (CST). The protocol represents an attempt to minimize center-to-center variability and to facilitate interpretation of the PbtO₂ information using local expertise.

An episode that requires intervention is triggered by abnormalities in ICP or PbtO₂ lasting more than 5 minutes. Treatments must be initiated within 15 minutes of the start of an episode. Patients may start in one type of scenario and then move to another scenario while they are receiving treatments. The initial choice of a treatment option from any tier for any particular scenario should be determined based on what is felt to be the most effective intervention for the current clinical situation, participant characteristics and local protocols. Any intervention chosen should be aimed at addressing the underlying pathophysiology that is contributing to the episode. At least one treatment in tier 1 must be tried before moving on to tier 2. Tier 3 treatments are optional. 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 Tier 1 interventions prior to moving on to Tier 2. The bedside treatment team has the option to progress to higher tiers as rapidly as they feel is clinically indicated.

Some interventions in tables 2 and 3 are noteworthy.

Optimizing CPP. Target range for CPP are unknown and may depend on the patient's autoregulatory status[4]. As such, optimization of CPP might be informed by cerebral autoregulation testing[22]. We advise there is a potential for harm related to augmentation of CPP above 70 mm Hg[23] but some patients may require it. We also recognized that lowering CPP below 60 mmHg might be an option to treat eICP when cerebral autoregulation is absent (Lund therapy) [24]. Finally, CPP optimization also includes improvement in CBF though improvement in cardiac output (inotropy).

Increasing PaO₂. Obtaining an arterial blood gas before treating with PaO₂ adjustments is mandatory. Increasing PaO₂ above 150 mmHg might imply overtreatment by PaO₂ and prevents detection of another potential cause of low PbtO₂. Calculating the brain oxygen ratio (BOx ratio= PbtO₂/PaO₂) might help recognize this situation[10]. Increasing PaO₂ above 150 mmHg should only be used if PbtO₂ is persistently less than 20 mmHg and other variables contributing to low PbtO₂ have been addressed and controlled first.

Reverse Robin Hood syndrome[25-27]. PbtO₂ probe located in an area already maximally vasodilated might measure a drop of flow (low PbtO₂) if other areas of the brain vasodilate (potentially because of hypoventilation), creating a “steal” by diverting flow from the area measured. Treatment requires vasoconstricting the normal brain to redirect the flow towards the area measured using hyperventilation.

Withdrawal of life sustaining treatments (WLST) during the first 5 days will only be considered in dire circumstances or if requested by the patient's family. If the study subject undergoes WLST during the first 5 days of treatment, the site PI will be required to notify the study leadership team. Reasons for WLST will be carefully documented.

Outcomes

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4 The primary outcome measure is the Glasgow Outcome Scale-Extended performed at 180 (+/-
5 30) days by a blinded central examiner.
6

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8 A complete battery of secondary measures will be administered in the following order: Galveston
9 Orientation and Amnesia Test (GOAT), structured interview, Functional Status Examination
10 (FSE), GOSE-TRACK, Rey Auditory Verbal Learning Test, Trail Making Test Part A and B,
11 WAIS-IV Symbol Search test and coding test, Rivermead Post-Concussion Symptoms
12 Questionnaire, Brief Symptom Inventory 18, Satisfaction with Life Scale and Rey Auditory
13 Verbal Learning Test.
14

15 **Data collection, data monitoring, and adverse events**

16
17 The study data will be managed using the WebDCU™ system. This web-based clinical trial
18 management system will be used for regulatory document management, subject randomization,
19 data entry, data validation, project progress monitoring, subject tracking, user customizable report
20 generation, and secure data transfer. Reports will be generated to monitor study progress and
21 patient recruitment at each site. These reports will provide center-specific information on the
22 number of subjects with missing or incomplete data and number of data queries.
23

24 Information specific to PbtO₂, ICP, and CPP monitoring will be collected for up to 5 days.
25 Continuous digital recordings of these values will be captured on a bedside dedicated integrated
26 platform (CNS Monitor, Moberg ICU Solutions, Amber, PA, USA). This will allow precise
27 calculation of ischemic burden (time spent with PbtO₂ below 20 mmHg) and eICP burden (time
28 spent above 22 mmHg). A custom built-in clinical decision algorithm based on the tier treatments
29 (CNS Carepath®, Moberg ICU Solutions, Amber, PA, USA) can be used to help guide bedside
30 clinicians to select the appropriate intervention for a given type of scenario. Local study
31 personnel can review Carepath® and the medical record to identify alarms and actions taken to
32 correct them on the electronic case report form (eCRF) for the first 5 days.
33

34
35 The clinical site PI, independent medical safety monitor (IMSM), and data and safety monitoring
36 board (DSMB) appointed by the NINDS are responsible for the timely review of the safety data.
37 The DSMB will operate in accordance with NINDS guidelines. The DSMB will evaluate open
38 and closed reports prepared by the Data Coordinating Center on a semiannual basis.
39

40
41 General data quality will be monitored by the Clinical Coordinating Center and will include a
42 combination of on-site monitoring, remote monitoring, and central monitoring (using web-based
43 data validation rules, data manager review of entered data, statistical analysis, and on-going
44 review of site metrics).
45

46 Adverse events (AE) are defined as any untoward event or complication not previously identified,
47 or that occurs with greater frequency or severity than previously reported, whether or not
48 considered related to the protocol intervention. The AEs listed in **table 4** are anticipated based on
49 the known complications of severe TBI, intracranial monitoring devices and prolonged use of
50 supraphysiologic levels of oxygen. In addition, new abnormal laboratory findings that are
51 considered by the treating physician to be clinically significant may be included as adverse
52 events.
53

54 Serious AEs are any adverse event that results in any of the following outcomes or actions: 1)
55 Death due to any cause; 2) a life-threatening adverse experience; 3) inpatient prolongation of
56 existing hospitalization; 4) a persistent or significant disability/incapacity; 5) an important
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3 medical event that may require medical or surgical intervention to prevent one of the outcomes
4 listed above. These must be reported within 24 hours of discovery.
5

6 All AEs are collected through day 6 or discharge, whichever comes first; serious AEs will be
7 reported through subject end of study. The IMSM will adjudicate serious AEs for seriousness,
8 relationship to the study intervention, and expectedness.
9

10 **Statistical considerations**

11
12 Favorable outcome is defined according to a sliding dichotomy (**figure 3**) [28], where the
13 definition of favorable outcome varies according to baseline severity. Severity will be defined
14 according to the probability of poor outcome predicted by the IMPACT core model[21]. The
15 favorable outcome definition is more stringent for subjects with a low probability of poor
16 outcome.
17

18
19 A clinically relevant effect size of 10% absolute difference in favorable outcome proportions is
20 prespecified. In order to achieve 85% power with a two-sided type I error probability of 0.05,
21 880 subjects are required. This calculation assumes a 50% favorable outcome proportion in the
22 control arm. Inflation to account for interim analysis and 7% non-adherence results in a
23 maximum sample size of 1094 subjects.
24

25 All subjects enrolled in the study are to be followed until the end of study or until consent is
26 withdrawn or declined and will be included in the primary intention-to-treat analysis.
27

28 **Study timescale**

29
30 Recruitment began Summer of 2019. The COVID-19 pandemic significantly affected early
31 recruitments. The trial is currently recruiting patients at the rate of 15 - 16 patients per month.
32 Once all sites are fully operational and recruiting, we expect recruitment to end by 2026.
33 Allowing for the 6 month follow-up assessment, data cleaning and closure of the database, data
34 analyses, manuscript writing and publication should take place in 2026.
35
36

37 **Patients and public involvement**

38
39 Community Consultation and Public Disclosure are completed regionally for all enrolling sites in
40 the United States, prior to the initiation of the clinical trial under CFR 50.24.
41

42 No patient or public representative was involved in the written design of the trial.
43

44 **Ethics and dissemination**

45
46 Because all patients meeting eligibility criteria for this trial will be unresponsive and unable to
47 provide informed consent, participants will be enrolled either with the informed consent of a
48 legally authorized representative (LAR) or with exception from informed consent (EFIC) for
49 emergency research (no EFIC in Canada). If no LAR is available before placement of the ICP and
50 PbtO₂ monitors, the patient may be enrolled under EFIC. If LAR is available prior to ICP and
51 PbtO₂ monitors being placed, consent will be sought from LAR. The complete EFIC process will
52 be the subject of another publication since it refers to a complex ethical process.
53

54
55 Publication of the results of this trial will be governed by the policies and procedures developed
56 by the Executive Committee consistent with the SIREN publication policy.
57
58
59

Discussion

BOOST-3 is a pragmatic, physiology based study that aims to demonstrate the superiority of combined PbtO₂ + ICP guided therapy over ICP guided therapy alone when comparing subject outcomes at 6 months. Classical TBI management based on ICP and CPP alone has demonstrated its limitations [29,30]. This management uses pressure as a surrogate of CBF and oxygen delivery, an approach that was developed when there was no ability to directly or reliably measure PbtO₂.

The development of cerebral hypoxia is now understood to be multifactorial, and at times occurs independent of ICP and CPP abnormalities [11]. PbtO₂ represents a balance between oxygen delivery and consumption measured directly in the brain parenchyma [31]. Analyzing the physiological parameters that influence PbtO₂ values at the bedside[10] allows for a more extensive and precise comprehension of brain pathophysiology and may result in more tailored and efficacious care to prevent secondary injuries[19].

Two other trials are going to study the added value of PbtO₂ monitoring: the ongoing OXY-TC trial in France[32] and the BONANZA trial in New-Zealand and Australia (not yet registered on clinical trial.gov). As designed, BOOST-3 will be the largest and is adequately powered to detect a clinically meaningful difference in clinical outcome that remains achievable (10% absolute difference). In comparison, the OXY-TC targets a 30% difference in outcome. Both BOOST-3 and BONANZA will be measuring PbtO₂ in a blinded fashion in the control arm allowing the evaluation of cumulative hypoxic burden between groups.

Recognizing the heterogeneity of TBI characteristics and complexity of its management, BOOST-3 has standardized therapy in both groups while allowing for flexibility in treatment options. These options reflect the various possible physiological manipulations required to correct anomalies identified by the bedside physician (tables 2 and 3). Of note, BOOST-3 protocol recognizes that cerebral autoregulation status plays an important role in managing CPP threshold[33]. Optimization of CPP according to the autoregulation status might improve outcome but its management remains difficult clinically[34-37]. PbtO₂ might facilitate recognition of the autoregulation status[38,39]. Analysis of the continuous data capture within the BOOST3 cohort, may inform future study of the relationship between cerebral autoregulation, goal directed therapy, and patient outcome.

The BOOST3 protocol also clearly emphasizes that increasing PaO₂ in order to correct a low PbtO₂ value should be used very cautiously. Increasing PaO₂ above 150 mmHg might imply overtreatment by PaO₂ and prevents detection of another potential cause of low PbtO₂[10]. It is possible to compensate for a decrease in PbtO₂ due to low CBF by increasing PaO₂[40]. Hyperoxia is known to induce cerebral vasoconstriction[41], potentially increase free radical production[42] and has been associated with worse outcome in other brain ischemic injuries[43-46]. If FiO₂ is increased as a therapeutic maneuver, a specific FiO₂ weaning protocol is suggested. That being said, it is expected that TBI patients managed with a PbtO₂ probe will have a higher mean PaO₂ since it is the only possible therapeutic option to address the diffusion and microcirculatory failure often seen with severe TBI[13,14]. Adverse events related to pulmonary pathology will be closely tracked in both study groups.

The limitations of standardization in BOOST-3 are inherent to the nature of TBI. First, there is wide variation in the phenotype of brain injury. For example, patients may have diffuse axonal injury, intraparenchymal contusion, extra-axial hematomas, subarachnoid hemorrhage, or any

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3 combination of these injuries [1]. The fact that multiparametric and PbtO₂ monitoring allow for a
4 physiology driven approach may globally improve the delivery of care despite the heterogeneity
5 of disease phenotype. BOOST3 is slated to recruit a large number of patients, which will likely
6 help to achieve balance of injury phenotype across study groups. Furthermore, the specificity
7 gained by measuring functional outcome through a sliding dichotomy based on initial injury
8 should also reduce heterogeneity bias.
9

10
11 Withdrawal of life sustaining therapy, although strongly discouraged in the first 5 days after TBI,
12 can still influence outcome measures. No specific protocol for prognostication and decision to
13 withdraw care is suggested in the research protocol; treating physician acumen will determine end
14 of life decisions.
15

16
17 An additional limitation is the relatively short time window from TBI to randomization (less than
18 12 hours after injury and 6 hours after presentation at enrolling hospital), this will likely reduce
19 generalizability of the findings to underserved communities, or those lacking access to
20 neurosurgical expertise. This timeframe was chosen to appropriately test the biological basis of
21 PbtO₂ monitoring in the acute phase of brain injury to prevent secondary injuries. A longer
22 interval from injury may allow for significant cerebral hypoxia before randomization. A
23 challenge that has been identified after start-up relates to the 6 hour time window after arrival at
24 enrolling site, which poses a problem if the patient needs urgent surgical intervention. Allowing
25 some flexibility in the 6 hour window allows urgent clinical needs to be addressed prior to
26 placement of intracranial monitors. A final challenge after study start-up included the COVID
27 pandemic putting a hold on research activities thus lowering expected enrollment.
28

29
30 The annual cost to society resulting from TBI has been estimated to range from \$83 billion to
31 \$244 billion (in 2014 dollars) [47]. Improvements in functional outcome will benefit not only
32 affected patients but society globally. Multiple trials targeting a specific medication or
33 pathophysiological mechanism have failed to demonstrate improvement in outcome so far[48].
34 We feel that the early use of a PbtO₂ guided bundle of care will yield a different result.
35

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43
44

45 Figures Legends

46
47 Figure 1: Randomization, inclusion and exclusion criteria
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50 Figure 2 : Four possible clinical scenarios based on monitoring information
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53 Figures 3 : Outcome defined according to sliding dichotomy
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Table 1

Initial general targets for both groups	
Physiologic Variable	Desired Range
Pulse Oximetry	$\geq 94\%$
PaO ₂	≥ 80 mmHg
PaCO ₂	35-45 mmHg
pH	7.35-7.45
Systolic Blood Pressure before CPP management	> 100 mmHg if age 50-69 years old > 110 mmHg if age 15-49 or >70 years old
Temperature	36.5—37.5°C
Maintain Normovolemia	As per local protocol
Sodium	135-145 mmol/L
Glucose	80-180 mg/dL
PT and PTT	Normal range as per local hospital guidelines
INR	≤ 1.6
Hemoglobin	≥ 7 gm/dl
Platelets for insertion of monitors	$\geq 80 \times 10^3/\text{mm}^3$

Table 2

Scenario B: Treatment Options for Isolated ICP increase > 22 mmHg

TIER 1: must begin within 15 minutes of abnormality. No particular order.

- Adjust head of bed to lower ICP
- Ensure Temperature < 38°C
- Titrate pharmacologic analgesia or sedation to effect
- CSF drainage (if EVD available)
- Optimize CPP to max 70 mmHg with fluid boluses or vasopressors as clinically appropriate. May assess cerebral autoregulation as per local protocol to manage CPP targets.
- Adjust ventilator for a target PaCO₂ of 35 - 40 mm Hg (target pH of 7.35 - 7.45).
- Low dose Mannitol (0.25 - 0.5 g/kg)
- Low dose HTS (include 1.5% to 3%). This tier does not include higher concentrations of HTS. Titrate to effect (ICP control) and maintain Na ≤ 160 mEq/L.
- Initiate or titrate anti-epileptic medications

TIER 2: initiate within 60 minutes if tier 1 therapies are ineffective. No particular order.

- Repeat head CT; treat surgically remediable lesions according to guidelines.
- Adjust temperature to 35 – 36°C, using active cooling measures.
- NMB, use a bolus dose to determine effect. If effective, perfusion may be used. NMB should be rapidly weaned upon clinical stabilization.
- Optimize CPP: may increase CPP above 70 mm Hg with fluid boluses or vasopressors*.
- Adjust ventilatory rate to target PaCO₂ of 33 – 38 mm Hg (target pH of 7.35-7.45).
- High dose mannitol (1-1.5 g/kg) or higher frequency of low dose mannitol (0.25-0.5g/kg) if osm <320.
- High dose hypertonic saline bolus (7.5%, 30 ml of 23.4%). May repeat if Na levels are <160mEq/L.

TIER 3 (tier 3 therapies are optional). No particular order.

- Adjust ventilatory rate for target PaCO₂ of 30 – 35 mm Hg (target pH of less than 7.5).
- Pentobarbital coma, according to local protocol. An initial bolus dose of 5 mg/kg should be used to determine effectiveness. If effective, a continuous infusion may be used. Pentobarbital should be rapidly weaned upon clinical stabilization
- Decompressive craniectomy
- Adjust temperature to 32-35°C, using active cooling measures.
- Other salvage therapy per local protocol and practice patterns.

Note: CSF: cerebrospinal fluid; EVD: external ventricular drain; HTS: hypertonic saline; NMB: neuromuscular blockade; *There is a potential for harm related to augmentation of CPP above 70 mm Hg with vasopressors

Table 3

Scenario C: Treatment Options for Isolated PbtO₂ < 20 mmHg

TIER 1: must begin within 15 minutes of abnormality. No particular order.

- Adjust head of the bed.
- Ensure Temperature < 38° C.
- Optimize hemodynamics to ensure adequate CBF and avoid diffusion gradient:
 - Resuscitation: address hypovolemia.
 - Diuresis: Avoid hypervolemia, consider furosemide or other agent for diuresis.
- Optimize CPP up to 70 mmHg maximum with fluid boluses or vasopressors as clinically appropriate. May assess cerebral autoregulation as per local protocol to manage CPP targets.
- PaO₂ adjustment (obtain ABG first*) :
 - Pulmonary toilet with suctioning of secretions (bronchoscopy is not included in this tier as an option).
 - Increase FiO₂ to a maximum of 60%.
 - Adjust PEEP by a maximum of 5 cm H₂O over baseline.
- Adjust minute ventilation to achieve a PaCO₂ of 38 - 42 mmHg (target pH of 7.35 - 7.45). Further lowering of PaCO₂ should not be done if pH >7.45. PaCO₂ should not be increased if pH is <7.35.
- Initiate or titrate anti-epileptic medications (AEDs).

TIER 2: initiate within 60 minutes if tier 1 therapies are ineffective. No particular order.

- Increased sedation.
- Decrease ICP to < 15 mm Hg.
- CSF drainage.
- NMB, use a bolus dose to determine effect. If effective, perfusion may be used. NMB should be rapidly weaned upon clinical stabilization.
- Optimize CPP: may increase CPP above 70 mm Hg with fluid boluses or vasopressors.
- PaO₂ adjustment (obtain ABG first*) :
 - Perform bronchoscopy.
 - Increase FiO₂ a maximum of 100% †. Wean rapidly when clinically stable (decrease FiO₂ by 5% every 30 min).
 - Adjust PEEP in increments of 3 - 5 cm H₂O.
- Adjust minute ventilation to increase PaCO₂ to 40 – 45 mm Hg (target pH of 7.35 - 7.45).
- Transfusion of red blood cells.

