6-19-2020

Cerebral Oxygenation Monitoring by Near-Infrared Spectroscopy in Severe Traumatic Brain Injury

Drew Harvard Zimmerman
Yale Physician Associate Program, drew.zimmerman@yale.edu

CEREBRAL OXYGENATION MONITORING BY NEAR-INFRARED SPECTROSCOPY IN SEVERE TRAUMATIC BRAIN INJURY

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the degree of
Master of Medical Science

June 2020

Drew Harvard Zimmerman, PA-SII
Class of 2020
Yale Physician Associate Program

Emily J. Gilmore, MD
Associate Professor of Neurology
Yale School of Medicine

Table of Contents

List of Tables

Abstract

Traumatic brain injury is a significant cause of death and disability and accounts for 16% of injury-related emergency department visits in the United States. Current guidelines for management of traumatic brain injury are focused on identifying and preventing secondary brain injury using multimodal invasive monitoring techniques, including cerebral oxygenation monitoring. However, these approaches have risks and there is currently no clinical consensus that use of invasive monitoring improves patient functional outcome. **We will evaluate whether noninvasive monitoring of cerebral oxygenation with near infrared spectroscopy can reduce the median duration of brain tissue hypoxia in patients with severe traumatic brain injury.** Specifically, we will determine whether this method has benefit in combination with current guidelines, versus management based on current guidelines alone. This study will provide evidence that noninvasive cerebral oxygenation monitoring is a physiologic parameter that may modify interventions to direct targeted treatments and improve outcomes in traumatic brain injury.

Chapter 1: Introduction

1.1 Overview

Traumatic brain injury (TBI) is a leading cause of death and disability among people in the United States. In 2010, a report by the Centers for Disease Control (CDC) estimated that of those diagnosed with a TBI, 87% (2,213,826) were treated and released from the emergency department, 11% (282,630) were admitted and then discharged, and 2% (52,844) died.[1] More than 3 million people in the United States are currently living with long-term disability from secondary injury related to TBI, and self-report a higher prevalence of activity limitation and reduction of life satisfaction, most notably in those who had suffered a severe TBI.[2,3] Severe TBI, defined as Glasgow Coma Scale (GCS) of ≤8, or motor score <5 if intubated, is associated with significant mortality and disability among survivors due to prolonged hospital stays and sequelae of secondary brain injury.[4,5]

Primary brain injury is defined as the direct mechanical forces that occur at the time of traumatic impact to brain tissue and include traumatic shearing and tearing of axons, diffuse axonal injury, and focal injuries such as intracranial hematomas.[6,7] While primary brain injuries occur seconds to minutes after trauma, they trigger a cascade of secondary brain injury over time.[8] Secondary brain injury may lead to the development of decreased cerebral blood flow, cerebral hypoxia, intracranial hypertension, and cerebral edema. It may also contribute to long-term complications, including seizures and the development of epilepsy, dysautonomia and behavioral disturbances in the ensuing days to months following the initial trauma.[6,8,9]

1.2 Multimodal Monitoring in Traumatic Brain Injury

Modern management of TBI is centered on multimodal monitoring of biochemical and physiological processes with the goal of identifying and preventing secondary brain injury, which can improve functional and cognitive outcome and reduce mortality.[10,11] Although no single modality can recognize a detrimental physiologic event with complete certainty, the simultaneous use of multiple monitoring techniques has been accepted as an optimal strategy to guide treatments of TBI patients.[10-13]

When TBI occurs, intracranial hemorrhage or cerebral edema may cause a rise in intracranial pressure (ICP). ICP depends on a fixed ratio of volumes within the skull: brain parenchyma, cerebrospinal fluid (CSF), and blood. Based on the Monroe-Kellie Doctrine, this intracranial volume is stable and an increase in one volume is offset by a decrease in one or both of the remaining two.[14] When compensatory mechanisms are intact, this principle describes the ability of the brain to manage small increases in volume without significant changes in ICP. However, when compensatory mechanisms fail, even small increases in volume result in increased ICP, decreased cerebral perfusion pressure (CPP), and reduced cerebral blood flow (CBF), which can compromise brain tissue perfusion and lead to ischemia.[11,15] Elevated ICP has been shown to be highly predictive of mortality, and has been a focal point of monitoring and guiding TBI treatment in the current literature.[16,17] Therefore, ICP monitoring is currently recommended by the *Guidelines for the Management of Severe Traumatic Brain Injury* in all patients with a severe TBI and an abnormal computed tomography (CT) scan revealing hematomas, contusions, swelling, or herniation.[12,18]

