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

Francis Bernard, William Barsan, Ramon Diaz-Arrastia, Lisa H Merck, Sharon Yeatts, Lori A Shutter

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 tissue oxygenation (PbtO2) monitor prevents more secondary injuries that will translate into improved functional outcome.

Methods and analysis  Multicentre, randomised, blinded-endpoint comparative effectiveness study enrolling 1094 patients with severe TBI monitored with both ICP and PbtO2. Patients will be randomised to medical management guided by ICP alone (treating team blinded to PbtO2 values) or both ICP and PbtO2. Management is protocolised according to international guidelines in a tiered approach fashion to maintain ICP <22 mm Hg and PbtO2 >20 mm Hg. 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. Favourable outcome is defined according to a sliding dichotomy where the definition of favourable 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 neuropsychological 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.

Trial registration number  ClinicalTrials.gov Registry (NCT03754114).

INTRODUCTION

Traumatic brain injury (TBI) is a major cause of death and disability in modern industrialised societies. The most recent estimates from the Centers for Disease Control and Prevention indicate that in the USA alone, 3.5 million individuals experience a TBI annually, of which 300,000 are hospitalised and discharged alive. Among the 300,000 hospitalised survivors, over 40% experience long-term disability.

Historically, monitoring of patients with severe TBI focused on intracranial pressure (ICP) and cerebral perfusion pressure (CPP) to prevent secondary injury. Although limiting elevation of ICP is an important part of TBI management, the only randomised
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. 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 individualised care.

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. In fact, oxygen diffusion in the brain parenchyma is the rate limiting step of delivery and is affected by the presence of oedema or microcirculatory failure. 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 ischaemic burden and independently associated with functional outcome. The use of PbtO₂ was recently the subject of a consensus statement highlighting the fact that multimodal monitoring allows for management refinement compared with ICP management alone.

TBI management heterogeneity requires that any multicentre clinical trial protocol allows various treatment options based on bedside evaluation of cerebral physiology while maintaining the rigour and clinical standardisation necessary to conduct a randomised clinical trial (RCT). BOOST-2, a multicentre RCT, found that treatment of elevated ICP and correction of low PbtO₂ decreased the total cumulative ischaemic burden compared with treatment of elevated ICP alone (p=0.0000002). Furthermore, a trend in improved functional outcome at 6 months was supportive of the predeterminded non-futility hypothesis.

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

METHODS

Trial design, study setting and study population

BOOST-3 is a two-arm, single-blind, randomised, controlled, phase III, multicentre trial to determine whether treatment algorithms informed by PbtO₂ and ICP monitoring improve subject outcomes more than treatment informed by ICP alone. 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 summarised in figure 1.

BOOST-3 includes 47 level 1 trauma centres that are experienced with active clinical use of PbtO₂-guided patient management across the USA and Canada. These sites place PbtO₂ and ICP monitors according to Brain Trauma Foundation (BTF) guidelines as part of their standard of care for patients with severe TBI. Monitors will thus be inserted following local standard practice patterns. Of these patients, those who meet eligibility criteria for the study will be randomised. Specifically as per inclusion criteria, randomisation will occur if the decision to place catheters is made within 6 hours from arrival to the enrolling centre 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 a fractional inspired oxygen (FiO₂) challenge (blinded in the ICP-only group) with an appropriate response defined by an increase of at least 5 mm Hg. 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 and the National Center for Advancing Translational Science to improve outcomes of subjects with acute illness and injury.

Randomisation and blinding

Subjects are randomised in a 1:1 ratio to a treatment protocol informed by both ICP and PbtO₂ or by ICP alone, using a covariate-adjusted randomisation scheme (figure 1). The randomisation 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 the Outcome section).

Intervention

A Clinical Standardization Committee (CST) for the BOOST-3 trial developed general targets for physiological variables for both groups (table 1) and finalised the MOP. Arterial blood pressure monitoring for CPP purposes will be standardised to the level of the heart.

The patient’s clinical course will fall into four different clinical scenarios based on monitoring information, three 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 (box 1) and type C (box 2) 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 manoeuvres. Interventions in this protocol were adapted from the BTF 2016 Guidelines for the Management of Severe Traumatic Brain Injury and the American College of Surgeons–Trauma Quality Improvement Program 2015 guidelines. Some interventions represent expert opinions. Treatment algorithms were developed.