TIER 3 (tier 3 therapies are optional). No particular order.

- Adjust minute ventilation to increase PaCO₂ > 45 mmHg (target pH of 7.30 – 7.45).
- Increase cardiac output with inotropes (milrinone, dobutamine).
- Assess for vasospasm with transcranial dopplers, CT angiogram, or cerebral angiogram.
- Hyperventilation to address possible reverse Robin-Hood syndrome.
- Other potential causes / interventions for low PbtO₂ should be considered:
 - Consider cortical spreading depolarization via ECoG
 - Assess for pulmonary embolism.
 - Assess for cerebral venous thrombosis.
- Other salvage therapy based on local protocol and practice patterns.

Note : NMB: neuromuscular blockade; *Obtain arterial blood gas to confirm that oxygenation is in desired range before treating with PaO₂ adjustments. Note that increasing PaO₂ above 150 mmHg might imply overtreatment by PaO₂ and prevents detection of another potential cause of low PbtO₂. † This option should only be used when PbtO₂ is persistently less than 20 mm Hg and other variables contributing to low PbtO₂ have been addressed and controlled. There is a potential for harm related to augmentation of CPP above 70 mm Hg with vasopressors.

Table 4

Adverse event	Expected Incidence
ARDS	5%
Pneumonia	25%
Sepsis	5 %
Septic Shock	3%
Hematoma requiring craniotomy for evacuation	0.5%
CNS infection	<0.5%

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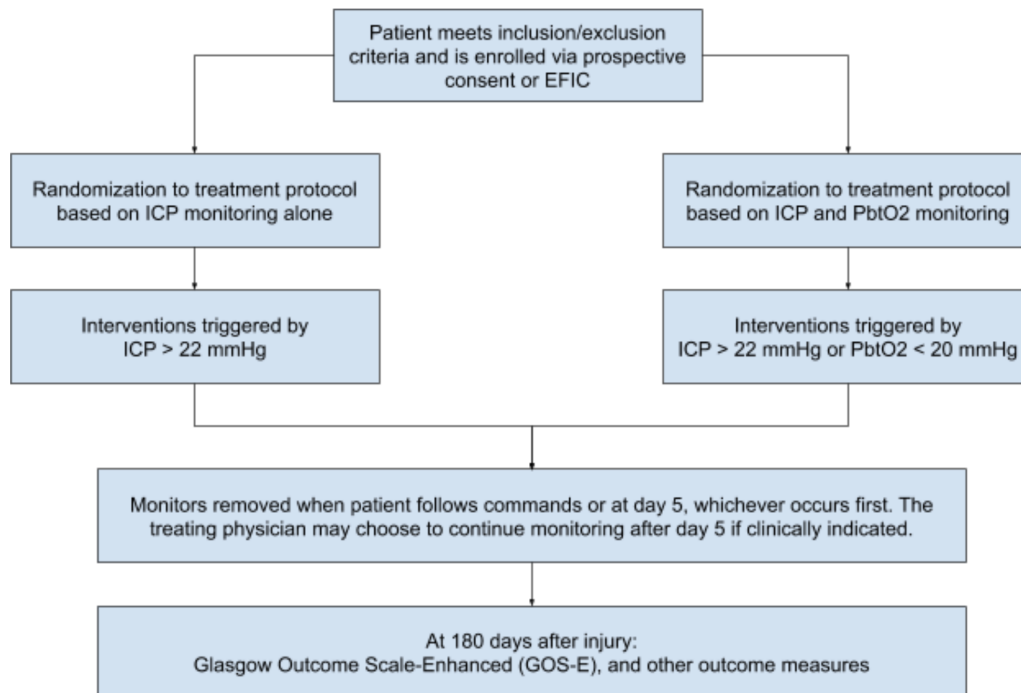
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Figure 1



Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> • 14 years of age • Non penetrating TBI • Glasgow Coma Score (GCS) of 3 to 8 measured off paralytics after resuscitation (with a motor component score less than 6) • evidence of intracranial trauma on a head CT scan (skull fracture alone is not sufficient) • Decision to insert intracranial monitors within 6 hours of arrival at the enrolling hospital, but no later than 12 hours after the injury 	<ul style="list-style-type: none"> • GCS = 3 and bilaterally absent pupil responses off paralytics • Medical contraindications for placement of intracranial monitors • Treatment of brain tissue oxygen values prior to randomization • Planned use of devices that would allow unblinding of medical care team to the treatment group • Severe sepsis at randomization • Refractory hypotension prior to randomization (SBP < 90 mmHg for two consecutive readings at least 15 minutes apart) • Refractory hypoxia prior to randomization (SaO₂ < 90% on FiO₂ > 0.5 for two consecutive readings at least 15 minutes apart) • Sustained PaO₂/FiO₂ ratio < 150 • Known pre-existing neurologic disease with confounding residual neurologic deficits • Known pre-existing condition resulting in an inability to perform activities of daily living without assistance • Known active drug or alcohol dependence that would interfere with physiological response to PbtO₂ treatments or follow-up care • Non-survivable injury in the opinion of the site investigator • Pregnancy • Prisoner or ward of the state • Person is known to have opted out of EFIC or study enrollment prior to injury (see ethics section).

Figure 2

Values in mmHg	ICP \leq 22	ICP $>$ 22
PbtO ₂ \geq 20	Type A No interventions needed	Type B Interventions to lower ICP
PbtO ₂ $<$ 20	Type C Interventions to increase PbtO ₂	Type D Interventions to lower ICP and increase PbtO ₂

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Figure 3

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	Favorable Outcome						
0.41 to <0.56	Favorable Outcome						
0.56 to ≤1	Favorable Outcome						

For peer review only

Note from the Editors: Instructions for reviewers of study protocols

Since launching in 2011, BMJ Open has published study protocols for planned or ongoing research studies. If data collection is complete, we will not consider the manuscript.

Publishing study protocols enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity that may not otherwise be widely publicised. This can help prevent unnecessary duplication of work and will hopefully enable collaboration. Publishing protocols in full also makes available more information than is currently required by trial registries and increases transparency, making it easier for others (editors, reviewers and readers) to see and understand any deviations from the protocol that occur during the conduct of the study.

The scientific integrity and the credibility of the study data depend substantially on the study design and methodology, which is why the study protocol requires a thorough peer-review.

BMJ Open will consider for publication protocols for any study design, including observational studies and systematic reviews.

Some things to keep in mind when reviewing the study protocol:

- Protocol papers should report planned or ongoing studies. The dates of the study should be included in the manuscript.
- Unfortunately we are unable to customize the reviewer report form for study protocols. As such, some of the items (i.e., those pertaining to results) on the form should be scores as Not Applicable (N/A).
- While some baseline data can be presented, there should be no results or conclusions present in the study protocol.
- For studies that are ongoing, it is generally the case that very few changes can be made to the methodology. As such, requests for revisions are generally clarifications for the rationale or details relating to the methods. If there is a major flaw in the study that would prevent a sound interpretation of the data, we would expect the study protocol to be rejected.

BMJ Open

Brain Oxygen Optimization in Severe Traumatic Brain Injury (BOOST-3): A multicenter, randomized, blinded-endpoint, comparative effectiveness study of brain tissue oxygen and intracranial pressure monitoring versus intracranial pressure alone.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-060188.R1
Article Type:	Protocol
Date Submitted by the Author:	24-Jan-2022
Complete List of Authors:	Bernard, Francis ; Hôpital du Sacré-Coeur de Montréal, Critical care; Université de Montréal, Department of Medicine Barsan, William; University of Michigan Michigan Medicine, Emergency Medicine Diaz-Arrastia, Ramon; University of Pennsylvania Perelman School of Medicine, Neurology Merck, Lisa; University of Florida College of Medicine, Emergency Medicine and neurology, neuro critical care Yeatts, Sharon; Medical University of South Carolina, Public Health Sciences Shutter, Lori; University of Pittsburgh School of Medicine, Critical Care Medicine, Neurology, & Neurosurgery
Primary Subject Heading:	Intensive care
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Keywords:	Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Neurological injury < NEUROLOGY, Trauma management < ORTHOPAEDIC & TRAUMA SURGERY, NEUROSURGERY, NEUROPHYSIOLOGY

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1 **Brain Oxygen Optimization in Severe Traumatic Brain Injury**
2 **(BOOST-3): A multicenter, randomized, blinded-endpoint, comparative**
3 **effectiveness study of brain tissue oxygen and intracranial pressure**
4 **monitoring versus intracranial pressure alone.**

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40 **Key words :** protocol and guidelines, adult intensive and critical care, neurological
41 injury, trauma management, neurosurgery, neurophysiology

43 **Word count :** 3455

Abstract

Introduction: Management of traumatic brain injury (TBI) includes invasive monitoring to prevent secondary brain injuries. Intracranial pressure (ICP) monitor is the main measurement used to that intent but cerebral hypoxia can occur despite normal ICP. This study will assess whether the addition of a brain oxygenation monitor (PbtO₂) prevents more secondary injuries that will translate into improved functional outcome.

Methods and analysis: Multicenter, randomized, blinded-endpoint comparative effectiveness study enrolling 1094 severe TBI patients monitored with both ICP and PbtO₂. Patients will be randomized to medical management guided by ICP alone (treating team blinded to PbtO₂ values) or both ICP and PbtO₂. Management is protocolized according to international guidelines in a tiered approach fashion to maintain ICP < 22mmHg and PbtO₂ > 20 mmHg. ICP and PbtO₂ will be continuously recorded for a minimum of 5 days. The primary outcome measure is the Glasgow Outcome Scale-Extended performed at 180 (+/- 30) days by a blinded central examiner. Favorable outcome is defined according to a sliding dichotomy 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. A large battery of secondary outcomes including granular neuropsychologic and quality of life measures will be performed.

Ethics and dissemination: This has been approved by Advarra ethics committee (Pro00030585). Results will be presented at scientific meetings and published in peer-reviewed publications. The trial is registered at clinicaltrials.gov: NCT03754114

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5 3 **Strengths and limitations of this study (3 to 5 bullet points)**
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- BOOST-3, a blinded outcome RCT, will determine whether a treatment protocol, informed by PbtO₂ plus ICP monitoring, results in improved neurologic outcome measured by the Glasgow Outcome Scale-Extended (GOS-E) 6 months after injury compared to treatment guided by ICP monitoring alone.
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 - BOOST-3 is adequately powered to detect a clinically meaningful difference in outcome that remains achievable (10% absolute difference).
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 - The relatively short time window from TBI to randomization (less than 12 hours after injury and 6 hours after presentation at enrolling hospital) will likely reduce generalizability of the findings to underserved communities.
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 - Extensive secondary outcome tests (12 in total) exploring functional and emotional outcome will be performed by blinded centralized examiners.
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1 Introduction

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3 TBI is a major cause of death and disability in modern industrialized societies[1]. The most recent
4 estimates from the Centers for Disease Control and Prevention (CDC) indicate that in the United
5 States alone, 3.5 million individuals experience a TBI annually, of which 300,000 are
6 hospitalized and discharged alive[2]. Among the 300,000 hospitalized survivors, over 40%
7 experience long-term disability[3].

8
9 Historically, monitoring of patients with severe TBI focused on intracranial pressure (ICP) and
10 cerebral perfusion pressure (CPP) to prevent secondary injury[4-6]. Although limiting elevation
11 of ICP is an important part of TBI management, the only randomized controlled trial comparing
12 an ICP driven management versus clinical management based on imaging and physical
13 examination did not show improvement in outcome with invasive monitoring[7]. The
14 management of elevated ICP (eICP) is complex and heterogeneous, this likely reflects the
15 difficulty of applying a one size fits all protocol to a heterogeneous population of patients who
16 require individualized care[8,9].

17
18 The physiological rationale underlying ICP management is to preserve oxygen delivery to the
19 brain, using CPP as a surrogate for cerebral blood flow (CBF). There are numerous reasons why
20 brain oxygen delivery can be affected despite ICP or CPP being normal [10-12]. In fact, oxygen
21 diffusion in the brain parenchyma is the rate limiting step of delivery[13] and is affected by the
22 presence of edema or microcirculatory failure[14]. Devices that measure brain tissue oxygen
23 (PbtO₂) are now readily available at bedside. Numerous studies have shown that cerebral hypoxia
24 is common, reversible, may be able to measure cerebral ischemic burden, and independently
25 associated with functional outcome [11,15-18]. The use of PbtO₂ was recently the subject of a
26 consensus statement guideline, highlighting the fact that multimodal monitoring allows for
27 management refinement compared to ICP management alone [19].

28
29 TBI management heterogeneity requires that any multicenter clinical trial protocol allows various
30 treatment options based on bedside evaluation of cerebral physiology while maintaining the rigor
31 and clinical standardization necessary to conduct a randomized clinical trial (RCT). BOOST-2, a
32 multicenter RCT, found that treatment of elevated ICP and correction of low PbtO₂ decreased the
33 total cumulative ischemic burden compared to treatment of elevated ICP alone (p = 0.0000002)
34 [20]. Furthermore, a trend in improved functional outcome at 6 months was supportive of the
35 pre-determined non-futility hypothesis.

36
37 The primary objective of BOOST-3 is to determine whether a treatment protocol, informed by
38 PbtO₂ plus ICP monitoring, results in improved neurologic outcome measured by the Glasgow
39 Outcome Scale-Extended (GOS-E) 6 months after injury compared to treatment guided by ICP
40 monitoring alone.

41 Methods

42 Trial design, study setting and study population

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44 BOOST-3 is a two-arm, single-blind, randomized, controlled, phase III, multi-center trial to
45 determine whether treatment algorithms informed by PbtO₂ and ICP monitoring improve subject
46 outcomes more than treatment informed by ICP alone. The trial is registered at clinicaltrials.gov:
47 NCT03754114. The complete study protocol, manual of operating procedures (MOP) and other
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documentation can be found on the study website: siren.network/clinical-trials/boost-3. Inclusion and exclusion criteria are summarized in **figure 1**.

BOOST-3 includes 47 level 1 trauma centers that are experienced with active clinical use of PbtO₂ guided patient management across the United States and Canada. These sites place PbtO₂ and ICP monitors according to BTF guidelines as part of their standard of care for severe TBI patients. Monitors will thus be inserted following local standard practice patterns. Of these patients, those who meet eligibility criteria for the study will be randomized. Specifically as per inclusion criteria, randomisation will occur if the decision to place catheters is made within 6 hours from arrival to the enrolling center and no later than 12 hours from injury (**figure 1**).

Both ICP (Codman®, Camino® or EVD) and PbtO₂ monitors (Integra Licox or Raumedic Neurovent) will be used as per local standard practice. Correct catheter placement will be confirmed by a head CT scan within 24 hours of placement. PbtO₂ probe reliability will be assessed performing an FiO₂ challenge (blinded in the ICP only group) with an appropriate response defined by an increase of at least 5 mmHg. In the PbtO₂+ICP group, non-functioning PbtO₂ probes will be replaced.

The trial is being conducted in the SIREN (Strategies to Innovate EmeRgENcy Care Clinical Trials Network) network, which is an emergency care clinical trials network funded by the National Institute for Neurological Disorders and Stroke (NINDS), the National Heart Lung and Blood Institute (NHLBI) and the National Center for Advancing Translational Science (NCATS) to improve outcomes of subjects with acute illness and injury.

Randomization and blinding

Subjects are randomized in a 1:1 ratio to a treatment protocol informed by both ICP and PbtO₂ or by ICP alone, using a covariate-adjusted randomization scheme (**figure 1**). The randomization scheme controls imbalances in the overall treatment distribution, within injury severity category, and within clinical site.

Both arms will have a PbtO₂ probe inserted, but the clinical teams will be blinded to PbtO₂ values in the ICP only group. Daily FiO₂ challenges will be conducted by unblinded study personnel not involved in patient care to assess probe reliability.

The primary outcome assessment will be centrally performed by trained personnel blinded to group assignment (see outcome section).

Intervention

A Clinical Standardization Committee (CST) for the BOOST3 trial developed general targets for physiological variables for both groups (**Table 1**) and finalized the MOP. Arterial blood pressure monitoring for CPP purposes will be standardized to the level of the heart.

The patient's clinical course will fall into 4 different clinical scenarios based on monitoring information, 3 of which (types B, C, and D, defined in **Figure 2**) will require management strategies. Type D combines the treatment options of type B and C scenarios.

Scenarios for type B (**Table 2**) and type C (**Table 3**) are addressed with a set of physiologically based interventions to correct ICP and PbtO₂. The treatment protocol is tiered in a hierarchical fashion, with less aggressive interventions attempted before more aggressive maneuvers.

Interventions in this protocol were adapted from the Brain Trauma Foundation (BTF) 2016 *Guidelines for the Management of Severe Traumatic Brain Injury* [5] and the American College of Surgeons – Trauma Quality Improvement Program (ACS TQIP) 2015 guidelines[6]. Some interventions represent expert opinions. Treatment algorithms were developed through discussions between BOOST investigators with expertise in critical care medicine and neurosurgery (CST). The protocol represents an attempt to minimize center-to-center variability and to facilitate interpretation of the PbtO₂ information using local expertise.

An episode that requires intervention is triggered by abnormalities in ICP or PbtO₂ lasting more than 5 minutes. Treatments must be initiated within 15 minutes of the start of an episode. Patients may start in one type of scenario and then move to another scenario while they are receiving treatments. The initial choice of a treatment option from any tier for any particular scenario should be determined based on what is felt to be the most effective intervention for the current clinical situation, participant characteristics and local protocols. Any intervention chosen should be aimed at addressing the underlying pathophysiology that is contributing to the episode. At least one treatment in tier 1 must be tried before moving on to tier 2. Tier 3 treatments are optional. 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 Tier 1 interventions prior to moving on to Tier 2. The bedside treatment team has the option to progress to higher tiers as rapidly as they feel is clinically indicated.

Some interventions in tables 2 and 3 are noteworthy.

Optimizing CPP. Target range for CPP are unknown and may depend on the patient's autoregulatory status[4]. As such, optimization of CPP might be informed by cerebral autoregulation testing[21]. We advise there is a potential for harm related to augmentation of CPP above 70 mm Hg[22] but some patients may require it. We also recognized that lowering CPP below 60 mmHg might be an option to treat eICP when cerebral autoregulation is absent (Lund therapy) [23]. Finally, CPP optimization also includes improvement in CBF though improvement in cardiac output (inotropy).

Increasing PaO₂. Obtaining an arterial blood gas before treating with PaO₂ adjustments is mandatory. Increasing PaO₂ above 150 mmHg might imply overtreatment by PaO₂ and prevents detection of another potential cause of low PbtO₂. Calculating the brain oxygen ratio (BOx ratio= PbtO₂/PaO₂) might help recognize this situation[10]. Increasing PaO₂ above 150 mmHg should only be used if PbtO₂ is persistently less than 20 mmHg and other variables contributing to low PbtO₂ have been addressed and controlled first.