CPP is an important physiologic parameter that is often monitored simultaneously with ICP in the management of TBI. CPP is the difference between mean arterial

pressure (MAP) and ICP (CPP= MAP-ICP), and is therefore extrapolated from blood pressure and ICP measurements. It represents the pressure gradient driving CBF, which describes the extent to which oxygen and metabolites are being delivered to the brain tissue.[11,12] Optimizing CPP ensures adequate perfusion and prevents brain tissue hypoxia (BTH) that may ultimately lead to ischemia.[13] However, there is still uncertainty about whether management should be focused on CPP, ICP, or both, and if directing management towards one may be minimizing the importance of the other.[13] Although a multimodal monitoring approach has been widely adopted as the optimal strategy in TBI care, there remains a lack of clinical consensus on specific monitoring modalities and treatment protocols that are informed by those values.[11]

Table 1. *Glasgow Coma Scale*[19]

Category	Response	Score
Eye Opening	Opens spontaneously	4
	Opens to verbal stimulus	3
	Opens to painful stimulus	2
	No eye opening	1
Best Verbal Response	Oriented	5
	Confused	4
	Inappropriate	3
	Incomprehensible	2
	No verbal response	1
Best Motor Response	Obeys commands	6
	Purposeful movement to painful stimulus	5
	Withdraws from pain	4
	Abnormal (spastic) flexion, decorticate posturing	3
	Extensor (rigid) response, decerebrate posturing	2
	No motor response	1

1.3 Cerebral Oxygenation Monitoring

Cerebral oxygenation involves three main factors: CBF, arterial content of oxygen, and cerebral oxygen consumption.[13] In TBI, an imbalance between oxygen delivery and consumption may ultimately lead to BTH.[9] Increased incidence, duration,

and extent of BTH is associated with poor prognosis and functional outcomes; therefore, a critical goal of multimodal monitoring is to ensure sufficient perfusion and oxygenation of brain tissue.[9] However, studies have shown that BTH is common in TBI and can occur even in the presence of normal ICP and CPP.[8,18] This highlights the importance of an additional monitoring modality focused on cerebral oxygenation to supplement ICP and CPP monitoring, and necessitates that care of TBI patients without cerebral oxygenation incorporated into a multimodal monitoring approach is incomplete.[6]

1.4 Limitations of Cerebral Oxygenation Monitoring

Prior studies have suggested that the addition of invasive brain tissue oxygenation (PbtO2) directed care in addition to the conventional ICP/CPP monitoring based management may be associated with reduced burden of BTH.[20-22] Some studies have even suggested that management based on PbtO2 was associated with better short-term outcomes and was a better indicator of long-term prognosis than ICP and CPP management alone.[23]

However, obtaining PbtO2 requires an invasive monitoring technique that does not come without limitations and risk.[11] Although PbtO2 catheters can be placed through a similar sized burr hole as an ICP monitor, they introduce post-surgical risk of infection and bleeding, and there is a need for precise placement for accurate measurements.[24] PbtO2 catheters only measure BTH regionally, and may provide vastly different data based on the location and depth that the catheter is placed in the brain parenchyma.[24,25] Placement on the more injured side of the brain may reflect the area most at risk for secondary injury, but will not provide an accurate assessment of the cerebral oxygenation in other areas. Alternatively, placement into a relatively healthy area of tissue may

provide a falsely reassuring value that is not indicative of potential hypoxia in more injured areas.[24] Beyond its regional limitations, values are dependent on the patient's blood CO_2 and O_2 concentrations, temperature, and hypermetabolic states such as fever, shivering and seizure activity.[26-28] Therefore, a broader, noninvasive equivalent of cerebral oxygenation monitoring would make a substantial contribution for those whom invasive PbtO2 monitoring may be insufficient or introduce unnecessary risk.[29]