Figure 1  Randomisation, inclusion and exclusion criteria. EFIC, exception from informed consent; FiO2, fractional inspired oxygen; ICP, intracranial pressure; PaO2, arterial oxygen pressure; PbtO2, brain tissue oxygenation; SaO2, arterial oxygen saturation; SBP, systolic blood pressure; TBI, traumatic brain injury
through discussions between BOOST investigators with expertise in critical care medicine and neurosurgery (CST). The protocol represents an attempt to minimise centre-to-centre 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 min. Treatments must be initiated within 15 min 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 min 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 boxes 1 and 2 are noteworthy.
Box 2  Scenario C: treatment options for isolated PbtO$_2$ <20 mm Hg

TIER 1: must begin within 15 min of abnormality. No particular order.
► Adjust head of the bed.
► Ensure temperature <38°C.
► Optimise haemodynamics to ensure adequate CBF and avoid diffusion gradient:
  - Resuscitation: address hypovolaemia.
  - Diuresis: avoid hypervolaemia, consider furosemide or other agent for diuresis.
► Optimise CPP up to 70 mm Hg maximum with fluid boluses or vasopressors as clinically appropriate. May assess cerebral autoregulation as per local protocol to manage CPP targets.
► PaO$_2$ adjustment (obtain ABG first†):
  - Pulmonary toilet with suctioning of secretions (bronchoscopy is not included in this tier as an option).
  - Increase FiO$_2$ to a maximum of 60%.
  - Adjust PEEP by a maximum of 5 cm H$_2$O over baseline.
► Adjust minute ventilation to achieve a PaCO$_2$ of 38–42 mm Hg (target pH of 7.35–7.45). Lowering further of PaCO$_2$ should not be done if pH >7.45. PaCO$_2$ should not be increased if pH is <7.35.
► Initiate or titrate anti-epileptic medications.

TIER 2: initiate within 60 min 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 stabilisation.
► Optimise CPP: may increase CPP above 70 mm Hg with fluid boluses or vasopressors.
► PaO$_2$ adjustment (obtain ABG first†):
  - Perform bronchoscopy.
  - Increase FiO$_2$ to a maximum of 100%†. Wean rapidly when clinically stable (decrease FiO$_2$ by 5% every 30 min).
  - Adjust PEEP in increments of 3–5 cm H$_2$O.
► Adjust minute ventilation to increase PaCO$_2$ 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 PaCO$_2$ >45 mm Hg (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 PbtO$_2$ should be considered:
  - Consider cortical spreading depolarisation via ECog.
  - Assess for pulmonary embolism.
  - Assess for cerebral venous thrombosis.
► Other salvage therapy based on local protocol and practice patterns.

*Obtain ABG to confirm that oxygenation is in desired range before treating with PaO$_2$ adjustments. Note that increasing PaO$_2$ above 150 mm Hg might imply overtreatment by PaO$_2$, and prevents detection of another potential cause of low PbtO$_2$.

†This option should only be used when PbtO$_2$ is persistently less than 20 mm Hg and other variables contributing to low PbtO$_2$ have been addressed and controlled. There is a potential for harm related to augmentation of CPP above 70 mm Hg with vasopressors.

Box 2  Continued

Optimising CPP

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

Increasing arterial oxygen pressure

Obtaining an arterial blood gas before treating with arterial oxygen pressure (PaO$_2$) adjustments is mandatory. Increasing PaO$_2$ above 150 mm Hg might imply overtreatment by PaO$_2$ and prevents detection of another potential cause of low PbtO$_2$. Calculating the brain oxygen ratio (BOX ratio = PbtO$_2$/PaO$_2$) might help recognise this situation. Increasing PaO$_2$ above 150 mm Hg should only be used if PbtO$_2$ is persistently less than 20 mm Hg and other variables contributing to low PbtO$_2$ have been addressed and controlled first.

Reverse Robin Hood syndrome

PbtO$_2$ probe located in an area already maximally vasodilated might measure a drop of flow (low PbtO$_2$) 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 principal investigator (PI) will be required to notify the study leadership team. Reasons for WLST will be carefully documented.