Reverse Robin Hood syndrome[24-26]. PbtO₂ probe located in an area already maximally vasodilated might measure a drop of flow (low PbtO₂) if other areas of the brain vasodilate (potentially because of hypoventilation), creating a “steal” by diverting flow from the area measured. Treatment requires vasoconstricting the normal brain to redirect the flow towards the area measured using hyperventilation.

Withdrawal of life sustaining treatments (WLST) during the first 5 days will only be considered in dire circumstances or if requested by the patient's family. If the study subject undergoes WLST during the first 5 days of treatment, the site PI will be required to notify the study leadership team. Reasons for WLST will be carefully documented.

Outcomes

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5 2 The primary outcome measure is the Glasgow Outcome Scale-Extended performed at 180 (+/-
6 3 30) days by a blinded central examiner.
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8 5 A complete battery of secondary measures will be administered in the following order: Galveston
9 6 Orientation and Amnesia Test (GOAT), structured interview, Functional Status Examination
10 7 (FSE), GOSE-TRACK, Rey Auditory Verbal Learning Test, Trail Making Test Part A and B,
11 8 WAIS-IV Symbol Search test and coding test, Rivermead Post-Concussion Symptoms
12 9 Questionnaire, Brief Symptom Inventory 18, Satisfaction with Life Scale and Rey Auditory
13 10 Verbal Learning Test.
14 11

12 Data collection, data monitoring, and adverse events

14 14 The study data will be managed using the WebDCU™ system. This web-based clinical trial
15 15 management system will be used for regulatory document management, subject randomization,
16 16 data entry, data validation, project progress monitoring, subject tracking, user customizable report
17 17 generation, and secure data transfer. Reports will be generated to monitor study progress and
18 18 patient recruitment at each site. These reports will provide center-specific information on the
19 19 number of subjects with missing or incomplete data and number of data queries.
20 20

21 21 Information specific to PbtO₂, ICP, and CPP monitoring will be collected for up to 5 days.
22 22 Continuous digital recordings of these values will be captured on a bedside dedicated integrated
23 23 platform (CNS Monitor, Moberg ICU Solutions, Amber, PA, USA). This will allow precise
24 24 calculation of ischemic burden (time spent with PbtO₂ below 20 mmHg) and eICP burden (time
25 25 spent above 22 mmHg). A custom built-in clinical decision algorithm based on the tier treatments
26 26 (CNS Carepath®, Moberg ICU Solutions, Amber, PA, USA) can be used to help guide bedside
27 27 clinicians to select the appropriate intervention for a given type of scenario. Local study
28 28 personnel can review Carepath® and the medical record to identify alarms and actions taken to
29 29 correct them on the electronic case report form (eCRF) for the first 5 days.
30 30

31 31 The clinical site PI, independent medical safety monitor (IMSM), and data and safety monitoring
32 32 board (DSMB) appointed by the NINDS are responsible for the timely review of the safety data.
33 33 The DSMB will operate in accordance with NINDS guidelines. The DSMB will evaluate open
34 34 and closed reports prepared by the Data Coordinating Center on a semiannual basis.
35 35

36 36 General data quality will be monitored by the Clinical Coordinating Center and will include a
37 37 combination of on-site monitoring, remote monitoring, and central monitoring (using web-based
38 38 data validation rules, data manager review of entered data, statistical analysis, and on-going
39 39 review of site metrics).
40 40

41 41 Adverse events (AE) are defined as any untoward event or complication not previously identified,
42 42 or that occurs with greater frequency or severity than previously reported, whether or not
43 43 considered related to the protocol intervention. The AEs listed in **table 4** are anticipated based on
44 44 the known complications of severe TBI, intracranial monitoring devices and prolonged use of
45 45 supraphysiologic levels of oxygen. In addition, new abnormal laboratory findings that are
46 46 considered by the treating physician to be clinically significant may be included as adverse
47 47 events.
48 48

49 49 Serious AEs are any adverse event that results in any of the following outcomes or actions: 1)
50 50 Death due to any cause; 2) a life-threatening adverse experience; 3) inpatient prolongation of
51 51 existing hospitalization; 4) a persistent or significant disability/incapacity; 5) an important

1 medical event that may require medical or surgical intervention to prevent one of the outcomes
2 listed above. These must be reported within 24 hours of discovery.

3
4 All AEs are collected through day 6 or discharge, whichever comes first; serious AEs will be
5 reported through subject end of study. The IMSM will adjudicate serious AEs for seriousness,
6 relationship to the study intervention, and expectedness.

7 8 **Statistical considerations**

9
10 Favorable outcome is defined according to a sliding dichotomy (**figure 3**) [27], where the
11 definition of favorable outcome varies according to baseline severity. Severity will be defined
12 according to the probability of poor outcome predicted by the IMPACT core model[28]. The
13 favorable outcome definition is more stringent for subjects with a low probability of poor
14 outcome.

15
16 A clinically relevant effect size of 10% absolute difference in favorable outcome proportions is
17 prespecified. In order to achieve 85% power with a two-sided type I error probability of 0.05,
18 880 subjects are required. This calculation assumes a 50% favorable outcome proportion in the
19 control arm. Inflation to account for interim analysis and 7% non-adherence results in a
20 maximum sample size of 1094 subjects.

21
22 All subjects enrolled in the study are to be followed until the end of study or until consent is
23 withdrawn or declined and will be included in the primary intention-to-treat analysis.

24 25 **Study timescale**

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27 Recruitment began Summer of 2019. The COVID-19 pandemic significantly affected early
28 recruitments. The trial is currently recruiting patients at the rate of 15 - 16 patients per month.
29 Once all sites are fully operational and recruiting, we expect recruitment to end by 2026.
30 Allowing for the 6 month follow-up assessment, data cleaning and closure of the database, data
31 analyses, manuscript writing and publication should take place in 2026.

32 33 **Patients and public involvement**

34
35 Community Consultation and Public Disclosure are completed regionally for all enrolling sites in
36 the United States, prior to the initiation of the clinical trial under CFR 50.24.

37
38 No patient or public representative was involved in the written design of the trial.

39 40 **Ethics and dissemination**

41
42 Because all patients meeting eligibility criteria for this trial will be unresponsive and unable to
43 provide informed consent, participants will be enrolled either with the informed consent of a
44 legally authorized representative (LAR) or with exception from informed consent (EFIC) for
45 emergency research (no EFIC in Canada). If no LAR is available before placement of the ICP and
46 PbtO₂ monitors, the patient may be enrolled under EFIC. If LAR is available prior to ICP and
47 PbtO₂ monitors being placed, consent will be sought from LAR. The complete EFIC process will
48 be the subject of another publication since it refers to a complex ethical process.

49
50 Publication of the results of this trial will be governed by the policies and procedures developed
51 by the Executive Committee consistent with the SIREN publication policy.

Discussion

BOOST-3 is a pragmatic, physiology based study that aims to demonstrate the superiority of combined PbtO₂ + ICP guided therapy over ICP guided therapy alone when comparing subject outcomes at 6 months. Classical TBI management based on ICP and CPP alone has demonstrated its limitations [29,30]. This management uses pressure as a surrogate of CBF and oxygen delivery, an approach that was developed when there was no ability to directly or reliably measure PbtO₂.

The development of cerebral hypoxia is now understood to be multifactorial, and at times occurs independent of ICP and CPP abnormalities [11]. PbtO₂ represents a balance between oxygen delivery and consumption measured directly in the brain parenchyma [31]. Analyzing the physiological parameters that influence PbtO₂ values at the bedside[10] allows for a more extensive and precise comprehension of brain pathophysiology and may result in more tailored and efficacious care to prevent secondary injuries[19].

Two other trials are going to study the added value of PbtO₂ monitoring: the ongoing OXY-TC trial in France[32] and the BONANZA trial in New-Zealand and Australia (not yet registered on clinical trial.gov). As designed, BOOST-3 will be the largest and is adequately powered to detect a clinically meaningful difference in clinical outcome that remains achievable (10% absolute difference). In comparison, the OXY-TC targets a 30% difference in outcome. Both BOOST-3 and BONANZA will be measuring PbtO₂ in a blinded fashion in the control arm allowing the evaluation of cumulative hypoxic burden between groups.

Recognizing the heterogeneity of TBI characteristics and complexity of its management, BOOST-3 has standardized therapy in both groups while allowing for flexibility in treatment options. These options reflect the various possible physiological manipulations required to correct anomalies identified by the bedside physician (tables 2 and 3). Of note, BOOST-3 protocol recognizes that cerebral autoregulation status plays an important role in managing CPP threshold[33]. Optimization of CPP according to the autoregulation status might improve outcome but its management remains difficult clinically[34-37]. PbtO₂ might facilitate recognition of the autoregulation status[38,39]. Analysis of the continuous data capture within the BOOST3 cohort, may inform future study of the relationship between cerebral autoregulation, goal directed therapy, and patient outcome.

The BOOST3 protocol also clearly emphasizes that increasing PaO₂ in order to correct a low PbtO₂ value should be used very cautiously. Increasing PaO₂ above 150 mmHg might imply overtreatment by PaO₂ and prevents detection of another potential cause of low PbtO₂[10]. It is possible to compensate for a decrease in PbtO₂ due to low CBF by increasing PaO₂[40]. Hyperoxia is known to induce cerebral vasoconstriction[41], potentially increase free radical production[42] and has been associated with worse outcome in other brain ischemic injuries[43-46]. If FiO₂ is increased as a therapeutic maneuver, a specific FiO₂ weaning protocol is suggested. That being said, it is expected that TBI patients managed with a PbtO₂ probe will have a higher mean PaO₂ since it is the only possible therapeutic option to address the diffusion and microcirculatory failure often seen with severe TBI[13,14]. Adverse events related to pulmonary pathology will be closely tracked in both study groups.

The limitations of standardization in BOOST-3 are inherent to the nature of TBI. First, there is wide variation in the phenotype of brain injury. For example, patients may have diffuse axonal injury, intraparenchymal contusion, extra-axial hematomas, subarachnoid hemorrhage, or any

1 combination of these injuries [1]. The fact that multiparametric and PbtO₂ monitoring allow for a
2 physiology driven approach may globally improve the delivery of care despite the heterogeneity
3 of disease phenotype. BOOST3 is slated to recruit a large number of patients, which will likely
4 help to achieve balance of injury phenotype across study groups. Furthermore, the specificity
5 gained by measuring functional outcome through a sliding dichotomy based on initial injury
6 should also reduce heterogeneity bias.

7
8 Withdrawal of life sustaining therapy, although strongly discouraged in the first 5 days after TBI,
9 can still influence outcome measures. No specific protocol for prognostication and decision to
10 withdraw care is suggested in the research protocol; treating physician acumen will determine end
11 of life decisions.

12
13 An additional limitation is the relatively short time window from TBI to randomization (less than
14 12 hours after injury and 6 hours after presentation at enrolling hospital), this will likely reduce
15 generalizability of the findings to underserved communities, or those lacking access to
16 neurosurgical expertise. This timeframe was chosen to appropriately test the biological basis of
17 PbtO₂ monitoring in the acute phase of brain injury to prevent secondary injuries. A longer
18 interval from injury may allow for significant cerebral hypoxia before randomization. A
19 challenge that has been identified after start-up relates to the 6 hour time window after arrival at
20 enrolling site, which poses a problem if the patient needs urgent surgical intervention. Allowing
21 some flexibility in the 6 hour window allows urgent clinical needs to be addressed prior to
22 placement of intracranial monitors. A final challenge after study start-up included the COVID
23 pandemic putting a hold on research activities thus lowering expected enrollment.

24
25 The annual cost to society resulting from TBI has been estimated to range from \$83 billion to
26 \$244 billion (in 2014 dollars) [47]. Improvements in functional outcome will benefit not only
27 affected patients but society globally. Multiple trials targeting a specific medication or
28 pathophysiological mechanism have failed to demonstrate improvement in outcome so far[48].
29 We feel that the early use of a PbtO₂ guided bundle of care will yield a different result.

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38 Robertson, Uzma Samadani, Danielle Sandsmark, Robert Silbergleit

39 40 Figures Legends

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42 Figure 1: Randomization, inclusion and exclusion criteria

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44 Figure 2 : Four possible clinical scenarios based on monitoring information

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46 Figures 3 : Outcome defined according to sliding dichotomy

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Table 2**Scenario B: Treatment Options for Isolated ICP increase > 22 mmHg**

TIER 1: must begin within 15 minutes of abnormality. No particular order.

- Adjust head of bed to lower ICP
- Ensure Temperature < 38°C
- Titrate pharmacologic analgesia or sedation to effect
- CSF drainage (if EVD available)
- Optimize CPP to max 70 mmHg with fluid boluses or vasopressors as clinically appropriate. May assess cerebral autoregulation as per local protocol to manage CPP targets.
- Adjust ventilator for a target PaCO₂ of 35 - 40 mm Hg (target pH of 7.35 - 7.45).
- Low dose Mannitol (0.25 – 0.5 g/kg)
- Low dose HTS (include 1.5% to 3%). This tier does not include higher concentrations of HTS. Titrate to effect (ICP control) and maintain Na ≤ 160 mEq/L.
- Initiate or titrate anti-epileptic medications

TIER 2: initiate within 60 minutes if tier 1 therapies are ineffective. No particular order.

- Repeat head CT; treat surgically remediable lesions according to guidelines.
- Adjust temperature to 35 – 36°C, using active cooling measures.
- NMB, use a bolus dose to determine effect. If effective, perfusion may be used. NMB should be rapidly weaned upon clinical stabilization.
- Optimize CPP: may increase CPP above 70 mm Hg with fluid boluses or vasopressors*.
- Adjust ventilatory rate to target PaCO₂ of 33 – 38 mm Hg (target pH of 7.35-7.45).
- High dose mannitol (1-1.5 g/kg) or higher frequency of low dose mannitol (0.25-0.5g/kg) if osm <320.
- High dose hypertonic saline bolus (7.5%, 30 ml of 23.4%). May repeat if Na levels are <160mEq/L.

TIER 3 (tier 3 therapies are optional). No particular order.

- Adjust ventilatory rate for target PaCO₂ of 30 – 35 mm Hg (target pH of less than 7.5).
- Pentobarbital coma, according to local protocol. An initial bolus dose of 5 mg/kg should be used to determine effectiveness. If effective, a continuous infusion may be used. Pentobarbital should be rapidly weaned upon clinical stabilization
- Decompressive craniectomy
- Adjust temperature to 32-35°C, using active cooling measures.
- Other salvage therapy per local protocol and practice patterns.

Note: CSF: cerebrospinal fluid; EVD: external ventricular drain; HTS: hypertonic saline; NMB: neuromuscular blockade; *There is a potential for harm related to augmentation of CPP above 70 mm Hg with vasopressors

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3 **Table 4**
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Adverse event	Expected Incidence
ARDS	5%
Pneumonia	25%
Sepsis	5 %
Septic Shock	3%
Hematoma requiring craniotomy for evacuation	0.5%
CNS infection	<0.5%

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3 **1 Statements**
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5 3 RDA wrote the protocol of this study. LS, RDA, SY and WB are the principal investigators of the
6 4 trial and compose the steering committee. SY is responsible for the statistics and data
7 5 management of the trial. WB is administering the trial. FB and LS wrote the first draft of this
8 6 manuscript. FB, LS and LHM are part of the clinical standardization team responsible of protocol
9 7 implementation and the manual of operating procedure. FB, LS, RDA, SY and WB all revised
10 8 and approved the final version of this manuscript.
11 9

12 10 None of the authors have competing interest.
13 11

14 12 This trial is funded by the National Institute of neurological Disorders and Stroke (NINDS),
15 13 Grant number U01 NS099046.
16 14

17 15 The primary results of the clinical trial will be disseminated by publication in the peer reviewed
18 16 medical literature in accordance with the NIH Public Access Policy. After completion of the
19 17 study and dissemination of primary study results, the CRF data will be made publicly available
20 18 for download through the Federal Interagency Traumatic Brain Injury Research Foundation
21 19 (FITBIR) Informatics System as required by the NINDS. The public use dataset will be stripped
22 20 of any and all personal identifiers and will undergo a de-identification process.
23 21
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25 23 **References**
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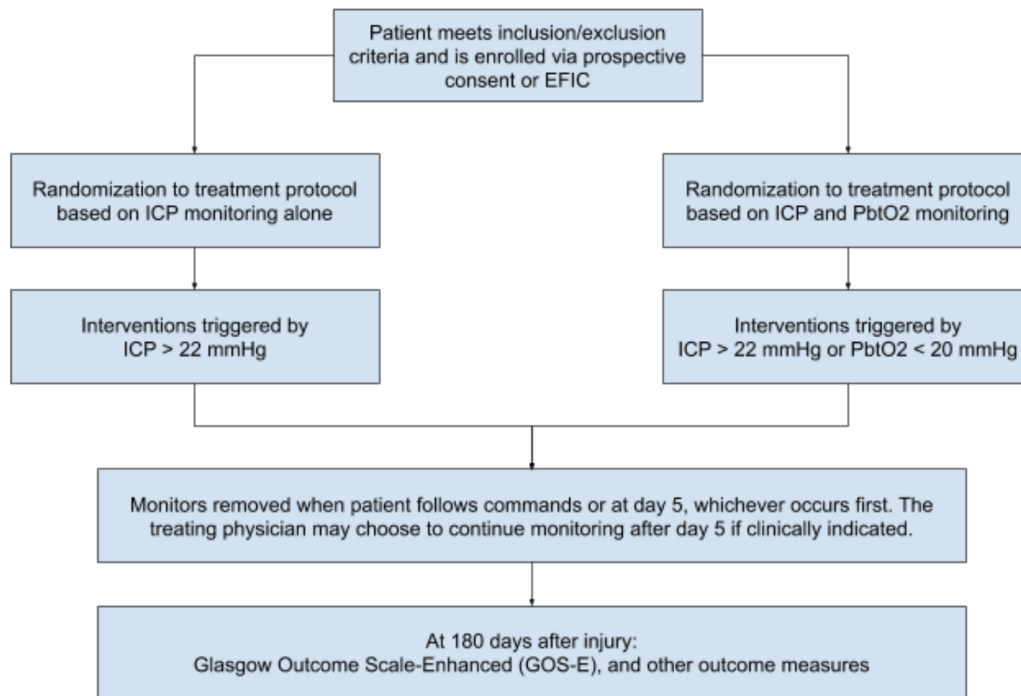
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Figure 1



Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> • 14 years of age • Non penetrating TBI • Glasgow Coma Score (GCS) of 3 to 8 measured off paralytics after resuscitation (with a motor component score less than 6) • evidence of intracranial trauma on a head CT scan (skull fracture alone is not sufficient) • Decision to insert intracranial monitors within 6 hours of arrival at the enrolling hospital, but no later than 12 hours after the injury 	<ul style="list-style-type: none"> • GCS = 3 and bilaterally absent pupil responses off paralytics • Medical contraindications for placement of intracranial monitors • Treatment of brain tissue oxygen values prior to randomization • Planned use of devices that would allow unblinding of medical care team to the treatment group • Severe sepsis at randomization • Refractory hypotension prior to randomization (SBP < 90 mmHg for two consecutive readings at least 15 minutes apart) • Refractory hypoxia prior to randomization (SaO₂ < 90% on FiO₂ > 0.5 for two consecutive readings at least 15 minutes apart) • Sustained PaO₂/FiO₂ ratio < 150 • Known pre-existing neurologic disease with confounding residual neurologic deficits • Known pre-existing condition resulting in an inability to perform activities of daily living without assistance • Known active drug or alcohol dependence that would interfere with physiological response to PbtO₂ treatments or follow-up care • Non-survivable injury in the opinion of the site investigator • Pregnancy • Prisoner or ward of the state • Person is known to have opted out of EFIC or study enrollment prior to injury (see ethics section).