1.5 Near Infrared Spectroscopy

Near infrared spectroscopy (NIRS) is a noninvasive monitoring modality suitable for continuous monitoring of surrogate changes in cerebral blood volume and cerebral oxygenation.[11,30] Although similar in technology to pulse oximetry, which measures arterial oxygen saturation, NIRS measures tissue oxygen saturation, which consists of a combination of measures from arterial, venous, and capillary blood.[31] The principle behind the technique is that infrared light is delivered via multiple emitters through the scalp and into brain tissue noninvasively and can detect cerebral oxygenation and measures of autoregulation on a global scale.[32] Benefits of NIRS in the monitoring of cerebral oxygenation include that is that it is noninvasive, does not require frequent calibration, can be placed when an intracranial monitor may be unsafe, and minimizes the challenge of a constant and precise location of probes.[33]

NIRS monitoring in TBI patients provides distinct advantages through its noninvasive approach of detecting global rather than regional measures of cerebral oxygenation, has resistance to motion artifacts, and is flexible in location and patient positioning.[34,35] In this way NIRS can be feasibly integrated into the clinical environment to directly monitor total hemoglobin, deoxyhemoglobin, and oxyhemoglobin, which

provides a parameter of cerebral oxygenation as well as a surrogate for measurement of CBF.[36]

NIRS technology is applied using various devices which quantify cerebral tissue oxygenation using equal (but device specific) indices such as tissue oxygen index (TOI), as measured by the NIRO2 200NX, or the cerebral oxygenation saturation (SctO2), as measured by CASMED-Foresight.[37] Previous studies have shown that invasively measured PbtO2 and noninvasively measured TOI respond to changes in arterial pressure and ICP and that the direction of changes of TOI is concordant to that of PbtO2 in 77% of the analyzed events.[38] A study by Suzuki, et al. compared TOI to a blood gas analyzer and showed excellent correlation between the two parameters, therefore validating its efficacy in clinical use.[39] Furthermore, a study by Al-Rawi, et al. defined a drop in TOI (13%) based on NIRS that can be adopted as a threshold for identification of severe cerebral ischemia with high sensitivity and specificity.[32] These data demonstrate the potential to identify NIRS derived thresholds for cerebral ischemia in the adult brain and support the use of NIRS cerebral oxygenation monitoring in a clinical setting.[32]

1.6 Statement of the Problem

Use of ICP monitoring in severe TBI remains the gold standard in guiding treatment, and there is a well-described relationship between mortality and elevated ICP after TBI. However, there is still no large randomized clinical trial confirming its effectiveness in guiding management, and to date there is no Level 1 clinical evidence proving its mortality benefit. Additionally, ICP monitoring facilitates calculating the CPP through the relationship that CPP= MAP-ICP. Similar to NIRS, ICP monitoring allows for surrogate measures of cerebral perfusion. Optimal ICP or CPP thresholds have yet to

be determined, and there is still debate over whether management of patients should be targeted towards ICP or CPP as the main physiologic determinant.[13,23] Once the primary injury has occurred, therapy is directed towards preventing secondary brain injury by ensuring the adequate delivery of oxygenated blood and nutrients to brain tissue to minimize the risk of supply-demand mismatch. Prior studies have suggested that reduced duration of BTH is associated with lower mortality rates, but authors acknowledge that using PbtO2 as a monitoring technique has limitations. Monitoring with PbtO2 reflects a regional rather than a global measure of cerebral oxygenation and requires an invasive surgical procedure for placement of the catheter.[12,18,40-42] NIRS as a noninvasive modality of monitoring cerebral oxygenation has shown promise, but a larger randomized clinical trial in TBI is necessary to provide definitive evidence of its benefit.[10,29,43]

Authors agree that the absence of sufficiently powered prospective studies and clinical trials investigating the efficacy of these modalities has resulted in a lack of clinical consensus in the monitoring algorithm of TBI. There has yet to be a functional integration of all of these modalities that allow clinicians to make informed decisions regarding management and intervention.[10] Given the limitations of the current literature and lack of definitive clinical data, further clinical trials are vital to establish optimal methods and establish a standard of care among providers. Our proposed study will help to clarify the clinical utility of noninvasive cerebral oxygenation monitoring as a surrogate for cerebral perfusion in reducing BTH and whether its integration into the multimodal monitoring approach is warranted to guide TBI treatment.