Outcomes

The primary outcome measure is the GOS-E performed at 180 (±30) days by a blinded central examiner. All injury-related disabilities are assessed for the primary measure. A complete battery of secondary measures will be assessed, including: survival at hospital discharge, total brain hypoxia burden, Functional Status Examination, Rey Auditory Verbal Learning Test, Trail Making Test...
Part A and B, Wechsler Adult Intelligence Scale (WAIS-IV), Processing Speed Index, Rivermead Post-Concussion Symptoms Questionnaire, Brief Symptom Inventory 18 and Satisfaction with Life Scale.

Data collection, data monitoring and adverse events

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

Information specific to PbtO$_2$, ICP and CPP monitoring will be collected for up to 5 days. Continuous digital recordings of these values will be captured on a bedside dedicated integrated platform (CNS Monitor, Moberg ICU Solutions, Amber, Pennsylvania, USA). This will allow precise calculation of ischaemic burden (time spent with PbtO$_2$ below 20 mm Hg) and eICP burden (time spent above 22 mm Hg). A custom built clinical decision algorithm based on the tier treatments (CNS Carepath, Moberg ICU Solutions, Amber, Pennsylvania, USA) can be used to help guide bedside clinicians to select the appropriate intervention for a given type of scenario. Local study personnel can review Carepath and the medical record to identify alarms and actions taken to correct them on the electronic case report form for the first 5 days.

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

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

Adverse events (AEs) are defined as any untoward event or complication not previously identified, or that occurs with greater frequency or severity than previously reported, whether or not considered related to the protocol intervention. The AEs listed in table 2 are anticipated based on the known complications of severe TBI, intracranial monitoring devices and prolonged use of supraphysiological levels of oxygen. In addition, new abnormal laboratory findings that are considered by the treating physician to be clinically significant may be included as AEs.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Adverse event</th>
<th>Expected incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute respiratory distress syndrome (ARDS)</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Septic shock</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Haematoma requiring craniotomy for evacuation</td>
<td>0.5%</td>
<td></td>
</tr>
<tr>
<td>Central nervous system infection</td>
<td>&lt;0.5%</td>
<td></td>
</tr>
</tbody>
</table>

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

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

Statistical considerations

Favourable outcome is defined according to a sliding dichotomy (figure 3), where the definition of favourable outcome varies according to baseline severity. Severity will be defined according to the probability of poor outcome predicted by the IMPACT core model. The favourable outcome definition is more stringent for subjects with a low probability of poor outcome.

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

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

Study timescale

Recruitment began Summer of 2019. The COVID-19 pandemic significantly affected early recruitment. The trial is currently recruiting patients at the rate of 15–16 patients per month. Once all sites are fully operational and recruiting, we expect recruitment to end by 2026. Allowing for the 6-month follow-up assessment, data cleaning and closure of the database, data analyses, manuscript writing and publication should take place in 2026.
Figure 3  Outcome defined according to sliding dichotomy.

Patient and public involvement
Community consultation and public disclosure are completed regionally for all enrolling sites in the USA, prior to the initiation of the clinical trial under CFR 50.24. No patient or public representative was involved in the written design of the trial.

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

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

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. Classic TBI management based on ICP and CPP alone has demonstrated its limitations. This management uses pressure as a surrogate for 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. PbtO₂ represents a balance between oxygen delivery and consumption measured directly in the brain parenchyma. Analysing the physiological parameters that influence PbtO₂ values at the bedside allows for a more extensive and precise comprehension of brain pathophysiology and may result in more tailored and efficacious care to prevent secondary injuries.

Two other trials are going to study the added value of PbtO₂ monitoring: the ongoing OXY-TC trial in France and the BONANZA trial in New Zealand and Australia (not yet registered on ClinicalTrials.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.

Recognising the heterogeneity of TBI characteristics and complexity of its management, BOOST-3 has standardised therapy in both groups while allowing for flexibility in treatment options. These options reflect the various possible physiological manipulations required to correct abnormalities identified by the bedside physician (boxes 1 and 2). Of note, BOOST-3 protocol recognises that cerebral autoregulation status plays an important role in managing CPP threshold. Optimisation of CPP according to the autoregulation status might improve outcome but its management remains difficult clinically. PbtO₂ might facilitate recognition of the autoregulation status. Analysis of the continuous data capture within the BOOST-3 cohort may inform future study of the relationship between cerebral autoregulation, goal-directed therapy and patient outcome.