Figure 2

Values in mmHg	ICP \leq 22	ICP $>$ 22
PbtO ₂ \geq 20	Type A No interventions needed	Type B Interventions to lower ICP
PbtO ₂ $<$ 20	Type C Interventions to increase PbtO ₂	Type D Interventions to lower ICP and increase PbtO ₂

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Figure 3

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	Favorable Outcome						
0.41 to <0.56	Favorable Outcome						
0.56 to ≤1	Favorable Outcome						

For peer review only

SIREN Informed Consent Forms

The Sponsor/Investigator of BOOST-3 does not allow edits to this central IRB approved main consent form for this multicenter trial. This is to ensure equity of the language across the enrolling sites. Your site may add site-specific content in a single contained section below the universal text if necessary. This section is limited to information that pertains specifically to your local institution.

Please note the process for submitting informed consent forms for BOOST-3 as sites submit ceding applications to local IRBs. All SIREN informed consent forms are approved by the Advarra Central IRB (ER-CIRB) with the parent protocol. The informed consent form is a completely locked down form, to be used consistently across BOOST-3 sites. Please submit this form to your local IRB as is, without making any site specific changes. The current ER-CIRB approved form to be used is located in the BOOST-3 Toolbox and the Getting Started page.

Where local site and study team contact information needs to be included, this will populate directly into the form after the site application is submitted to and approved by the ER-CIRB. In very limited circumstances, when institutionally required language is requested by the IRB, there is potential to add a separate site specific section at the end of the form prior to the signature page. However, for the time being, please submit the form as is. Additions will only be considered per a request from the IRB, and will be discussed on a case by case basis. Should this request from the IRB be made, please provide at the earliest time the additional requested language in a separate document for review by the SIREN CCC. Please do not edit or insert language into the body of the trial-wide approved ICF.

Please note that while HIPAA language is already included in the body of the consent form, a separate local HIPAA form is acceptable for use, so long as it is signed and dated by subject/LAR.

We understand that this process differs from how the ICF review process has operated for other trials. We are happy to help as we move along with this process; please let us know if we can be of assistance. Please also note the below statement from Advarra regarding this process for SIREN trials.

As you know, Advarra is the single IRB for the SIREN network trials. If your organization has a negotiated process in place with Advarra specifically as it pertains to the Informed Consent language, please note that the established process that has been in place with your site and Advarra is suspended for the SIREN network's trials. SIREN has their own IC process which Advarra will follow for these specific trials. Any non-SIREN trials will follow the established process you already have in place with Advarra.

If you have any questions regarding this please contact boost-contact@umich.edu.

Thank you for your attention with this matter,
Best regards,
Advarra Institutional Services Team & SIREN

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3 **CONSENT TO TAKE PART IN A CLINICAL RESEARCH STUDY**
4 **AND**
5 **AUTHORIZATION TO DISCLOSE HEALTH INFORMATION**
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7 **ADULTS/SUBJECTS WHO TURN 18/PARENTAL/GUARDIAN PERMISSION**
8 **& ASSENT FOR AGES 14 TO AGE OF MAJORITY**
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12 **Study Title:** "Brain Oxygen Optimization in Severe Traumatic Brain
13 **Injury - A multi-center, randomized, blinded-endpoint,**
14 **comparative effectiveness study of goal-directed critical**
15 **care based upon monitoring of brain tissue oxygen and**
16 **intracranial pressure versus monitoring of intracranial**
17 **pressure alone in patients with severe traumatic brain**
18 **injury"**
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22 **Granting Agency:** The National Institute of Neurological Disorders and
23 **Stroke (NINDS)**
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25 **Protocol Number:** BOOST-3
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28 **Principal Investigator:** «PiFullName»
29 **(Study Doctor)**
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31 **Telephone:** «IcfPhoneNumber»
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34 **Additional Contact(s):** «AdditionalStaffMemberContacts»
35 **(Study Staff)**
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37 **Address:** «PiLocations»
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41 This form is for use in a research study that involves participants who are unconscious or in
42 coma, and do not have the capacity to consent to take part in the study. You are the legally
43 authorized representative of the patient. In cases where the participant's representative gives
44 consent, the participant should be informed about the study to the extent possible if the
45 participant regains consciousness. During the course of the study, if the subject regains the
46 capacity to consent, informed consent will be obtained from the subject and the subject offered
47 the ability to leave the study if desired.
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SUMMARY OF KEY INFORMATION

Your family member (or a person you represent) has had a severe traumatic brain injury (TBI). He or she may be eligible to participate, or continue to participate, in a research study. The study is to compare two ways of treating patients with brain injury. Physicians do not know which standard of care treatment is better. Neither treatment being studied are investigational. We are talking with you because patients with severe TBI are unconscious or in a coma; and they cannot tell us if they want to participate in a study. You are the patient's representative. In an effort to provide immediate emergency care, the person you represent may have already been entered in this study. If not, we are asking you to consent or refuse consent for his or her participation. If the patient was already entered in the study, we are asking you for your consent to allow them to continue or to stop participation in the study. The remainder of this document should help you in this decision.

Participants in this study are placed at random, that is by chance, in one of two groups. One group has medical care based on monitoring of pressure in the brain (intracranial pressure or ICP) alone. The other group has medical care based on both ICP and the amount of oxygen in the brain (brain tissue oxygen or PbtO₂). It is unknown if measuring and treating low brain oxygen is more effective, less effective, or the same as monitoring and treating high brain pressure alone. Treatment differs by group because doctors make decisions guided by ICP and PbtO₂ goals. These decisions include the kinds and doses of medications given. They also include the amount of fluids given by vein. Other treatments that may differ can also include changing ventilator (breathing machine) settings, blood transfusions, and other parts of medical care. ICP and PbtO₂ are monitored by small sensor probes placed in the brain through one or two small holes made in the skull. Placing one or both of these probes is standard care for people with severe TBI. They are placed within hours of arrival at the hospital. Those in the study will have both probes placed.

After the initial hospitalization, we will contact participants or their caregivers about once per month for 5 months to see how they are doing. A study team member will schedule a follow up visit to the clinic about 6 months after the injury to learn about how the participant is doing. The study team will review the participant's medical records while they are in the study as needed. About 1,000 participants will be enrolled at about 45 hospitals.

Participation in the study will help doctors learn if one way of treating future victims of TBI is better. Participants may or may not directly benefit from being in the study. Some participants may benefit directly if recovery turns out to be more likely with the management they receive. Participation may also have risks. Some possible risks are currently unforeseeable. Known risks from study participation include accidental release of private information. Other risks may include bleeding around the sensors, infection, lung problems, or other medical complications. Risks will be discussed later in this consent form.

Participation in the study, or ongoing participation if your family member was already enrolled before we could reach you, is voluntary. The alternative to being a part of this study is to receive the usual standard of care. Usual care may be either of the ways of treating patients being compared in the study. Usual care often varies based on the injury, the choice of the doctor, or the treating hospital. There is no penalty for choosing not to participate. A participant can withdraw from the study at any time.

Medical records and data collected in the study will remain as private as possible. Participants' records may be viewed by the study team here or from the study coordinating centers. Records may also be seen by those responsible for reviewing the safety and conduct of the study. This oversight is provided by this institution and by government regulatory and funding agencies.

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3 There is no payment or compensation for being in the study. There is no cost to being in the
4 study. Charges for all standard medical care will be billed the same way whether or not
5 someone is in the study.
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7 Please contact us for any questions about the research, participants' rights, or other concerns.

- 8
- 9 • Please carefully read this form, additional detail about each item just described is found below
 - 10 • Please listen to the study team explain the study and this form to you
 - 11 • Please ask questions about anything that is not clear

12 If you consent, you will be asked to sign and date this form.
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15 MORE DETAILED INFORMATION

16 What is the purpose of this research study?

17 The purpose of the research study is to learn if either of two strategies for monitoring and
18 treating patients with TBI in the intensive care unit (ICU) is more likely to help them get better.
19 Both of these alternative strategies are used in standard care. It is unknown if one is more
20 effective than the other. In both strategies, doctors monitor the patient's brain and modify the
21 medical care provided in order to try to improve some measure of the brain's health. However,
22 it is not known which measure of the brain's health, intracranial pressure or oxygen level, is
23 more important. In one strategy doctors concentrate only on preventing high ICP (intracranial
24 pressure) caused by a swollen brain. In the other strategy doctors try to prevent high ICP, and
25 also try to prevent low PbtO₂ (brain oxygen). Some hospitals and doctors tend to use one or
26 the other strategy more often. It is unknown if measuring and treating low brain oxygen is more
27 effective, less effective, or the same as monitoring and treating high brain pressure alone. The
28 results of this study will help doctors discover if using both of these methods is better than using
29 one alone in treating TBI.
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32 Why is this an important question to study?

33 When a person has a TBI, their injured brain can swell over a period of hours or days. If the
34 brain swells too much, the pressure in the skull increases and becomes dangerous, causing
35 further injury to the brain. To try to prevent this, doctors usually insert a device, an ICP probe,
36 into the brain through a hole in the skull of people with severe TBI. An ICP monitor connected
37 to the probe measures the pressure inside the skull. Most doctors agree that it is important to
38 measure and prevent high ICP.
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41 Patients with injured brains also suffer additional injury to the brain if the amount of oxygen in
42 the brain gets too low. Some doctors also insert a second device, a PbtO₂ probe, in the brain
43 through the same or a second hole in the skull to measure brain tissue oxygen. A PbtO₂
44 monitor connected to the probe measures how much oxygen is in a small area of the brain near
45 the tip of the probe. Doctors disagree about whether monitoring oxygen levels is helpful or
46 necessary.
47

48 Both monitoring devices are approved by the US Food and Drug Administration (FDA) and
49 Health Canada for patients with TBI. Both are commonly used. The ICP and PbtO₂ goals
50 guided by these monitors are used to help doctors adjust their treatment choices. Treatments
51 include kinds and doses of medications and the amount of intravenous fluids given, ventilator
52 (breathing machine) settings, need for blood transfusions, and other medical care. Each of
53 these treatment decisions is intended to improve outcomes. However, each treatment decision
54 also involves potential risks. Different treatment decisions may result in different risks. This
55 study will also help doctors better understand these risks.
56
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This study is funded by the National Institutes of Health because it answers questions important to the care of patients with TBI.

How long will the participant be in the study? How many people will be in the study?

- Participants are in the study for about 6 months. The treatments being studied all occur in the first 5 days.
- About 1,000 participants will be enrolled at about 45 hospitals.
- We will call participants (or their caregivers) about 5 times after their injury. We will call about once each month for 5 months. Each phone call will last about 15 minutes. During the phone call, we will ask how they are doing, if they are having any additional problems, and if any of their contact information has changed.
- We will ask the participant to come in for a study visit about 6 months after their brain injury. If they are not well enough to travel, a member of the study team can visit them where they are living, if they agree. The visit will take about 1 hour. During the visit, a study team member will ask questions about the participant's recovery. There will be a questionnaire and some pencil and paper exercises. There are no risks anticipated from this visit.
- If the participant is unable to have an in-person interview, a telephone interview with the participant or caregiver can be done instead. If possible, the telephone interview will collect the same information as the visit except for the pencil and paper exercises. It may also take up to 1 hour.
- Translators will be available for calls and visits with individuals whose preferred language is not English.

What happens in this study?

- All participants will have both an ICP probe and a PbtO2 oxygen probe placed.
- Participants will have an equal chance (like the flip of a coin) of being allocated to one of the two groups. The groups determine which information about the brain will be used to guide medical care.
 - Group 1: medical care guided by ICP monitoring (the PbtO2 monitor is covered and not used)
 - Group 2: medical care guided by ICP and PbtO2 monitoring
- This random (like the flip of a coin) allocation to one group or another is research.
- Medical care of the participant will be guided by this group allocation (which group the participant is in) for 5 days.
- Medical care of the participant affected by group allocation might include the choices and doses of medications and the amount of intravenous fluids given, how the participant's ventilator is adjusted, the need for blood transfusions, and other components of ICU care.
- Other than which monitoring information is used to guide care in the first 5 days, all participants receive usual care. Use of monitoring beyond 5 days is also based on usual care.
- Doctors caring for participants in group 1 will make decisions based on the ICP monitor. They will not see the information from the PbtO2 monitor. They will not make any decisions based on PbtO2 information. Having a PbtO2 monitor, but not using the information to guide care is part of the research.
- One or both probes may be removed before 5 days if there is a clinical reason to do so. This may include the participant waking from coma, infection of the probe, or 3 or more days without abnormal readings on the monitors.
- Information is collected for the study from participants' medical record, diagnostic images, and monitors. Information collected includes the condition of the patient and the treatments being provided.

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- We will visit the participant daily during the first 5 days in the ICU, and periodically while in the hospital. We will review the medical record at these times, at discharge, and at any return visits during participation.
 - Contact information for the participant, you, family members, close friends, or caregivers is collected in order to arrange follow up during the study. These include phone numbers, email and mailing addresses.

10 **What risks may participants experience?**

11 There are potential clinical risks to all the treatments used in the medical care of patients with
12 severe TBI. These risks are the same whether or not they participate in the study. Participation
13 in research may also have risks.
14

15 Clinical risks potentially related to the monitors and treatments include, but are not limited to, the
16 following:
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- Pneumonia (infection of the lung) is common in those with severe TBI (about 1 in 4), and may rarely be increased because of efforts to optimize PbtO₂ (fewer than 5 in 100).
- Lung injury, sometimes related to ventilator settings or the amount of intravenous fluids given, which may be affected by brain monitoring, is also common (about 1 in 20).
- Severe sepsis, a dangerous infection spread in the blood, is common (about 1 in 20), usually unrelated to monitoring.
- Placement or removal of probe can sometimes cause slight bleeding at the site of insertion (fewer than 2 in 100). Rarely, a medicine or procedure to reduce bleeding might be used (fewer than 1 in 5000).
- Infection in the brain, possibly related to brain probe placement, is rare (fewer than 1 in 5000).

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31 Risks related to being a study participant include:

- Breach of confidentiality is a rare risk of participation in research studies (fewer than 1 in 10,000).
- If you request it, you may be emailed a PDF copy of this signed and dated consent form. There may be risks of loss of privacy and confidentiality if the PDF copy of this consent form is viewed and/or stored on a personal electronic device (PED), especially if that PED is shared with other users or is lost, hacked, or subject to a search warrant or subpoena. Also, the PDF copy of the consent may not be able to be permanently removed from a PED.

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41 The researchers have taken steps to minimize these risks. The study team will monitor
42 closely for these possible risks and complications will be treated if needed.

43 To reduce any potential risk to an unborn child, women of childbearing potential will
44 have a pregnancy test and if pregnant, will not be included in this research study.

45 As with any research study, there may be additional risks that are unknown or
46 unexpected.
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49 **What is the possible benefit?**

50 The participant may or may not benefit from being in this study. Some participants may benefit
51 directly if recovery turns out to be more likely with the management they receive. Discovery that
52 one strategy or the other helps traumatic brain injury patients recover with less disability will be
53 an important advancement in the treatment of future patients with brain injury.
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55 **What is the alternative to participating in this study?**

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3 Participation, or ongoing participation, in this study is voluntary. The alternative to participating
4 in the trial is usual care. Usual care may be medical care guided by ICP monitoring or it may be
5 medical care guided by ICP and PbtO2 monitoring. The usual care offered may depend on the
6 treating hospital, opinion of the doctors caring for the individual, or upon characteristics of the
7 patient or their injury. There is no penalty for choosing not to participate. The participant may
8 withdraw from the study at any time, either by his/her choice or at the direction of the
9 participant's legally authorized representative. Choosing not to participate, not to continue
10 participation, or choosing to withdraw will not alter the usual care available. Nor does it alter or
11 waive any legal rights or benefits.
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13 **What if new information becomes available?**

14 We will provide any new information that may affect a participant's willingness to continue in the
15 study. Participants may be contacted about future available studies. We may also contact
16 participants with periodic updates about the study. We may also contact participants after the
17 trial has been completed to share results from the study.
18

19 **AUTHORIZATION TO DISCLOSE HEALTH INFORMATION**

20 **How will personal information be protected?**

21 The study investigator and his/her collaborators will consider the participants' personal
22 information confidential to the extent permitted by law. "Personal Information" means
23 information that can be used to identify the participant or health information about the
24 participant. This includes name or initials, date of birth, gender, ethnic origin and medical and
25 health-related information such as blood tests, diagnostic imaging and results, the results of
26 physical examinations, medical history and hospital records, and information directly observed
27 in the study.
28

29 Information about the participant collected for the study may be stored electronically or on
30 paper. The information stored on the computer is kept in password protected files that are
31 maintained on password protected computers. The information stored on paper is stored in a
32 locked file cabinet in a locked office. Only the members of the study team and the persons and
33 groups listed below will have access to the participants' medical information for this study.
34

35 The government agencies responsible for making sure that studies are conducted and handled
36 correctly, and other organizations involved in this research study may look at the participant's
37 study records in order to perform their duties. These include: the US National Institutes of
38 Health (NIH), the US Office for Human Research Protections, the US Food and Drug
39 Administration (FDA), Health Canada, researchers from University of Pennsylvania and the
40 University of Pittsburgh, representatives from The Strategies to Innovate Emergency Care
41 Clinical Trials Network (SIREN) Clinical Coordinating Center at the University of Michigan,
42 representatives from the Data Coordination Unit at the Medical University of South Carolina, the
43 Central Institutional Review Board, and/or other agents of the study who will be bound by the
44 same provisions of confidentiality. Information from this study may be submitted to the US Food
45 and Drug Administration (FDA) and Health Canada.
46