1.7 Goals and Objectives

Our proposed multicenter randomized controlled trial (RCT) aims to determine whether cerebral oxygenation monitoring by NIRS can reduce the burden of BTH and be incorporated into a standardized multimodal monitoring approach to guiding treatment of severe TBI. The primary outcome will be to determine if treatment guided by cerebral oxygenation monitoring with NIRS in addition to ICP monitoring can reduce the median duration of BTH in the first 72 hours of injury as compared to ICP monitoring alone. This outcome will determine the efficacy of NIRS as a monitoring modality in guiding clinical decision making based on brain tissue oxygenation.

Our secondary outcome will be to determine functional outcome in each of our groups at 6 months post initial injury utilizing the Glasgow Outcome Scale-Extended (GOS-E) on an 8-point rating system. This information will determine whether the NIRS based interventions improve functional outcome.

1.8 Hypothesis

We hypothesize that goal directed therapy based on brain tissue oxygenation monitoring by NIRS plus ICP monitoring will show a **difference in median duration of brain tissue hypoxia over 72 hours**, as compared to therapy guided by ICP monitoring alone in the treatment of adults with severe traumatic brain injury.

1.9 Definitions

Median duration of BTH: median duration of time spent below threshold, defined as SctO2 ≤ 50%, continuously measured and transmitted at 5 minute intervals over a 72 hour span.

Goal directed therapy: predetermined treatment protocol directed at a set combination of physiological interventions that will address elevated ICP alone, or BTH and elevated

ICP in conjunction, in treatment of TBI in each group. Specific protocol is defined in section 3.5.1.

1.10 References

1. Centers for Disease Control and Prevention. Report to Congress on Traumatic Brain Injury in the United States: Epidemiology and Rehabilitation. *National Center for Injury Prevention and Control; Division of Unintentional Injury Prevention.* 2015.
2. Jacobsson L, Lexell J. Functioning and disability from 10 to 16 years after traumatic brain injury. *Acta Neurologica Scandinavica.* 2019;n/a(n/a).
3. Whiteneck GG, Cuthbert JP, Corrigan JD, Bogner JA. Prevalence of Self-Reported Lifetime History of Traumatic Brain Injury and Associated Disability: A Statewide Population-Based Survey. *The Journal of head trauma rehabilitation.* 2016;31(1):E55-62.
4. Thurman DJ, Alverson C, Dunn KA, Guerrero J, Sniezek JE. Traumatic brain injury in the United States: A public health perspective. *The Journal of head trauma rehabilitation.* 1999;14(6):602-615.
5. Nangunoori R, Maloney-Wilensky E, Stiefel M, et al. Brain tissue oxygen-based therapy and outcome after severe traumatic brain injury: a systematic literature review. *Neurocritical care.* 2012;17(1):131-138.
6. Kinoshita K. Traumatic brain injury: pathophysiology for neurocritical care. *Journal of Intensive Care.* 2016;4(1):29.
7. Marehbian J, Muehlschlegel S, Edlow BL, Hinson HE, Hwang DY. Medical Management of the Severe Traumatic Brain Injury Patient. *Neurocritical care.* 2017;27(3):430-446.
8. Werner C, Engelhard K. Pathophysiology of traumatic brain injury. *Br J Anaesth.* 2007;99(1):4-9.
9. Parmeet K, Saurabh S. Recent Advances in Pathophysiology of Traumatic Brain Injury. *Current Neuropharmacology.* 2018;16(8):1224-1238.
10. Al-Mufti F, Lander M, Smith B, et al. Multimodality Monitoring in Neurocritical Care: Decision-Making Utilizing Direct And Indirect Surrogate Markers. *Journal of Intensive Care Medicine.* 2018;34(6):449-463.
11. Tasneem N, Samaniego EA, Pieper C, et al. Brain Multimodality Monitoring: A New Tool in Neurocritical Care of Comatose Patients. *Critical care research and practice.* 2017;2017:6097265.
12. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery.* 2017;80(1):6-15.
13. Prabhakar H, Sandhu K, Bhagat H, Durga P, Chawla R. Current concepts of optimal cerebral perfusion pressure in traumatic brain injury. *J Anaesthesiol Clin Pharmacol.* 2014;30(3):318-327.
14. Mokri B. The Monro-Kellie hypothesis: applications in CSF volume depletion. *Neurology.* 2001;56(12):1746-1748.
15. Godoy DA, Lubillo S, Rabinstein AA. Pathophysiology and Management of Intracranial Hypertension and Tissular Brain Hypoxia After Severe Traumatic