The BOOST-3 protocol also clearly emphasises that increasing PaO₂ in order to correct a low PbtO₂ value should be used very cautiously. Increasing PaO₂ above 150 mm Hg might imply overtreatment by PaO₂ and prevents detection of another potential cause of low PbtO₂. It is possible to compensate for a decrease in PbtO₂ due to low CBF by increasing PaO₂. Hyperoxia is known to induce cerebral vasodilatation, potentially increase free radical production and has been associated with worse outcome in other brain ischaemic injuries. If FiO₂ is increased as a therapeutic manoeuvre, a specific FiO₂ weaning protocol is suggested. That being said, it is expected that patients with TBI 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. AEs related to pulmonary pathology will be closely tracked in both study groups.
The limitations of standardisation 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 haematomas, subarachnoid haemorrhage or any combination of these injuries. The fact that multiparametric and PbtO₂ monitoring allow for a physiology-driven approach may globally improve the delivery of care despite the heterogeneity of disease phenotype. BOOST-3 is slated to recruit a large number of patients, which will likely help to achieve balance of injury phenotype across study groups. Furthermore, the specificity gained by measuring functional outcome through a sliding dichotomy based on initial injury should also reduce heterogeneity bias.

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

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

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

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Contributors RD-A wrote the protocol of this study, LAS, RD-A, SY and WB are the principal investigators of the trial and compose the steering committee. WB is responsible for the statistics and data management of the trial. WB is administering the trial. FB and LAS wrote the first draft of this manuscript. FB, LAS and LHM are part of the clinical standardisation team responsible for protocol implementation and the manual of operating procedure. FB, LAS, LHM, RD-A, SY and WB all revised and approved the final version of this manuscript.

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Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES


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
CONSENT TO TAKE PART IN A CLINICAL RESEARCH STUDY
AND
AUTHORIZATION TO DISCLOSE HEALTH INFORMATION
ADULTS/SUBJECTS WHO TURN 18/PARENTAL/GUARDIAN PERMISSION
& ASSENT FOR AGES 14 TO AGE OF MAJORITY


Granting Agency: The National Institute of Neurological Disorders and Stroke (NINDS)

Protocol Number: BOOST-3

Principal Investigator: «PiFullName»
(Study Doctor)

Telephone: «IcfPhoneNumber»

Additional Contact(s): «AdditionalStaffMemberContacts»
(Study Staff)

Address: «PiLocations»

This form is for use in a research study that involves participants who are unconscious or in coma, and do not have the capacity to consent to take part in the study. You are the legally authorized representative of the patient. In cases where the participant’s representative gives consent, the participant should be informed about the study to the extent possible if the participant regains consciousness. During the course of the study, if the subject regains the capacity to consent, informed consent will be obtained from the subject and the subject offered the ability to leave the study if desired.
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.
There is no payment or compensation for being in the study. There is no cost to being in the study. Charges for all standard medical care will be billed the same way whether or not someone is in the study.

Please contact us for any questions about the research, participants' rights, or other concerns.

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

If you consent, you will be asked to sign and date this form.

MORE DETAILED INFORMATION

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

Why is this an important question to study?
When a person has a TBI, their injured brain can swell over a period of hours or days. If the brain swells too much, the pressure in the skull increases and becomes dangerous, causing further injury to the brain. To try to prevent this, doctors usually insert a device, an ICP probe, into the brain through a hole in the skull of people with severe TBI. An ICP monitor connected to the probe measures the pressure inside the skull. Most doctors agree that it is important to measure and prevent high ICP.

Patients with injured brains also suffer additional injury to the brain if the amount of oxygen in the brain gets too low. Some doctors also insert a second device, a PbtO2 probe, in the brain through the same or a second hole in the skull to measure brain tissue oxygen. A PbtO2 monitor connected to the probe measures how much oxygen is in a small area of the brain near the tip of the probe. Doctors disagree about whether monitoring oxygen levels is helpful or necessary.