47 To help us protect the participant's privacy, this research is covered by a Certificate of
48 Confidentiality from the US National Institute-Institutes of Health. With this Certificate, the
49 investigators may not disclose or use information, documents, or biospecimens that may identify
50 the participant in any federal, state, or local civil, criminal, administrative, legislative, or other
51 action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, in
52 the US unless the participant has consented for this use. Information, documents, or
53 biospecimens protected by this Certificate cannot be disclosed to anyone else who is not
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3 connected with the research except, if there is a federal, state, or local law that requires
4 disclosure (see below); if the participant has consented to the disclosure, including for the
5 participant's medical treatment; or if it is used for other scientific research, as allowed by federal
6 regulations protecting research subjects.
7

8 Disclosure is required, however, for audit or program evaluation requested by the NIH or when
9 required by the FDA or Health Canada. A Certificate of Confidentiality does not prevent the
10 participant from voluntarily releasing information about themselves or their involvement in this
11 research. If the participant wants research information released to someone, the participant
12 must provide consent to allow the researchers to release it. The certificate covers disclosures
13 involving participants enrolled in Canada in US legal proceedings, but does not cover
14 disclosures in proceedings outside the US.
15

16 The Certificate of Confidentiality will not be used to prevent disclosure as required by federal,
17 state, or local law of, for instance, child abuse or neglect, harm to self or others, and
18 communicable diseases.
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20 The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have
21 consented to in this informed consent document.
22

23
24 Although every effort will be made to maintain confidentiality of the participant's medical and
25 health records, absolute confidentiality cannot be guaranteed. We will use a study number
26 rather than the participant's name on study records where we can. The participant's name and
27 other facts that might point to the participant will not appear when we present this study or
28 publish its results. Viewing or storing this electronic informed consent form on a personal
29 electronic device may allow information provided on this form (such as names and email
30 addresses) to be inadvertently shared with others if the device is lost, hacked, or otherwise
31 compromised.
32

33 When ready to leave the hospital, typically well after the 5 days of study treatment is complete,
34 the participant may be discharged to a rehabilitation or nursing facility. The participant might
35 also be discharged home and then readmitted to another medical facility later. Your signature
36 on this document authorizes those facilities to release medical records to the researchers and
37 research staff of this study for the 6 months the participant is in the study.
38

39 We will keep any records that we produce private to the extent we are allowed or required by
40 law. The participant's records will be kept for as long as necessary for purposes of the research
41 study.
42

43 The study doctor and treating institution are required by law to protect the study participants'
44 health information. With this form, you authorize the study doctor to use and disclose the
45 participant's health information, as described in this section, in order to conduct this research
46 study. You have the right to revoke this authorization, at any time, and can do so by writing to
47 the study doctor at the address on the first page. Even if you revoke the authorization, the study
48 doctor and/or sponsor may still use health information they have collected about the study
49 participant, if necessary, for the conduct of the study. However, no new information will be
50 collected.
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52 Your authorization does not have an expiration date unless indicated elsewhere. You do not
53 have to sign this information and consent form, but if you do not, the person you represent will
54 not be able to take part in this research study. Those persons who receive the participant's
55 health information may not be required by US Federal privacy laws (such as the Privacy Rule)
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3 to protect it and may share the information with others without your permission, if permitted by
4 laws governing them.

5
6 By signing this information and consent form, you consent to the collection, access, use and
7 disclosure of the participant's information as described above. State law or the enrolling
8 institution may require an additional separate form on which you can authorize sharing of the
9 participant's health information. If so, you will have to sign both forms for your authorization to
10 be valid.

11 12 **How may the participants' data and samples be shared?**

13 US Federal rules require that data be securely stored in the Federal Interagency Traumatic
14 Brain Injury Research (FITBIR) informatics system where it can also be accessed by
15 researchers in a de-identified manner. For more information see the website <http://fitbir.nih.gov>

16 17 **Will the participant have to pay anything?**

18 There is no additional cost to participate in the study. Charges for all standard medical care will
19 be billed in the same manner regardless of participation. Participants who receive the brain
20 oxygen probe in the study will not be charged for it, nor will a public health plan, or the
21 participant's private medical insurer (if any). Funds are not available to cover the costs of any
22 ongoing medical care and participants remain responsible for the cost of non-research related
23 care. For questions about the participant's medical bills relative to research participation,
24 contact the study investigator listed on this form.

25 26 27 **Will the participant be paid for being in the study?**

28 No. There will not be any payment to the participant for being in this study.

29 30 **What if the participant is injured as result of being in this study?**

31 If a participant is injured or becomes ill from participating in the study, medical treatment will be
32 available at this institution or elsewhere consistent with the care provided for any medical
33 problem. Payment for this care will be billed the same as any other care for any medical
34 problem. If the hospital at which the participant was enrolled has any additional answers to this
35 question, this information is found at the bottom of this form.

36
37 In the event that the participant suffers injury as a result of their participation in this
38 research study, no compensation will be provided to the participant by the granting
39 agency (National Institute of Neurological Disorders and Stroke), the treating institution,
40 or the researchers. The participant still has all of their legal rights. Nothing said here
41 about treatment or compensation in any way alters the participants' right to recover
42 damages.

43 44 45 **Is there anything else I need to know?**

46 Continued participation in this study is voluntary. The participant may withdraw from the
47 study at any time and for any reason without penalty. The researcher may discontinue
48 participation if the study is discontinued or suspended. No more information will be
49 collected about a participant after they withdraw from the study or complete their
50 participation.

51
52 You may ask to stop having the study affect the participant's medical care. If so, usual care
53 will resume. Usual care is based on the individual patient and their injury, the opinion of the
54 treating doctors, and the treating institution. Usual care may be medical care guided by ICP
55 alone, or medical care guided by ICP and PbtO2 monitoring.

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3 Doctors caring for the participant during this hospitalization may also be researchers in
4 this study. If so, the doctors are interested both in the participant's medical care and in
5 the conduct of this research. There is no obligation to participate in any research study
6 just because it is offered by the participant's doctors.
7

8 A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as
9 required by U.S. Law. This Web site will not include information that can identify you. At
10 most, the Web site will include a summary of the results. You can search this Web site
11 at any time.
12

13 **What if I have questions?**

14 You or the participant may ask and will receive answers to any questions you have during
15 the course of the study. For any questions regarding this study or if the participant
16 experiences any side effects or medical problems, contact the site researcher listed on
17 this form.
18

19 Advarra serves as the Central Institutional Review Board (CIRB) for this study. The
20 CIRB is not part of the research or the research team. Please contact Advarra, if you:
21

- 22 • have questions about your role and rights as a research participant;
- 23 • wish to obtain more information about clinical research in general;
- 24 • have concerns, complaints or general questions about the research, or;
- 25 • wish to provide input about the research study
26

27 You can do so in the following ways:

- 28 • By mail:
29 Study Subject Adviser
30 Advarra IRB
31 6940 Columbia Gateway Drive, Suite 110
32 Columbia, MD 21046
- 33 • or call **toll free:** 877-992-4724
- 34 • or by **email:** adviser@advarra.com
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37 Please reference the following number when contacting Advarra: Pro00030585.
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CONSENT STATEMENTS

PARTICIPANT'S CONSENT (should the participant become cognizant during the study)

I have read and understand the information in this informed consent document. I have had an opportunity to ask questions and all of my questions have been answered to my satisfaction. I voluntarily agree to participate in this study until I decide otherwise. I do not give up any of my legal rights by signing this consent document. I will receive a copy of this signed and dated consent document.

Participant's Printed Name

Participant's Signature

____/____/____
Date

STATEMENT OF ASSENT (should the adolescent become cognizant during the study)

I would like to be in this study.

Printed Name of Adolescent Participant

Adolescent Assent Signature

Date

STATEMENT OF PARENTAL / LEGAL GUARDIAN PERMISSION

I have read and understand the information in this informed consent document. I have had an opportunity to ask questions and all of my questions have been answered to my satisfaction. I voluntarily agree for my child to participate in this study until I decide otherwise. I do not give up any of my or my child's legal rights by signing this consent document. I will receive a copy of this signed and dated consent document.

Signature of Parent/Legal Guardian (if subject is under age 18)

____/____/____
Date

Printed Name of Parent/Legal Guardian (if subject is under age 18)

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3 **INFORMED REFUSAL OF FURTHER PARTICIPATION**
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5

6 You should feel that you have been told enough about this study to give your informed consent
7 before signing this form. Signing this form does not waive any legal rights to which you or the
8 person you represent are entitled. You will receive a copy of this form after it is signed and
9 dated.
10

11 If you DO NOT want your family member (or the person you represent) to continue to participate
12 in this study, please sign below.
13

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15 _____
16 Participant Name
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19 _____
20 Printed Name of Legally Authorized Representative (LAR)
21

22 Your relationship to act on behalf of Participant (i.e., spouse, child, parent, sibling, other [if
23 other, please describe])
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29 _____ / ____ / ____ : ____ AM/PM
30 Signature of LAR Date Time
31

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35 _____
36 Principal Investigator/Designee Name

_____ Title
37

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39 _____
40 Designee Signature

_____ / ____ / ____ : ____ AM/PM
41 Date Time
42

BMJ Open

Brain Oxygen Optimization in Severe Traumatic Brain Injury (BOOST-3): A multicenter, randomized, blinded-endpoint, comparative effectiveness study of brain tissue oxygen and intracranial pressure monitoring versus intracranial pressure alone.

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Keywords:	Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Neurological injury < NEUROLOGY, Trauma management < ORTHOPAEDIC & TRAUMA SURGERY, NEUROSURGERY, NEUROPHYSIOLOGY

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1 **Brain Oxygen Optimization in Severe Traumatic Brain Injury**
2 **(BOOST-3): A multicenter, randomized, blinded-endpoint, comparative**
3 **effectiveness study of brain tissue oxygen and intracranial pressure**
4 **monitoring versus intracranial pressure alone.**

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37 **Funder:** National Institute of neurological Disorders and Stroke (NINDS),
38 Grant number U01 NS099046

40 **Key words :** protocol and guidelines, adult intensive and critical care, neurological
41 injury, trauma management, neurosurgery, neurophysiology

43 **Word count :** 3455

Abstract

Introduction: Management of traumatic brain injury (TBI) includes invasive monitoring to prevent secondary brain injuries. Intracranial pressure (ICP) monitor is the main measurement used to that intent but cerebral hypoxia can occur despite normal ICP. This study will assess whether the addition of a brain oxygenation monitor (PbtO₂) prevents more secondary injuries that will translate into improved functional outcome.

Methods and analysis: Multicenter, randomized, blinded-endpoint comparative effectiveness study enrolling 1094 severe TBI patients monitored with both ICP and PbtO₂. Patients will be randomized to medical management guided by ICP alone (treating team blinded to PbtO₂ values) or both ICP and PbtO₂. Management is protocolized according to international guidelines in a tiered approach fashion to maintain ICP < 22mmHg and PbtO₂ > 20 mmHg. ICP and PbtO₂ will be continuously recorded for a minimum of 5 days. The primary outcome measure is the Glasgow Outcome Scale-Extended performed at 180 (+/- 30) days by a blinded central examiner. Favorable outcome is defined according to a sliding dichotomy 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. A large battery of secondary outcomes including granular neuropsychologic and quality of life measures will be performed.

Ethics and dissemination: This has been approved by Advarra ethics committee (Pro00030585). Results will be presented at scientific meetings and published in peer-reviewed publications. The trial is registered at clinicaltrials.gov: NCT03754114

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5 3 **Strengths and limitations of this study**
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- 8 6 • BOOST-3, a blinded outcome RCT, will determine whether a treatment protocol,
9 7 informed by PbtO₂ plus ICP monitoring, results in improved neurologic outcome
10 8 measured by the Glasgow Outcome Scale-Extended (GOS-E) 6 months after injury
11 9 compared to treatment guided by ICP monitoring alone.
 - 12 10 • BOOST-3 is adequately powered to detect a clinically meaningful difference in outcome
13 11 that remains achievable (10% absolute difference).
 - 14 12 • The relatively short time window from TBI to randomization (less than 12 hours after
15 13 injury and 6 hours after presentation at enrolling hospital) will likely reduce
16 14 generalizability of the findings to underserved communities.
 - 17 15 • Extensive secondary outcome tests (12 in total) exploring functional and emotional
18 16 outcome will be performed by blinded centralized examiners.
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1 Introduction

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3 TBI is a major cause of death and disability in modern industrialized societies[1]. The most recent
4 estimates from the Centers for Disease Control and Prevention (CDC) indicate that in the United
5 States alone, 3.5 million individuals experience a TBI annually, of which 300,000 are
6 hospitalized and discharged alive[2]. Among the 300,000 hospitalized survivors, over 40%
7 experience long-term disability[3].

8
9 Historically, monitoring of patients with severe TBI focused on intracranial pressure (ICP) and
10 cerebral perfusion pressure (CPP) to prevent secondary injury[4-6]. Although limiting elevation
11 of ICP is an important part of TBI management, the only randomized controlled trial comparing
12 an ICP driven management versus clinical management based on imaging and physical
13 examination did not show improvement in outcome with invasive monitoring[7]. The
14 management of elevated ICP (eICP) is complex and heterogeneous, this likely reflects the
15 difficulty of applying a one size fits all protocol to a heterogeneous population of patients who
16 require individualized care[8,9].

17
18 The physiological rationale underlying ICP management is to preserve oxygen delivery to the
19 brain, using CPP as a surrogate for cerebral blood flow (CBF). There are numerous reasons why
20 brain oxygen delivery can be affected despite ICP or CPP being normal [10-12]. In fact, oxygen
21 diffusion in the brain parenchyma is the rate limiting step of delivery[13] and is affected by the
22 presence of edema or microcirculatory failure[14]. Devices that measure brain tissue oxygen
23 (PbtO₂) are now readily available at bedside. Numerous studies have shown that cerebral hypoxia
24 is common, reversible, may be able to measure cerebral ischemic burden, and independently
25 associated with functional outcome [11,15-18]. The use of PbtO₂ was recently the subject of a
26 consensus statement guideline, highlighting the fact that multimodal monitoring allows for
27 management refinement compared to ICP management alone [19].

28
29 TBI management heterogeneity requires that any multicenter clinical trial protocol allows various
30 treatment options based on bedside evaluation of cerebral physiology while maintaining the rigor
31 and clinical standardization necessary to conduct a randomized clinical trial (RCT). BOOST-2, a
32 multicenter RCT, found that treatment of elevated ICP and correction of low PbtO₂ decreased the
33 total cumulative ischemic burden compared to treatment of elevated ICP alone (p = 0.0000002)
34 [20]. Furthermore, a trend in improved functional outcome at 6 months was supportive of the
35 pre-determined non-futility hypothesis.

36
37 The primary objective of BOOST-3 is to determine whether a treatment protocol, informed by
38 PbtO₂ plus ICP monitoring, results in improved neurologic outcome measured by the Glasgow
39 Outcome Scale-Extended (GOS-E) 6 months after injury compared to treatment guided by ICP
40 monitoring alone.

41 Methods

42 Trial design, study setting and study population

43
44 BOOST-3 is a two-arm, single-blind, randomized, controlled, phase III, multi-center trial to
45 determine whether treatment algorithms informed by PbtO₂ and ICP monitoring improve subject
46 outcomes more than treatment informed by ICP alone. The trial is registered at clinicaltrials.gov:
47 NCT03754114. The complete study protocol, manual of operating procedures (MOP) and other
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documentation can be found on the study website: siren.network/clinical-trials/boost-3. Inclusion and exclusion criteria are summarized in **figure 1**.

BOOST-3 includes 47 level 1 trauma centers that are experienced with active clinical use of PbtO₂ guided patient management across the United States and Canada. These sites place PbtO₂ and ICP monitors according to BTF guidelines as part of their standard of care for severe TBI patients. Monitors will thus be inserted following local standard practice patterns. Of these patients, those who meet eligibility criteria for the study will be randomized. Specifically as per inclusion criteria, randomisation will occur if the decision to place catheters is made within 6 hours from arrival to the enrolling center and no later than 12 hours from injury (**figure 1**).

Both ICP (Codman®, Camino® or EVD) and PbtO₂ monitors (Integra Licox or Raumedic Neurovent) will be used as per local standard practice. Correct catheter placement will be confirmed by a head CT scan within 24 hours of placement. PbtO₂ probe reliability will be assessed performing an FiO₂ challenge (blinded in the ICP only group) with an appropriate response defined by an increase of at least 5 mmHg. In the PbtO₂+ICP group, non-functioning PbtO₂ probes will be replaced.

The trial is being conducted in the SIREN (Strategies to Innovate EmeRgENcy Care Clinical Trials Network) network, which is an emergency care clinical trials network funded by the National Institute for Neurological Disorders and Stroke (NINDS), the National Heart Lung and Blood Institute (NHLBI) and the National Center for Advancing Translational Science (NCATS) to improve outcomes of subjects with acute illness and injury.

Randomization and blinding

Subjects are randomized in a 1:1 ratio to a treatment protocol informed by both ICP and PbtO₂ or by ICP alone, using a covariate-adjusted randomization scheme (**figure 1**). The randomization scheme controls imbalances in the overall treatment distribution, within injury severity category, and within clinical site.

Both arms will have a PbtO₂ probe inserted, but the clinical teams will be blinded to PbtO₂ values in the ICP only group. Daily FiO₂ challenges will be conducted by unblinded study personnel not involved in patient care to assess probe reliability.

The primary outcome assessment will be centrally performed by trained personnel blinded to group assignment (see outcome section).

Intervention

A Clinical Standardization Committee (CST) for the BOOST3 trial developed general targets for physiological variables for both groups (**Table 1**) and finalized the MOP. Arterial blood pressure monitoring for CPP purposes will be standardized to the level of the heart.

The patient's clinical course will fall into 4 different clinical scenarios based on monitoring information, 3 of which (types B, C, and D, defined in **Figure 2**) will require management strategies. Type D combines the treatment options of type B and C scenarios.

Scenarios for type B (**Table 2**) and type C (**Table 3**) are addressed with a set of physiologically based interventions to correct ICP and PbtO₂. The treatment protocol is tiered in a hierarchical fashion, with less aggressive interventions attempted before more aggressive maneuvers.

Interventions in this protocol were adapted from the Brain Trauma Foundation (BTF) 2016 *Guidelines for the Management of Severe Traumatic Brain Injury* [5] and the American College of Surgeons – Trauma Quality Improvement Program (ACS TQIP) 2015 guidelines[6]. Some interventions represent expert opinions. Treatment algorithms were developed through discussions between BOOST investigators with expertise in critical care medicine and neurosurgery (CST). The protocol represents an attempt to minimize center-to-center variability and to facilitate interpretation of the PbtO₂ information using local expertise.

An episode that requires intervention is triggered by abnormalities in ICP or PbtO₂ lasting more than 5 minutes. Treatments must be initiated within 15 minutes of the start of an episode. Patients may start in one type of scenario and then move to another scenario while they are receiving treatments. The initial choice of a treatment option from any tier for any particular scenario should be determined based on what is felt to be the most effective intervention for the current clinical situation, participant characteristics and local protocols. Any intervention chosen should be aimed at addressing the underlying pathophysiology that is contributing to the episode. At least one treatment in tier 1 must be tried before moving on to tier 2. Tier 3 treatments are optional. 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 Tier 1 interventions prior to moving on to Tier 2. The bedside treatment team has the option to progress to higher tiers as rapidly as they feel is clinically indicated.