Brain Injury: An Integrative Approach. *Neurosurgery Clinics of North America.* 2018;29(2):195-212.
16. Zoerle T, Lombardo A, Colombo A, et al. Intracranial pressure after subarachnoid hemorrhage. *Crit Care Med.* 2015;43(1):168-176.
17. Heuer GG, Smith MJ, Elliott JP, Winn HR, LeRoux PD. Relationship between intracranial pressure and other clinical variables in patients with aneurysmal subarachnoid hemorrhage. *Journal of neurosurgery.* 2004;101(3):408-416.
18. Okonkwo DO, Shutter LA, Moore C, et al. Brain Oxygen Optimization in Severe Traumatic Brain Injury Phase-II: A Phase II Randomized Trial. *Crit Care Med.* 2017;45(11):1907-1914.
19. Sternbach GL. The Glasgow coma scale. *The Journal of emergency medicine.* 2000;19(1):67-71.
20. Kiening KL, Hartl R, Unterberg AW, Schneider GH, Bardt T, Lanksch WR. Brain tissue pO2-monitoring in comatose patients: implications for therapy. *Neurological research.* 1997;19(3):233-240.
21. Bohman LE, Heuer GG, Macyszyn L, et al. Medical management of compromised brain oxygen in patients with severe traumatic brain injury. *Neurocritical care.* 2011;14(3):361-369.
22. Pascual JL, Georgoff P, Maloney-Wilensky E, et al. Reduced brain tissue oxygen in traumatic brain injury: are most commonly used interventions successful? *The Journal of trauma.* 2011;70(3):535-546.
23. Oddo M, Levine JM, Mackenzie L, et al. Brain hypoxia is associated with short-term outcome after severe traumatic brain injury independently of intracranial hypertension and low cerebral perfusion pressure. *Neurosurgery.* 2011;69(5):1037-1045; discussion 1045.
24. Martini RP, Deem S, Treggiari MM. Targeting Brain Tissue Oxygenation in Traumatic Brain Injury. *Respiratory Care.* 2013;58(1):162.
25. Roh D, Park S. Brain Multimodality Monitoring: Updated Perspectives. *Curr Neurol Neurosci Rep.* 2016;16(6):56-56.
26. Stewart C, Haitsma I, Zador Z, et al. The new Licox combined brain tissue oxygen and brain temperature monitor: assessment of in vitro accuracy and clinical experience in severe traumatic brain injury. *Neurosurgery.* 2008;63(6):1159-1164; discussion 1164-1155.
27. Stiefel MF, Udoetuk JD, Spiotta AM, et al. Conventional neurocritical care and cerebral oxygenation after traumatic brain injury. *Journal of neurosurgery.* 2006;105(4):568-575.
28. Jaeger M, Schuhmann MU, Soehle M, Nagel C, Meixensberger J. Continuous monitoring of cerebrovascular autoregulation after subarachnoid hemorrhage by brain tissue oxygen pressure reactivity and its relation to delayed cerebral infarction. *Stroke.* 2007;38(3):981-986.
29. Zweifel C, Castellani G, Czosnyka M, et al. Noninvasive Monitoring of Cerebrovascular Reactivity with Near Infrared Spectroscopy in Head-Injured Patients. *Journal of neurotrauma.* 2010;27(11):1951-1958.
30. Lee JK, Kibler KK, Benni PB, et al. Cerebrovascular Reactivity Measured by Near-Infrared Spectroscopy. *Stroke.* 2009;40(5):1820-1826.