Both monitoring devices are approved by the US Food and Drug Administration (FDA) and Health Canada for patients with TBI. Both are commonly used. The ICP and PbtO2 goals guided by these monitors are used to help doctors adjust their treatment choices. Treatments include kinds and doses of medications and the amount of intravenous fluids given, ventilator (breathing machine) settings, need for blood transfusions, and other medical care. Each of these treatment decisions is intended to improve outcomes. However, each treatment decision also involves potential risks. Different treatment decisions may result in different risks. This study will also help doctors better understand these risks.
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?
Participation, or ongoing participation, in this study is voluntary. The alternative to participating in the trial is usual care. Usual care may be medical care guided by ICP monitoring or it may be medical care guided by ICP and PbtO2 monitoring. The usual care offered may depend on the treating hospital, opinion of the doctors caring for the individual, or upon characteristics of the patient or their injury. There is no penalty for choosing not to participate. The participant may withdraw from the study at any time, either by his/her choice or at the direction of the participant’s legally authorized representative. Choosing not to participate, not to continue participation, or choosing to withdraw will not alter the usual care available. Nor does it alter or waive any legal rights or benefits.

What if new information becomes available?
We will provide any new information that may affect a participant’s willingness to continue in the study. Participants may be contacted about future available studies. We may also contact participants with periodic updates about the study. We may also contact participants after the trial has been completed to share results from the study.

AUTHORIZATION TO DISCLOSE HEALTH INFORMATION

How will personal information be protected?
The study investigator and his/her collaborators will consider the participants’ personal information confidential to the extent permitted by law. “Personal Information” means information that can be used to identify the participant or health information about the participant. This includes name or initials, date of birth, gender, ethnic origin and medical and health-related information such as blood tests, diagnostic imaging and results, the results of physical examinations, medical history and hospital records, and information directly observed in the study.

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

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

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

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

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

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

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

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

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

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

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

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

**How may the participants’ data and samples be shared?**

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

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

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

**Will the participant be paid for being in the study?**

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

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

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

In the event that the participant suffers injury as a result of their participation in this research study, 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. Nothing said here about treatment or compensation in any way alters the participants’ right to recover damages.

**Is there anything else I need to know?**

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

You may ask to stop having the study affect the participant's medical care. If so, usual care will resume. Usual care is based on the individual patient and their injury, the opinion of the treating doctors, and the treating institution. Usual care may be medical care guided by ICP alone, or medical care guided by ICP and PbtO2 monitoring.
Doctors caring for the participant during this hospitalization may also be researchers in this study. If so, the doctors are interested both in the participant’s medical care and in the conduct of this research. There is no obligation to participate in any research study just because it is offered by the participant’s doctors.

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

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

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

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

You can do so in the following ways:

- By mail:
  Study Subject Adviser
  Advarra IRB
  6940 Columbia Gateway Drive, Suite 110
  Columbia, MD 21046

- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting Advarra: Pro00030585.
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  Date

______________________________
Participant’s Signature

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

I would like to be in this study.

__________________________________   ___________________
Printed Name of Adolescent Participant  Date

______________________________
Adolescent Assent Signature

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)
STATEMENT OF LEGALLY AUTHORIZED REPRESENTATIVE

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

I want my family member (or the person I represent) to participate in this study.  
◯ Yes  ◯ No

If you want your family member (or the person you represent) to participate in this study, please sign below.

Participant Name

Printed Name of Legally Authorized Representative (LAR)

Your relationship to act on behalf of Participant (spouse, child, parent, sibling, other [if other, please describe]):

________________________________________

Signature of LAR                     Date                Time

Principal Investigator/Designee Name       Title

Designee Signature                     Date                Time
INFORMED REFUSAL OF FURTHER PARTICIPATION

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

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

________________________
Participant Name

________________________
Printed Name of Legally Authorized Representative (LAR)

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

__________________________________________________

______________________________           ____/____/____                _____: _____AM/PM
Signature of LAR             Date                 Time

______________________________           ____/____/____                _____: _____AM/PM
Principal Investigator/Desigee Name   Title

______________________________           ____/____/____                _____: _____AM/PM
Designee Signature             Date                 Time