Some interventions in tables 2 and 3 are noteworthy.

Optimizing CPP. Target range for CPP are unknown and may depend on the patient's autoregulatory status[4]. As such, optimization of CPP might be informed by cerebral autoregulation testing[21]. We advise there is a potential for harm related to augmentation of CPP above 70 mm Hg[22] but some patients may require it. We also recognized that lowering CPP below 60 mmHg might be an option to treat eICP when cerebral autoregulation is absent (Lund therapy) [23]. Finally, CPP optimization also includes improvement in CBF though improvement in cardiac output (inotropy).

Increasing PaO₂. Obtaining an arterial blood gas before treating with PaO₂ adjustments is mandatory. Increasing PaO₂ above 150 mmHg might imply overtreatment by PaO₂ and prevents detection of another potential cause of low PbtO₂. Calculating the brain oxygen ratio (BOx ratio= PbtO₂/PaO₂) might help recognize this situation[10]. Increasing PaO₂ above 150 mmHg should only be used if PbtO₂ is persistently less than 20 mmHg and other variables contributing to low PbtO₂ have been addressed and controlled first.

Reverse Robin Hood syndrome[24-26]. PbtO₂ probe located in an area already maximally vasodilated might measure a drop of flow (low PbtO₂) if other areas of the brain vasodilate (potentially because of hypoventilation), creating a “steal” by diverting flow from the area measured. Treatment requires vasoconstricting the normal brain to redirect the flow towards the area measured using hyperventilation.

Withdrawal of life sustaining treatments (WLST) during the first 5 days will only be considered in dire circumstances or if requested by the patient's family. If the study subject undergoes WLST during the first 5 days of treatment, the site PI will be required to notify the study leadership team. Reasons for WLST will be carefully documented.

Outcomes

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5 2 The primary outcome measure is the Glasgow Outcome Scale-Extended (GOSE) performed at
6 3 180 (+/- 30) days by a blinded central examiner. All injury related disabilities are assessed for the
7 4 primary measure.
8 5

9 6 A complete battery of secondary measures will be assessed, including: survival at hospital
10 7 discharge, total brain hypoxia burden, Functional Status Examination, Rey Auditory Verbal
11 8 Learning Test, Trail Making Test Part A and B, WAIS-IV Processing Speed Index, Rivermead
12 9 Post-Concussion Symptoms Questionnaire, Brief Symptom Inventory 18, and Satisfaction with
13 10 Life Scale.
14 11

15 12 **Data collection, data monitoring, and adverse events**

16 13

17 14 The study data will be managed using the WebDCU™ system. This web-based clinical trial
18 15 management system will be used for regulatory document management, subject randomization,
19 16 data entry, data validation, project progress monitoring, subject tracking, user customizable report
20 17 generation, and secure data transfer. Reports will be generated to monitor study progress and
21 18 patient recruitment at each site. These reports will provide center-specific information on the
22 19 number of subjects with missing or incomplete data and number of data queries.
23 20

24 21 Information specific to PbtO₂, ICP, and CPP monitoring will be collected for up to 5 days.
25 22 Continuous digital recordings of these values will be captured on a bedside dedicated integrated
26 23 platform (CNS Monitor, Moberg ICU Solutions, Amber, PA, USA). This will allow precise
27 24 calculation of ischemic burden (time spent with PbtO₂ below 20 mmHg) and eICP burden (time
28 25 spent above 22 mmHg). A custom built-in clinical decision algorithm based on the tier treatments
29 26 (CNS Carepath®, Moberg ICU Solutions, Amber, PA, USA) can be used to help guide bedside
30 27 clinicians to select the appropriate intervention for a given type of scenario. Local study
31 28 personnel can review Carepath® and the medical record to identify alarms and actions taken to
32 29 correct them on the electronic case report form (eCRF) for the first 5 days.
33 30

34 31 The clinical site PI, independent medical safety monitor (IMSM), and data and safety monitoring
35 32 board (DSMB) appointed by the NINDS are responsible for the timely review of the safety data.
36 33 The DSMB will operate in accordance with NINDS guidelines. The DSMB will evaluate open
37 34 and closed reports prepared by the Data Coordinating Center on a semiannual basis.
38 35

39 36 General data quality will be monitored by the Clinical Coordinating Center and will include a
40 37 combination of on-site monitoring, remote monitoring, and central monitoring (using web-based
41 38 data validation rules, data manager review of entered data, statistical analysis, and on-going
42 39 review of site metrics).
43 40

44 41 Adverse events (AE) are defined as any untoward event or complication not previously identified,
45 42 or that occurs with greater frequency or severity than previously reported, whether or not
46 43 considered related to the protocol intervention. The AEs listed in **table 4** are anticipated based on
47 44 the known complications of severe TBI, intracranial monitoring devices and prolonged use of
48 45 supraphysiologic levels of oxygen. In addition, new abnormal laboratory findings that are
49 46 considered by the treating physician to be clinically significant may be included as adverse
50 47 events.
51 48

52 49 Serious AEs are any adverse event that results in any of the following outcomes or actions: 1)
53 50 Death due to any cause; 2) a life-threatening adverse experience; 3) inpatient prolongation of
54 51 existing hospitalization; 4) a persistent or significant disability/incapacity; 5) an important
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1 medical event that may require medical or surgical intervention to prevent one of the outcomes
2 listed above. These must be reported within 24 hours of discovery.

3
4 All AEs are collected through day 6 or discharge, whichever comes first; serious AEs will be
5 reported through subject end of study. The IMSM will adjudicate serious AEs for seriousness,
6 relationship to the study intervention, and expectedness.

7 8 **Statistical considerations**

9
10 Favorable outcome is defined according to a sliding dichotomy (**figure 3**) [27], where the
11 definition of favorable outcome varies according to baseline severity. Severity will be defined
12 according to the probability of poor outcome predicted by the IMPACT core model[28]. The
13 favorable outcome definition is more stringent for subjects with a low probability of poor
14 outcome.

15
16 A clinically relevant effect size of 10% absolute difference in favorable outcome proportions is
17 prespecified. In order to achieve 85% power with a two-sided type I error probability of 0.05,
18 880 subjects are required. This calculation assumes a 50% favorable outcome proportion in the
19 control arm. Inflation to account for interim analysis and 7% non-adherence results in a
20 maximum sample size of 1094 subjects.

21
22 All subjects enrolled in the study are to be followed until the end of study or until consent is
23 withdrawn or declined and will be included in the primary intention-to-treat analysis.

24 25 **Study timescale**

26
27 Recruitment began Summer of 2019. The COVID-19 pandemic significantly affected early
28 recruitments. The trial is currently recruiting patients at the rate of 15 - 16 patients per month.
29 Once all sites are fully operational and recruiting, we expect recruitment to end by 2026.
30 Allowing for the 6 month follow-up assessment, data cleaning and closure of the database, data
31 analyses, manuscript writing and publication should take place in 2026.

32 33 **Patients and public involvement**

34
35 Community Consultation and Public Disclosure are completed regionally for all enrolling sites in
36 the United States, prior to the initiation of the clinical trial under CFR 50.24.

37
38 No patient or public representative was involved in the written design of the trial.

39 40 **Ethics and dissemination**

41
42 Because all patients meeting eligibility criteria for this trial will be unresponsive and unable to
43 provide informed consent, participants will be enrolled either with the informed consent of a
44 legally authorized representative (LAR – see supplemental material) or with exception from
45 informed consent (EFIC) for emergency research (no EFIC in Canada). If no LAR is available
46 before placement of the ICP and PbtO₂ monitors, the patient may be enrolled under EFIC. If
47 LAR is available prior to ICP and PbtO₂ monitors being placed, consent will be sought from
48 LAR. The complete EFIC process will be the subject of another publication since it refers to a
49 complex ethical process.

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3 1 Publication of the results of this trial will be governed by the policies and procedures developed
4 2 by the Executive Committee consistent with the SIREN publication policy.
5 3

6 4 **Discussion**

7 5
8 6 BOOST-3 is a pragmatic, physiology based study that aims to demonstrate the superiority of
9 7 combined PbtO₂ + ICP guided therapy over ICP guided therapy alone when comparing subject
10 8 outcomes at 6 months. Classical TBI management based on ICP and CPP alone has demonstrated
11 9 its limitations [29,30]. This management uses pressure as a surrogate of CBF and oxygen
12 10 delivery, an approach that was developed when there was no ability to directly or reliably
13 11 measure PbtO₂.
14 12

15 13 The development of cerebral hypoxia is now understood to be multifactorial, and at times occurs
16 14 independent of ICP and CPP abnormalities [11]. PbtO₂ represents a balance between oxygen
17 15 delivery and consumption measured directly in the brain parenchyma [31]. Analyzing the
18 16 physiological parameters that influence PbtO₂ values at the bedside[10] allows for a more
19 17 extensive and precise comprehension of brain pathophysiology and may result in more tailored
20 18 and efficacious care to prevent secondary injuries[19].
21 19

22 20 Two other trials are going to study the added value of PbtO₂ monitoring: the ongoing OXY-TC
23 21 trial in France[32] and the BONANZA trial in New-Zealand and Australia (not yet registered on
24 22 clinical trial.gov). As designed, BOOST-3 will be the largest and is adequately powered to detect
25 23 a clinically meaningful difference in clinical outcome that remains achievable (10% absolute
26 24 difference). In comparison, the OXY-TC targets a 30% difference in outcome. Both BOOST-3
27 25 and BONANZA will be measuring PbtO₂ in a blinded fashion in the control arm allowing the
28 26 evaluation of cumulative hypoxic burden between groups.
29 27

30 28 Recognizing the heterogeneity of TBI characteristics and complexity of its management,
31 29 BOOST-3 has standardized therapy in both groups while allowing for flexibility in treatment
32 30 options. These options reflect the various possible physiological manipulations required to correct
33 31 anomalies identified by the bedside physician (tables 2 and 3). Of note, BOOST-3 protocol
34 32 recognizes that cerebral autoregulation status plays an important role in managing CPP
35 33 threshold[33]. Optimization of CPP according to the autoregulation status might improve
36 34 outcome but its management remains difficult clinically[34-37]. PbtO₂ might facilitate
37 35 recognition of the autoregulation status[38,39]. Analysis of the continuous data capture within the
38 36 BOOST3 cohort, may inform future study of the relationship between cerebral autoregulation,
39 37 goal directed therapy, and patient outcome.
40 38

41 39 The BOOST3 protocol also clearly emphasizes that increasing PaO₂ in order to correct a low
42 40 PbtO₂ value should be used very cautiously. Increasing PaO₂ above 150 mmHg might imply
43 41 overtreatment by PaO₂ and prevents detection of another potential cause of low PbtO₂[10]. It is
44 42 possible to compensate for a decrease in PbtO₂ due to low CBF by increasing PaO₂[40].
45 43 Hyperoxia is known to induce cerebral vasoconstriction[41], potentially increase free radical
46 44 production[42] and has been associated with worse outcome in other brain ischemic injuries[43-
47 45 46]. If FiO₂ is increased as a therapeutic maneuver, a specific FiO₂ weaning protocol is suggested.
48 46 That being said, it is expected that TBI patients managed with a PbtO₂ probe will have a higher
49 47 mean PaO₂ since it is the only possible therapeutic option to address the diffusion and
50 48 microcirculatory failure often seen with severe TBI[13,14]. Adverse events related to pulmonary
51 49 pathology will be closely tracked in both study groups.
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1 The limitations of standardization in BOOST-3 are inherent to the nature of TBI. First, there is
2 wide variation in the phenotype of brain injury. For example, patients may have diffuse axonal
3 injury, intraparenchymal contusion, extra-axial hematomas, subarachnoid hemorrhage, or any
4 combination of these injuries [1]. The fact that multiparametric and PbtO₂ monitoring allow for a
5 physiology driven approach may globally improve the delivery of care despite the heterogeneity
6 of disease phenotype. BOOST3 is slated to recruit a large number of patients, which will likely
7 help to achieve balance of injury phenotype across study groups. Furthermore, the specificity
8 gained by measuring functional outcome through a sliding dichotomy based on initial injury
9 should also reduce heterogeneity bias.

10
11 Withdrawal of life sustaining therapy, although strongly discouraged in the first 5 days after TBI,
12 can still influence outcome measures. No specific protocol for prognostication and decision to
13 withdraw care is suggested in the research protocol; treating physician acumen will determine end
14 of life decisions.

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16 An additional limitation is the relatively short time window from TBI to randomization (less than
17 12 hours after injury and 6 hours after presentation at enrolling hospital), this will likely reduce
18 generalizability of the findings to underserved communities, or those lacking access to
19 neurosurgical expertise. This timeframe was chosen to appropriately test the biological basis of
20 PbtO₂ monitoring in the acute phase of brain injury to prevent secondary injuries. A longer
21 interval from injury may allow for significant cerebral hypoxia before randomization. A
22 challenge that has been identified after start-up relates to the 6 hour time window after arrival at
23 enrolling site, which poses a problem if the patient needs urgent surgical intervention. Allowing
24 some flexibility in the 6 hour window allows urgent clinical needs to be addressed prior to
25 placement of intracranial monitors. A final challenge after study start-up included the COVID
26 pandemic putting a hold on research activities thus lowering expected enrollment.

27
28 The annual cost to society resulting from TBI has been estimated to range from \$83 billion to
29 \$244 billion (in 2014 dollars) [47]. Improvements in functional outcome will benefit not only
30 affected patients but society globally. Multiple trials targeting a specific medication or
31 pathophysiological mechanism have failed to demonstrate improvement in outcome so far[48].
32 We feel that the early use of a PbtO₂ guided bundle of care will yield a different result.

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36
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40 Hemphill, Luke James, Ryan Kitagawa, Carol Moore, David Okonkwo, Ava Puccio, Claudia
41 Robertson, Uzma Samadani, Danielle Sandsmark, Robert Silbergleit

42 43 Figures Legends

44
45 Figure 1: Randomization, inclusion and exclusion criteria

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47 Figure 2 : Four possible clinical scenarios based on monitoring information

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49 Figures 3 : Outcome defined according to sliding dichotomy

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For peer review only

Table 1

Initial general targets for both groups	
Physiologic Variable	Desired Range
Pulse Oximetry	$\geq 94\%$
PaO ₂	≥ 80 mmHg
PaCO ₂	35-45 mmHg
pH	7.35-7.45
Systolic Blood Pressure before CPP management	> 100 mmHg if age 50-69 years old > 110 mmHg if age 15-49 or >70 years old
Temperature	36.5—37.5°C
Maintain Normovolemia	As per local protocol
Sodium	135-145 mmol/L
Glucose	80-180 mg/dL
PT and PTT	Normal range as per local hospital guidelines
INR	≤ 1.6
Hemoglobin	≥ 7 gm/dl
Platelets for insertion of monitors	$\geq 80 \times 10^3/\text{mm}^3$

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3 **Table 2**
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Scenario B: Treatment Options for Isolated ICP increase > 22 mmHg

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8 TIER 1: must begin within 15 minutes of abnormality. No particular order.

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- Adjust head of bed to lower ICP
 - Ensure Temperature < 38°C
 - Titrate pharmacologic analgesia or sedation to effect
 - CSF drainage (if EVD available)
 - Optimize CPP to max 70 mmHg with fluid boluses or vasopressors as clinically appropriate. May assess cerebral autoregulation as per local protocol to manage CPP targets.
 - Adjust ventilator for a target PaCO₂ of 35 - 40 mm Hg (target pH of 7.35 - 7.45).
 - Low dose Mannitol (0.25 – 0.5 g/kg)
 - Low dose HTS (include 1.5% to 3%). This tier does not include higher concentrations of HTS. Titrate to effect (ICP control) and maintain Na ≤ 160 mEq/L.
 - Initiate or titrate anti-epileptic medications

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21 **TIER 2: initiate within 60 minutes if tier 1 therapies are ineffective. No particular order.**

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- Repeat head CT; treat surgically remediable lesions according to guidelines.
 - Adjust temperature to 35 – 36°C, using active cooling measures.
 - NMB, use a bolus dose to determine effect. If effective, perfusion may be used. NMB should be rapidly weaned upon clinical stabilization.
 - Optimize CPP: may increase CPP above 70 mm Hg with fluid boluses or vasopressors*.
 - Adjust ventilatory rate to target PaCO₂ of 33 – 38 mm Hg (target pH of 7.35-7.45).
 - High dose mannitol (1-1.5 g/kg) or higher frequency of low dose mannitol (0.25-0.5g/kg) if osm <320.
 - High dose hypertonic saline bolus (7.5%, 30 ml of 23.4%). May repeat if Na levels are <160mEq/L.

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31 **TIER 3 (tier 3 therapies are optional). No particular order.**

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- Adjust ventilatory rate for target PaCO₂ of 30 – 35 mm Hg (target pH of less than 7.5).
 - Pentobarbital coma, according to local protocol. An initial bolus dose of 5 mg/kg should be used to determine effectiveness. If effective, a continuous infusion may be used. Pentobarbital should be rapidly weaned upon clinical stabilization
 - Decompressive craniectomy
 - Adjust temperature to 32-35°C, using active cooling measures.
 - Other salvage therapy per local protocol and practice patterns.