31. Garvey AA, Kooi EMW, Smith A, Dempsey EM. Interpretation of Cerebral Oxygenation Changes in the Preterm Infant. *Children (Basel, Switzerland).* 2018;5(7).
32. Al-Rawi PG, Kirkpatrick PJ. Tissue oxygen index: thresholds for cerebral ischemia using near-infrared spectroscopy. *Stroke.* 2006;37(11):2720-2725.
33. Steiner LA, Pfister D, Strebel SP, Radolovich D, Smielewski P, Czosnyka M. Near-infrared spectroscopy can monitor dynamic cerebral autoregulation in adults. *Neurocritical care.* 2009;10(1):122-128.
34. Di Domenico SI, Rodrigo AH, Dong M, et al. Chapter 28 - Functional Near-Infrared Spectroscopy: Proof of Concept for Its Application in Social Neuroscience. In: Ayaz H, Dehais F, eds. *Neuroergonomics.* Academic Press; 2019:169-173.
35. Ayaz H, Izzetoglu M, Izzetoglu K, Onaral B. Chapter 3 - The Use of Functional Near-Infrared Spectroscopy in Neuroergonomics. In: Ayaz H, Dehais F, eds. *Neuroergonomics.* Academic Press; 2019:17-25.
36. Drenckhahn C, Koch SP, Dümmler J, Kohl-Bareis M, Steinbrink J, Dreier JP. A validation study of the use of near-infrared spectroscopy imaging in primary and secondary motor areas of the human brain. *Epilepsy & Behavior.* 2015;49:118-125.
37. Klein SP, Depreitere B, Meyfroidt G. How I monitor cerebral autoregulation. *Critical care (London, England).* 2019;23(1):160-160.
38. Budohoski KP, Zweifel C, Kasprowicz M, et al. What comes first? The dynamics of cerebral oxygenation and blood flow in response to changes in arterial pressure and intracranial pressure after head injury. *Br J Anaesth.* 2012;108(1):89-99.
39. Suzuki S, Takasaki S, Ozaki T, Kobayashi Y. Tissue oxygenation monitor using NIR spatially resolved spectroscopy. Paper presented at: Proceedings of the 1999 Optical Tomography and Spectroscopy of Tissue III1999; Bellingham, WA, United States
San Jose, CA, USA.
40. Stiefel MF, Spiotta A, Gracias VH, et al. Reduced mortality rate in patients with severe traumatic brain injury treated with brain tissue oxygen monitoring. *Journal of neurosurgery.* 2005;103(5):805-811.
41. Bardt TF, Unterberg AW, Hartl R, Kiening KL, Schneider GH, Lanksch WR. Monitoring of brain tissue PO2 in traumatic brain injury: effect of cerebral hypoxia on outcome. *Acta neurochirurgica Supplement.* 1998;71:153-156.
42. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. VIII. Intracranial pressure thresholds. *Journal of neurotrauma.* 2007;24 Suppl 1:S55-58.
43. Hyttel-Sorensen S, Pellicer A, Alderliesten T, et al. Cerebral near infrared spectroscopy oximetry in extremely preterm infants: phase II randomised clinical trial. *BMJ (Clinical research ed).* 2015;350:g7635.

Chapter 2: Review of the Literature

2.1 Introduction- Literature Search Criteria

A thorough review of the literature was conducted between July 2019 and April 2020 using Ovid Medline, Embase, Cochrane Medical Library and Pubmed. Only English language articles were evaluated. Review of titles and abstracts determined relevance to the proposed study for analysis. Key terms used independently or in combination to search each database included: *traumatic brain injury, severe traumatic brain injury, monitoring, neurophysiological monitoring, intracranial pressure, cerebral oxygenation, brain tissue oxygenation, near infrared spectroscopy, cerebral perfusion pressure, autoregulation, brain tissue hypoxia, intracranial hypertension, Glasgow Coma Scale, Glasgow Outcome Scale, Glasgow Outcome Scale Extended, IMPACT, CRASH, functional outcome, and disability.* Most clinical studies reviewed were observational in nature, but a few influential RCTs were identified. Their analysis and review in relation to our proposed study are detailed below.