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4 Note: CSF: cerebrospinal fluid; EVD: external ventricular drain; HTS: hypertonic saline; NMB:
5 neuromuscular blockade; *There is a potential for harm related to augmentation of CPP above 70
6 mm Hg with vasopressors
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3 **Table 4**
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Adverse event	Expected Incidence
ARDS	5%
Pneumonia	25%
Sepsis	5 %
Septic Shock	3%
Hematoma requiring craniotomy for evacuation	0.5%
CNS infection	<0.5%

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3 **1 Statements**
4 2

5 3 RDA wrote the protocol of this study. LS, RDA, SY and WB are the principal investigators of the
6 4 trial and compose the steering committee. SY is responsible for the statistics and data
7 5 management of the trial. WB is administering the trial. FB and LS wrote the first draft of this
8 6 manuscript. FB, LS and LHM are part of the clinical standardization team responsible of protocol
9 7 implementation and the manual of operating procedure. FB, LS, RDA, SY and WB all revised
10 8 and approved the final version of this manuscript.
11 9

12 10 None of the authors have competing interest.
13 11

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15 13 Grant number U01 NS099046.
16 14

17 15 The primary results of the clinical trial will be disseminated by publication in the peer reviewed
18 16 medical literature in accordance with the NIH Public Access Policy. After completion of the
19 17 study and dissemination of primary study results, the CRF data will be made publicly available
20 18 for download through the Federal Interagency Traumatic Brain Injury Research Foundation
21 19 (FITBIR) Informatics System as required by the NINDS. The public use dataset will be stripped
22 20 of any and all personal identifiers and will undergo a de-identification process.
23 21
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25 23 **References**
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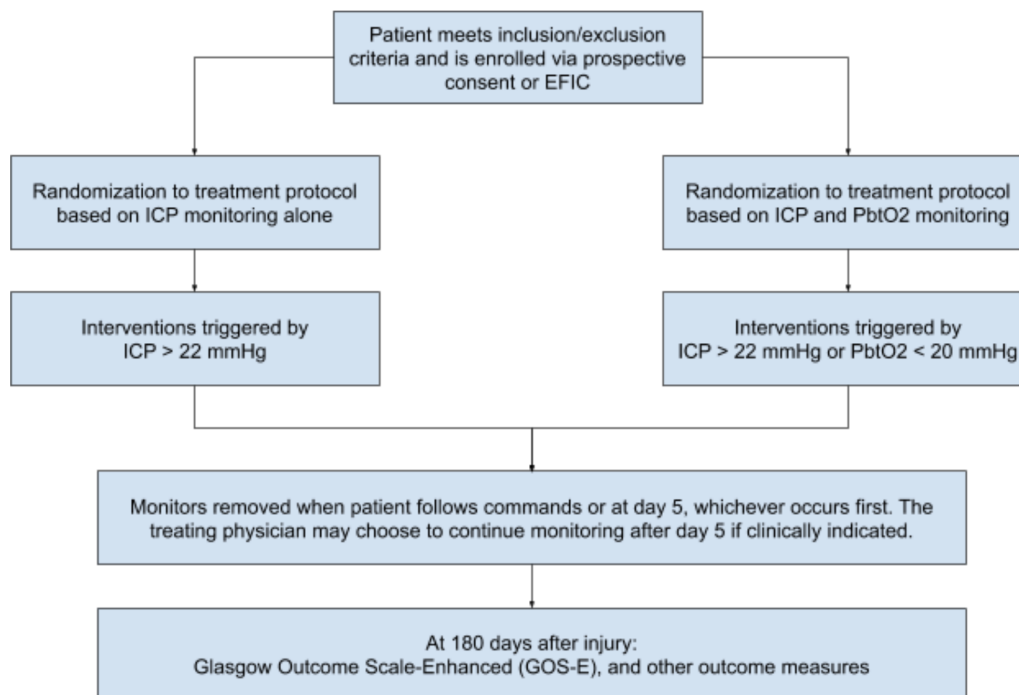
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Figure 1



Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> ● 14 years of age ● Non penetrating TBI ● Glasgow Coma Score (GCS) of 3 to 8 measured off paralytics after resuscitation (with a motor component score less than 6) ● evidence of intracranial trauma on a head CT scan (skull fracture alone is not sufficient) ● Decision to insert intracranial monitors within 6 hours of arrival at the enrolling hospital, but no later than 12 hours after the injury 	<ul style="list-style-type: none"> ● GCS = 3 and bilaterally absent pupil responses off paralytics ● Medical contraindications for placement of intracranial monitors ● Treatment of brain tissue oxygen values prior to randomization ● Planned use of devices that would allow unblinding of medical care team to the treatment group ● Severe sepsis at randomization ● Refractory hypotension prior to randomization (SBP < 90 mmHg for two consecutive readings at least 15 minutes apart) ● Refractory hypoxia prior to randomization (SaO₂ < 90% on FiO₂ > 0.5 for two consecutive readings at least 15 minutes apart) ● Sustained PaO₂/FiO₂ ratio < 150 ● Known pre-existing neurologic disease with confounding residual neurologic deficits ● Known pre-existing condition resulting in an inability to perform activities of daily living without assistance ● Known active drug or alcohol dependence that would interfere with physiological response to PbtO₂ treatments or follow-up care ● Non-survivable injury in the opinion of the site investigator ● Pregnancy ● Prisoner or ward of the state ● Person is known to have opted out of EFIC or study enrollment prior to injury (see ethics section).

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Figure 2

Values in mmHg	ICP \leq 22	ICP $>$ 22
PbtO ₂ \geq 20	Type A No interventions needed	Type B Interventions to lower ICP
PbtO ₂ $<$ 20	Type C Interventions to increase PbtO ₂	Type D Interventions to lower ICP and increase PbtO ₂

Figure 3

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	Favorable Outcome						
0.41 to <0.56	Favorable Outcome						
0.56 to ≤1	Favorable Outcome						

For peer review only

SIREN Informed Consent Forms

The Sponsor/Investigator of BOOST-3 does not allow edits to this central IRB approved main consent form for this multicenter trial. This is to ensure equity of the language across the enrolling sites. Your site may add site-specific content in a single contained section below the universal text if necessary. This section is limited to information that pertains specifically to your local institution.

Please note the process for submitting informed consent forms for BOOST-3 as sites submit ceding applications to local IRBs. All SIREN informed consent forms are approved by the Advarra Central IRB (ER-CIRB) with the parent protocol. The informed consent form is a completely locked down form, to be used consistently across BOOST-3 sites. Please submit this form to your local IRB as is, without making any site specific changes. The current ER-CIRB approved form to be used is located in the BOOST-3 Toolbox and the Getting Started page.

Where local site and study team contact information needs to be included, this will populate directly into the form after the site application is submitted to and approved by the ER-CIRB. In very limited circumstances, when institutionally required language is requested by the IRB, there is potential to add a separate site specific section at the end of the form prior to the signature page. However, for the time being, please submit the form as is. Additions will only be considered per a request from the IRB, and will be discussed on a case by case basis. Should this request from the IRB be made, please provide at the earliest time the additional requested language in a separate document for review by the SIREN CCC. Please do not edit or insert language into the body of the trial-wide approved ICF.

Please note that while HIPAA language is already included in the body of the consent form, a separate local HIPAA form is acceptable for use, so long as it is signed and dated by subject/LAR.

We understand that this process differs from how the ICF review process has operated for other trials. We are happy to help as we move along with this process; please let us know if we can be of assistance. Please also note the below statement from Advarra regarding this process for SIREN trials.

As you know, Advarra is the single IRB for the SIREN network trials. If your organization has a negotiated process in place with Advarra specifically as it pertains to the Informed Consent language, please note that the established process that has been in place with your site and Advarra is suspended for the SIREN network's trials. SIREN has their own IC process which Advarra will follow for these specific trials. Any non-SIREN trials will follow the established process you already have in place with Advarra.

If you have any questions regarding this please contact boost-contact@umich.edu.

Thank you for your attention with this matter,
Best regards,
Advarra Institutional Services Team & SIREN

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3 **CONSENT TO TAKE PART IN A CLINICAL RESEARCH STUDY**
4 **AND**
5 **AUTHORIZATION TO DISCLOSE HEALTH INFORMATION**
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7 **ADULTS/SUBJECTS WHO TURN 18/PARENTAL/GUARDIAN PERMISSION**
8 **& ASSENT FOR AGES 14 TO AGE OF MAJORITY**
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12 **Study Title:** "Brain Oxygen Optimization in Severe Traumatic Brain
13 **Injury - A multi-center, randomized, blinded-endpoint,**
14 **comparative effectiveness study of goal-directed critical**
15 **care based upon monitoring of brain tissue oxygen and**
16 **intracranial pressure versus monitoring of intracranial**
17 **pressure alone in patients with severe traumatic brain**
18 **injury"**
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22 **Granting Agency:** The National Institute of Neurological Disorders and
23 **Stroke (NINDS)**
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25 **Protocol Number:** BOOST-3
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27 **Principal Investigator:** «PiFullName»
28 **(Study Doctor)**
29
30
31 **Telephone:** «IcfPhoneNumber»
32
33 **Additional Contact(s):** «AdditionalStaffMemberContacts»
34 **(Study Staff)**
35
36
37 **Address:** «PiLocations»
38
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41 This form is for use in a research study that involves participants who are unconscious or in
42 coma, and do not have the capacity to consent to take part in the study. You are the legally
43 authorized representative of the patient. In cases where the participant's representative gives
44 consent, the participant should be informed about the study to the extent possible if the
45 participant regains consciousness. During the course of the study, if the subject regains the
46 capacity to consent, informed consent will be obtained from the subject and the subject offered
47 the ability to leave the study if desired.
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SUMMARY OF KEY INFORMATION

Your family member (or a person you represent) has had a severe traumatic brain injury (TBI). He or she may be eligible to participate, or continue to participate, in a research study. The study is to compare two ways of treating patients with brain injury. Physicians do not know which standard of care treatment is better. Neither treatment being studied are investigational. We are talking with you because patients with severe TBI are unconscious or in a coma; and they cannot tell us if they want to participate in a study. You are the patient's representative. In an effort to provide immediate emergency care, the person you represent may have already been entered in this study. If not, we are asking you to consent or refuse consent for his or her participation. If the patient was already entered in the study, we are asking you for your consent to allow them to continue or to stop participation in the study. The remainder of this document should help you in this decision.

Participants in this study are placed at random, that is by chance, in one of two groups. One group has medical care based on monitoring of pressure in the brain (intracranial pressure or ICP) alone. The other group has medical care based on both ICP and the amount of oxygen in the brain (brain tissue oxygen or PbtO₂). It is unknown if measuring and treating low brain oxygen is more effective, less effective, or the same as monitoring and treating high brain pressure alone. Treatment differs by group because doctors make decisions guided by ICP and PbtO₂ goals. These decisions include the kinds and doses of medications given. They also include the amount of fluids given by vein. Other treatments that may differ can also include changing ventilator (breathing machine) settings, blood transfusions, and other parts of medical care. ICP and PbtO₂ are monitored by small sensor probes placed in the brain through one or two small holes made in the skull. Placing one or both of these probes is standard care for people with severe TBI. They are placed within hours of arrival at the hospital. Those in the study will have both probes placed.

After the initial hospitalization, we will contact participants or their caregivers about once per month for 5 months to see how they are doing. A study team member will schedule a follow up visit to the clinic about 6 months after the injury to learn about how the participant is doing. The study team will review the participant's medical records while they are in the study as needed. About 1,000 participants will be enrolled at about 45 hospitals.

Participation in the study will help doctors learn if one way of treating future victims of TBI is better. Participants may or may not directly benefit from being in the study. Some participants may benefit directly if recovery turns out to be more likely with the management they receive. Participation may also have risks. Some possible risks are currently unforeseeable. Known risks from study participation include accidental release of private information. Other risks may include bleeding around the sensors, infection, lung problems, or other medical complications. Risks will be discussed later in this consent form.

Participation in the study, or ongoing participation if your family member was already enrolled before we could reach you, is voluntary. The alternative to being a part of this study is to receive the usual standard of care. Usual care may be either of the ways of treating patients being compared in the study. Usual care often varies based on the injury, the choice of the doctor, or the treating hospital. There is no penalty for choosing not to participate. A participant can withdraw from the study at any time.

Medical records and data collected in the study will remain as private as possible. Participants' records may be viewed by the study team here or from the study coordinating centers. Records may also be seen by those responsible for reviewing the safety and conduct of the study. This oversight is provided by this institution and by government regulatory and funding agencies.

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3 There is no payment or compensation for being in the study. There is no cost to being in the
4 study. Charges for all standard medical care will be billed the same way whether or not
5 someone is in the study.
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7 Please contact us for any questions about the research, participants' rights, or other concerns.

- 8 • Please carefully read this form, additional detail about each item just described is found below
9 • Please listen to the study team explain the study and this form to you
10 • Please ask questions about anything that is not clear
11

12 If you consent, you will be asked to sign and date this form.
13
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15 MORE DETAILED INFORMATION

16 **What is the purpose of this research study?**

17 The purpose of the research study is to learn if either of two strategies for monitoring and
18 treating patients with TBI in the intensive care unit (ICU) is more likely to help them get better.
19 Both of these alternative strategies are used in standard care. It is unknown if one is more
20 effective than the other. In both strategies, doctors monitor the patient's brain and modify the
21 medical care provided in order to try to improve some measure of the brain's health. However,
22 it is not known which measure of the brain's health, intracranial pressure or oxygen level, is
23 more important. In one strategy doctors concentrate only on preventing high ICP (intracranial
24 pressure) caused by a swollen brain. In the other strategy doctors try to prevent high ICP, and
25 also try to prevent low PbtO₂ (brain oxygen). Some hospitals and doctors tend to use one or
26 the other strategy more often. It is unknown if measuring and treating low brain oxygen is more
27 effective, less effective, or the same as monitoring and treating high brain pressure alone. The
28 results of this study will help doctors discover if using both of these methods is better than using
29 one alone in treating TBI.
30
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32 **Why is this an important question to study?**

33 When a person has a TBI, their injured brain can swell over a period of hours or days. If the
34 brain swells too much, the pressure in the skull increases and becomes dangerous, causing
35 further injury to the brain. To try to prevent this, doctors usually insert a device, an ICP probe,
36 into the brain through a hole in the skull of people with severe TBI. An ICP monitor connected
37 to the probe measures the pressure inside the skull. Most doctors agree that it is important to
38 measure and prevent high ICP.
39
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41 Patients with injured brains also suffer additional injury to the brain if the amount of oxygen in
42 the brain gets too low. Some doctors also insert a second device, a PbtO₂ probe, in the brain
43 through the same or a second hole in the skull to measure brain tissue oxygen. A PbtO₂
44 monitor connected to the probe measures how much oxygen is in a small area of the brain near
45 the tip of the probe. Doctors disagree about whether monitoring oxygen levels is helpful or
46 necessary.
47

48 Both monitoring devices are approved by the US Food and Drug Administration (FDA) and
49 Health Canada for patients with TBI. Both are commonly used. The ICP and PbtO₂ goals
50 guided by these monitors are used to help doctors adjust their treatment choices. Treatments
51 include kinds and doses of medications and the amount of intravenous fluids given, ventilator
52 (breathing machine) settings, need for blood transfusions, and other medical care. Each of
53 these treatment decisions is intended to improve outcomes. However, each treatment decision
54 also involves potential risks. Different treatment decisions may result in different risks. This
55 study will also help doctors better understand these risks.
56
57

This study is funded by the National Institutes of Health because it answers questions important to the care of patients with TBI.

How long will the participant be in the study? How many people will be in the study?

- Participants are in the study for about 6 months. The treatments being studied all occur in the first 5 days.
- About 1,000 participants will be enrolled at about 45 hospitals.
- We will call participants (or their caregivers) about 5 times after their injury. We will call about once each month for 5 months. Each phone call will last about 15 minutes. During the phone call, we will ask how they are doing, if they are having any additional problems, and if any of their contact information has changed.
- We will ask the participant to come in for a study visit about 6 months after their brain injury. If they are not well enough to travel, a member of the study team can visit them where they are living, if they agree. The visit will take about 1 hour. During the visit, a study team member will ask questions about the participant's recovery. There will be a questionnaire and some pencil and paper exercises. There are no risks anticipated from this visit.
- If the participant is unable to have an in-person interview, a telephone interview with the participant or caregiver can be done instead. If possible, the telephone interview will collect the same information as the visit except for the pencil and paper exercises. It may also take up to 1 hour.
- Translators will be available for calls and visits with individuals whose preferred language is not English.

What happens in this study?

- All participants will have both an ICP probe and a PbtO2 oxygen probe placed.
- Participants will have an equal chance (like the flip of a coin) of being allocated to one of the two groups. The groups determine which information about the brain will be used to guide medical care.
 - Group 1: medical care guided by ICP monitoring (the PbtO2 monitor is covered and not used)
 - Group 2: medical care guided by ICP and PbtO2 monitoring
- This random (like the flip of a coin) allocation to one group or another is research.
- Medical care of the participant will be guided by this group allocation (which group the participant is in) for 5 days.
- Medical care of the participant affected by group allocation might include the choices and doses of medications and the amount of intravenous fluids given, how the participant's ventilator is adjusted, the need for blood transfusions, and other components of ICU care.
- Other than which monitoring information is used to guide care in the first 5 days, all participants receive usual care. Use of monitoring beyond 5 days is also based on usual care.
- Doctors caring for participants in group 1 will make decisions based on the ICP monitor. They will not see the information from the PbtO2 monitor. They will not make any decisions based on PbtO2 information. Having a PbtO2 monitor, but not using the information to guide care is part of the research.
- One or both probes may be removed before 5 days if there is a clinical reason to do so. This may include the participant waking from coma, infection of the probe, or 3 or more days without abnormal readings on the monitors.
- Information is collected for the study from participants' medical record, diagnostic images, and monitors. Information collected includes the condition of the patient and the treatments being provided.

- We will visit the participant daily during the first 5 days in the ICU, and periodically while in the hospital. We will review the medical record at these times, at discharge, and at any return visits during participation.
- Contact information for the participant, you, family members, close friends, or caregivers is collected in order to arrange follow up during the study. These include phone numbers, email and mailing addresses.

What risks may participants experience?

There are potential clinical risks to all the treatments used in the medical care of patients with severe TBI. These risks are the same whether or not they participate in the study. Participation in research may also have risks.

Clinical risks potentially related to the monitors and treatments include, but are not limited to, the following:

- Pneumonia (infection of the lung) is common in those with severe TBI (about 1 in 4), and may rarely be increased because of efforts to optimize PbtO₂ (fewer than 5 in 100).
- Lung injury, sometimes related to ventilator settings or the amount of intravenous fluids given, which may be affected by brain monitoring, is also common (about 1 in 20).
- Severe sepsis, a dangerous infection spread in the blood, is common (about 1 in 20), usually unrelated to monitoring.
- Placement or removal of probe can sometimes cause slight bleeding at the site of insertion (fewer than 2 in 100). Rarely, a medicine or procedure to reduce bleeding might be used (fewer than 1 in 5000).
- Infection in the brain, possibly related to brain probe placement, is rare (fewer than 1 in 5000).

Risks related to being a study participant include:

- Breach of confidentiality is a rare risk of participation in research studies (fewer than 1 in 10,000).
- If you request it, you may be emailed a PDF copy of this signed and dated consent form. There may be risks of loss of privacy and confidentiality if the PDF copy of this consent form is viewed and/or stored on a personal electronic device (PED), especially if that PED is shared with other users or is lost, hacked, or subject to a search warrant or subpoena. Also, the PDF copy of the consent may not be able to be permanently removed from a PED.

The researchers have taken steps to minimize these risks. The study team will monitor closely for these possible risks and complications will be treated if needed.

To reduce any potential risk to an unborn child, women of childbearing potential will have a pregnancy test and if pregnant, will not be included in this research study.

As with any research study, there may be additional risks that are unknown or unexpected.

What is the possible benefit?

The participant may or may not benefit from being in this study. Some participants may benefit directly if recovery turns out to be more likely with the management they receive. Discovery that one strategy or the other helps traumatic brain injury patients recover with less disability will be an important advancement in the treatment of future patients with brain injury.

What is the alternative to participating in this study?

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3 Participation, or ongoing participation, in this study is voluntary. The alternative to participating
4 in the trial is usual care. Usual care may be medical care guided by ICP monitoring or it may be
5 medical care guided by ICP and PbtO2 monitoring. The usual care offered may depend on the
6 treating hospital, opinion of the doctors caring for the individual, or upon characteristics of the
7 patient or their injury. There is no penalty for choosing not to participate. The participant may
8 withdraw from the study at any time, either by his/her choice or at the direction of the
9 participant's legally authorized representative. Choosing not to participate, not to continue
10 participation, or choosing to withdraw will not alter the usual care available. Nor does it alter or
11 waive any legal rights or benefits.
12

13 **What if new information becomes available?**

14 We will provide any new information that may affect a participant's willingness to continue in the
15 study. Participants may be contacted about future available studies. We may also contact
16 participants with periodic updates about the study. We may also contact participants after the
17 trial has been completed to share results from the study.
18
19

20 **AUTHORIZATION TO DISCLOSE HEALTH INFORMATION**

21 **How will personal information be protected?**

22 The study investigator and his/her collaborators will consider the participants' personal
23 information confidential to the extent permitted by law. "Personal Information" means
24 information that can be used to identify the participant or health information about the
25 participant. This includes name or initials, date of birth, gender, ethnic origin and medical and
26 health-related information such as blood tests, diagnostic imaging and results, the results of
27 physical examinations, medical history and hospital records, and information directly observed
28 in the study.
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31 Information about the participant collected for the study may be stored electronically or on
32 paper. The information stored on the computer is kept in password protected files that are
33 maintained on password protected computers. The information stored on paper is stored in a
34 locked file cabinet in a locked office. Only the members of the study team and the persons and
35 groups listed below will have access to the participants' medical information for this study.
36

37 The government agencies responsible for making sure that studies are conducted and handled
38 correctly, and other organizations involved in this research study may look at the participant's
39 study records in order to perform their duties. These include: the US National Institutes of
40 Health (NIH), the US Office for Human Research Protections, the US Food and Drug
41 Administration (FDA), Health Canada, researchers from University of Pennsylvania and the
42 University of Pittsburgh, representatives from The Strategies to Innovate Emergency Care
43 Clinical Trials Network (SIREN) Clinical Coordinating Center at the University of Michigan,
44 representatives from the Data Coordination Unit at the Medical University of South Carolina, the
45 Central Institutional Review Board, and/or other agents of the study who will be bound by the
46 same provisions of confidentiality. Information from this study may be submitted to the US Food
47 and Drug Administration (FDA) and Health Canada.
48

49 To help us protect the participant's privacy, this research is covered by a Certificate of
50 Confidentiality from the US National Institutes of Health. With this Certificate, the
51 investigators may not disclose or use information, documents, or biospecimens that may identify
52 the participant in any federal, state, or local civil, criminal, administrative, legislative, or other
53 action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, in
54 the US unless the participant has consented for this use. Information, documents, or
55 biospecimens protected by this Certificate cannot be disclosed to anyone else who is not
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3 connected with the research except, if there is a federal, state, or local law that requires
4 disclosure (see below); if the participant has consented to the disclosure, including for the
5 participant's medical treatment; or if it is used for other scientific research, as allowed by federal
6 regulations protecting research subjects.
7

8 Disclosure is required, however, for audit or program evaluation requested by the NIH or when
9 required by the FDA or Health Canada. A Certificate of Confidentiality does not prevent the
10 participant from voluntarily releasing information about themselves or their involvement in this
11 research. If the participant wants research information released to someone, the participant
12 must provide consent to allow the researchers to release it. The certificate covers disclosures
13 involving participants enrolled in Canada in US legal proceedings, but does not cover
14 disclosures in proceedings outside the US.
15

16 The Certificate of Confidentiality will not be used to prevent disclosure as required by federal,
17 state, or local law of, for instance, child abuse or neglect, harm to self or others, and
18 communicable diseases.
19

20 The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have
21 consented to in this informed consent document.
22

23
24 Although every effort will be made to maintain confidentiality of the participant's medical and
25 health records, absolute confidentiality cannot be guaranteed. We will use a study number
26 rather than the participant's name on study records where we can. The participant's name and
27 other facts that might point to the participant will not appear when we present this study or
28 publish its results. Viewing or storing this electronic informed consent form on a personal
29 electronic device may allow information provided on this form (such as names and email
30 addresses) to be inadvertently shared with others if the device is lost, hacked, or otherwise
31 compromised.
32

33 When ready to leave the hospital, typically well after the 5 days of study treatment is complete,
34 the participant may be discharged to a rehabilitation or nursing facility. The participant might
35 also be discharged home and then readmitted to another medical facility later. Your signature
36 on this document authorizes those facilities to release medical records to the researchers and
37 research staff of this study for the 6 months the participant is in the study.
38

39 We will keep any records that we produce private to the extent we are allowed or required by
40 law. The participant's records will be kept for as long as necessary for purposes of the research
41 study.
42

43 The study doctor and treating institution are required by law to protect the study participants'
44 health information. With this form, you authorize the study doctor to use and disclose the
45 participant's health information, as described in this section, in order to conduct this research
46 study. You have the right to revoke this authorization, at any time, and can do so by writing to
47 the study doctor at the address on the first page. Even if you revoke the authorization, the study
48 doctor and/or sponsor may still use health information they have collected about the study
49 participant, if necessary, for the conduct of the study. However, no new information will be
50 collected.
51

52 Your authorization does not have an expiration date unless indicated elsewhere. You do not
53 have to sign this information and consent form, but if you do not, the person you represent will
54 not be able to take part in this research study. Those persons who receive the participant's
55 health information may not be required by US Federal privacy laws (such as the Privacy Rule)
56
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3 to protect it and may share the information with others without your permission, if permitted by
4 laws governing them.

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6 By signing this information and consent form, you consent to the collection, access, use and
7 disclosure of the participant's information as described above. State law or the enrolling
8 institution may require an additional separate form on which you can authorize sharing of the
9 participant's health information. If so, you will have to sign both forms for your authorization to
10 be valid.

11 12 **How may the participants' data and samples be shared?**

13 US Federal rules require that data be securely stored in the Federal Interagency Traumatic
14 Brain Injury Research (FITBIR) informatics system where it can also be accessed by
15 researchers in a de-identified manner. For more information see the website <http://fitbir.nih.gov>

16 17 **Will the participant have to pay anything?**

18 There is no additional cost to participate in the study. Charges for all standard medical care will
19 be billed in the same manner regardless of participation. Participants who receive the brain
20 oxygen probe in the study will not be charged for it, nor will a public health plan, or the
21 participant's private medical insurer (if any). Funds are not available to cover the costs of any
22 ongoing medical care and participants remain responsible for the cost of non-research related
23 care. For questions about the participant's medical bills relative to research participation,
24 contact the study investigator listed on this form.

25 26 27 **Will the participant be paid for being in the study?**

28 No. There will not be any payment to the participant for being in this study.

29 30 **What if the participant is injured as result of being in this study?**

31 If a participant is injured or becomes ill from participating in the study, medical treatment will be
32 available at this institution or elsewhere consistent with the care provided for any medical
33 problem. Payment for this care will be billed the same as any other care for any medical
34 problem. If the hospital at which the participant was enrolled has any additional answers to this
35 question, this information is found at the bottom of this form.

36
37 In the event that the participant suffers injury as a result of their participation in this
38 research study, no compensation will be provided to the participant by the granting
39 agency (National Institute of Neurological Disorders and Stroke), the treating institution,
40 or the researchers. The participant still has all of their legal rights. Nothing said here
41 about treatment or compensation in any way alters the participants' right to recover
42 damages.

43 44 45 **Is there anything else I need to know?**

46 Continued participation in this study is voluntary. The participant may withdraw from the
47 study at any time and for any reason without penalty. The researcher may discontinue
48 participation if the study is discontinued or suspended. No more information will be
49 collected about a participant after they withdraw from the study or complete their
50 participation.

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52 You may ask to stop having the study affect the participant's medical care. If so, usual care
53 will resume. Usual care is based on the individual patient and their injury, the opinion of the
54 treating doctors, and the treating institution. Usual care may be medical care guided by ICP
55 alone, or medical care guided by ICP and PbtO2 monitoring.

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3 Doctors caring for the participant during this hospitalization may also be researchers in
4 this study. If so, the doctors are interested both in the participant's medical care and in
5 the conduct of this research. There is no obligation to participate in any research study
6 just because it is offered by the participant's doctors.
7

8 A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as
9 required by U.S. Law. This Web site will not include information that can identify you. At
10 most, the Web site will include a summary of the results. You can search this Web site
11 at any time.
12

13 **What if I have questions?**

14 You or the participant may ask and will receive answers to any questions you have during
15 the course of the study. For any questions regarding this study or if the participant
16 experiences any side effects or medical problems, contact the site researcher listed on
17 this form.
18

19 Advarra serves as the Central Institutional Review Board (CIRB) for this study. The
20 CIRB is not part of the research or the research team. Please contact Advarra, if you:
21

- 22 • have questions about your role and rights as a research participant;
- 23 • wish to obtain more information about clinical research in general;
- 24 • have concerns, complaints or general questions about the research, or;
- 25 • wish to provide input about the research study
26

27 You can do so in the following ways:

- 28 • By mail:
29 Study Subject Adviser
30 Advarra IRB
31 6940 Columbia Gateway Drive, Suite 110
32 Columbia, MD 21046
- 33 • or call **toll free:** 877-992-4724
- 34 • or by **email:** adviser@advarra.com
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37 Please reference the following number when contacting Advarra: Pro00030585.
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CONSENT STATEMENTS

PARTICIPANT'S CONSENT (should the participant become cognizant during the study)

I have read and understand the information in this informed consent document. I have had an opportunity to ask questions and all of my questions have been answered to my satisfaction. I voluntarily agree to participate in this study until I decide otherwise. I do not give up any of my legal rights by signing this consent document. I will receive a copy of this signed and dated consent document.

Participant's Printed Name

Participant's Signature

____/____/____
Date

STATEMENT OF ASSENT (should the adolescent become cognizant during the study)

I would like to be in this study.

Printed Name of Adolescent Participant

Adolescent Assent Signature

Date

STATEMENT OF PARENTAL / LEGAL GUARDIAN PERMISSION

I have read and understand the information in this informed consent document. I have had an opportunity to ask questions and all of my questions have been answered to my satisfaction. I voluntarily agree for my child to participate in this study until I decide otherwise. I do not give up any of my or my child's legal rights by signing this consent document. I will receive a copy of this signed and dated consent document.

Signature of Parent/Legal Guardian (if subject is under age 18)

____/____/____
Date

Printed Name of Parent/Legal Guardian (if subject is under age 18)

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3 **INFORMED REFUSAL OF FURTHER PARTICIPATION**
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6 You should feel that you have been told enough about this study to give your informed consent
7 before signing this form. Signing this form does not waive any legal rights to which you or the
8 person you represent are entitled. You will receive a copy of this form after it is signed and
9 dated.
10

11 If you DO NOT want your family member (or the person you represent) to continue to participate
12 in this study, please sign below.
13

14
15 _____
16 Participant Name
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19 _____
20 Printed Name of Legally Authorized Representative (LAR)
21

22 Your relationship to act on behalf of Participant (i.e., spouse, child, parent, sibling, other [if
23 other, please describe])
24

25 _____
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28 _____ / ____ / ____ : ____ AM/PM
29 Signature of LAR Date Time
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35 _____
36 Principal Investigator/Designee Name Title
37

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39 _____ / ____ / ____ : ____ AM/PM
40 Designee Signature Date Time
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Brain Oxygen Optimization in Severe Traumatic Brain Injury (BOOST-3): A multicenter, randomized, blinded-endpoint, comparative effectiveness study of brain tissue oxygen and intracranial pressure monitoring versus intracranial pressure alone.
Trial registration	2a	Clinical trial.gov NCT03754114
	2b	n/a
Protocol version	3	13 May 2019 Version 2
Funding	4	This trial is funded by the National Institute of neurological Disorders and Stroke (NINDS), Grant number U01 NS099046.

Roles and responsibilities

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- 5a Bernard, Francis MD¹; Barsan, William MD²; Diaz-Arrastia, Ramon MD, PhD³; Merck, Lisa H⁴ MD MPH; Yeatts, Sharon PhD⁵; Shutter, Lori MD⁶
1. Hôpital du Sacré-Coeur de Montréal
Université de Montréal
Critical Care Department
Quebec, Canada
Responsibility: Site Principal Investigator, Member – Clinical Standardization Team, Lead author
 2. University of Michigan medicine
Emergency Medicine
Ann Arbor, Michigan, USA
Responsibility: BOOST Principal Investigator - Administration
 3. University of Pennsylvania Perelman School of Medicine
Neurology
Philadelphia, PA, USA
Responsibility: BOOST Co-Principal Investigator – Protocol Development
 4. University of Florida College of Medicine
Emergency Medicine & Neurology - Neurocritical care
Gainesville, Florida, USA
Responsibility: Site Principal Investigator, Co-lead – Clinical Standardization Team
 5. Medical University of South Carolina
Public Health Science
Charleston, SC, USA
Responsibility: BOOST Co-Principal Investigator – Biostatistics/Data Coordination
 6. University of Pittsburgh School of Medicine
Critical Care Medicine, Neurology, & Neurosurgery
Pittsburgh, Pennsylvania, USA
Responsibility: BOOST Co-Principal Investigator – Clinical Management
- 5b NIH National Institute of Neurological Disorders and Stroke
Project number: 1U01NS099046-01A1
Program Official: Maria Carolina Mendoza-Puccini
Phone: (301) 827-4007
eFax Number: 301-451-5639
Email: carolina.mendoza-puccini@nih.gov
- 5c The study sponsor had no role in the study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities

5d BOOST-3 is managed by the SIREN network. The structure is highly collaborative and multidisciplinary. Primary responsibilities for scientific/protocol leadership, clinical implementation, site coordination, and data management are allocated to 4 units, each led by one of the trial's multiple PIs and the PI of the data centre. Oversight is accomplished through Independent Medical Study Monitors and the NIH appointed Data and Safety Monitoring Board.

Introduction

Background and rationale	6a	Page 4
	6b	Page 4
Objectives	7	Page 4, line 37
Trial design	8	Page 4, line 47

Methods: Participants, interventions, and outcomes

Study setting	9	Page 5, line 4. Reference to where list of study sites can be obtained siren.network/clinical-trials/boost-3
Eligibility criteria	10	Figure 1. Centres are eligible if they have inserted and used both ICP and PbtO2 probes (at least 3 in the last 6 months).
Interventions	11a	Page 5
	11b	n/a
	11c	Carepath application on monitoring at bedside suggesting the appropriate intervention according to protocol. The Clinical Core will oversee the Quality Assurance procedures related to the ICU management of episodes of intracranial hypertension and brain tissue hypoxia. In addition, study monitors will review participants' medical and study records and perform source document verification against data submitted in WebDCU™.
	11d	Treatment according to table 2 and 3. Otherwise usual care.
Outcomes	12	Page 7, line 2
Participant timeline	13	Figure 1, Page 5, line 9.
Sample size	14	Page 8, line 16

1
2 Recruitment 15 Subjects will be recruited from patients admitted to the emergency
3 department, trauma, or neurosurgical services at participating clinical
4 sites through notification of study coordinators. Each site will have a
5 system for identification and early notification of potential participants
6 who qualify for the trial. Screening logs will be maintained in
7 WebDCU™ and reviewed by study leadership particularly to analysed
8 missed opportunities.

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10 **Methods: Assignment of interventions (for controlled trials)**

11 Allocation: Page 5, Line 27

12
13 Sequence generation 16a Page 5, line 29

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16 Allocation concealment mechanism 16b Treatment group assignment will be done through WebDCU™, the
17 electronic Clinical Trial Management System run by the SIREN Data
18 Coordinating Center (DCC) at the Medical University of South
19 Carolina.

20
21 Implementation 16c Local site study personnel will review the potential participant's
22 information and screen the patient for enrolment according to the
23 inclusion and exclusion criteria. This information will be entered into
24 WebDCU™, and allocation will be done through that system.

25
26 Blinding (masking) 17a Page 5, line 32 & 36. Treating physician and team will be blinded to
27 PbtO2 measure in the ICP only group. Outcome assessors are also
28 blinded.

29
30 17b Page 5, line 33. Daily FiO2 challenges will be conducted by unblinded
31 study personnel not involved in patient care to assess probe reliability

32
33 **Methods: Data collection, management, and analysis**

34 Data collection methods 18a Page 7, line 12

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37 18b Outcome assessments will be able to be done in person or over the
38 phone. In person assessments will be coordinated with scheduled
39 clinic visits whenever possible.

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41 Data management 19 Page 7, line 12

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43 Statistical methods 20a Page 8, line 10

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46 20b n/a

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49 20c We will use the Intent-to-treat (ITT) sample. The ITT sample will
50 include all subjects randomised, where subjects will be classified by
51 the treatment arm to which they are randomised, regardless of
52 protocol adherence. Standard multiple imputation methods are used
53 to account for missing data in the analyses.

54
55 **Methods: Monitoring**

56 Data monitoring 21a Page 7, line 32
57 The Data and Safety Monitoring Board was composed by NINDS.
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	21b	The study is designed for a total of three planned analyses of the primary outcome: two interim analyses and one final analysis. The interim analysis plan is based on error spending functions (Lan and DeMets, 1983; Pampallona et al, 2001) with an O'Brien and Fleming boundary (O'Brien and Fleming, 1979). The trial may be stopped for overwhelming efficacy or for futility if the test statistic crosses the corresponding boundary. The results of the interim analyses will be made available to the DSMB, who will make a recommendation to the NINDS regarding trial continuation or termination.
Harms	22	Page 7, line 41
Auditing	23	Page 7, line 36
Ethics and dissemination		
Research ethics approval	24	Ethic approval: Advarra approval, ID : Pro00030585
Protocol amendments	25	Any modification to the protocol will be submitted for review to the ethics committee: advarra
Consent or assent	26a	Research coordinators from each centers
	26b	BioBOOST is an ancillary study looking at blood biomarker levels of patients enrolled in the parent study. A separate consent is obtained for participation in this study.
Confidentiality	27	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 confidential, secure database. Subjects will not be personally identified in any publications resulting from this project.
Declaration of interests	28	No conflict of interest, page 15, line 9
Access to data	29	The Data Coordinating Center maintains the trial database. The data will be made publicly available through FITBIR as required.
Ancillary and post-trial care	30	There is no payment, compensation, or cost to being in the study. If a participant is harmed from participating in the study, medical care will be available at the study institution or any site of their choosing. Payment for this care will be billed the same as care for any medical problem. No compensation will be provided to the participant by the granting agency (National Institute of Neurological Disorders and Stroke), the treating institution, or the researchers. The participant still has all of their legal rights to recover damages.
Dissemination policy	31a	page 15, line 14
	31b	page 15, line 3
	31c	page 15, line 14

Appendices

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Informed consent materials	32	Uploaded in ScholarOne
Biological specimens	33	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

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