2.2 Overview of Traumatic Brain Injury

TBI is caused by a blunt force, blast or penetrating wound that disrupts the normal function of the brain.[1] TBI has a range of short and long-term clinical outcomes including cognitive and psychological impairments, functional disability, and death.[1] Currently, TBI severity is classified by the 15-point GCS based on a patients level of consciousness and assessed by verbal, motor and eye opening response.[2] Patients are then further categorized into ranges from mild (GCS score 13-15), moderate (9-12) and severe (3-8).[2,3] Recovery from TBI and return to baseline function is dependent on a complex

pathophysiology that includes biochemical and cerebral metabolic disruptions, diffuse axonal injury, hemorrhagic contusions, cerebral edema, and BTH, among others.[3-5]

In the prehospital and emergency room setting after TBI, the focus is on resuscitating and supporting the primary brain injury, which is caused by the direct mechanical forces of traumatic impact to brain tissue.[2,4] Once a patient is transferred to the intensive care unit (ICU), the effort shifts towards stabilization of hemodynamics and systemic oxygenation to prevent secondary brain injury.[4] Secondary brain injury can result in irreversible damage if undetected; thus the goal is detecting it when there is still time to intervene.[6] Utilizing various physiological monitors, patient care is centered on identification and management of secondary brain injuries that evolve in the hours to days following the primary injury, which requires careful monitoring of cranial and systemic physiology throughout their ICU stay.[7-9]

2.3 Review of Current Monitoring Strategies in Traumatic Brain Injury

Use of monitoring in TBI has been used for decades and is considered the basis from which we guide our treatment. However, it is not the monitoring alone that affects patient outcomes, but the ability to use that information to guide goal directed therapy. There is no single monitoring modality that can guide management with complete certainty, but use of a multimodal approach has been accepted as the optimal strategy in maintaining cerebral physiology, improving functional outcomes, and reducing mortality rates.[6,10-12] It is widely believed that treatment informed by data from monitoring may result in better outcomes than treatment informed solely by clinical assessment, as patients with severe TBI are comatose. However, to date there have been no large RCTs

confirming which monitoring modalities alone, or in combination, provide superior guidance in directing therapy in TBI.[10]

2.3.1 Intracranial Pressure Monitoring

ICP monitoring has been the focal point of physiological monitoring in TBI care, and is currently recommended by the *Guidelines for the Management of Severe Traumatic Brain Injury* for all salvageable patients with a severe TBI and an abnormal CT scan.[10]

In 2013, Alali, et al. conducted an observational retrospective cohort throughout the United States and Canada from 2009-2011 that examined the relationship between invasive ICP monitoring and in-hospital mortality. The study identified a large population of patients with severe TBI who met the guidelines for ICP monitoring and compared those who received ICP monitoring with those that did not.[10] Data from more than 10,000 patients and 155 centers were utilized in determining that ICP monitoring was associated with significantly lower odds of in-hospital mortality at the patient level (adjusted OR, 0.44; 95% confidence interval [CI] 0.31–0.63; $p < 0.0001$).[13]Although the large sample size of this study provides external validity and is generalizable in the United States, treatments based on monitoring were not controlled for, and details about those specific protocols were not reported. Internal validity suffers due to the observational nature of the study, and the authors admit to large variability of care among institutions at the hospital level. This variability was thought to be due to treatment differences based on clinical judgments of prognosis, which makes it more difficult to attribute success to ICP monitoring guided treatment alone on a larger scale.[10,13]

A 2013 prospective observational study by Talving, et al. studied a similar population of 216 severe TBI patients who met the Brain Trauma Foundation's (BTF) criteria for ICP monitoring, and observed rates of in-hospital mortality and length of stay.[14] Their results supported Alali, et al. in their findings that ICP monitoring was an independent predictor of overall in-hospital mortality, (adjusted OR 0.13 [95% CI 0.02–0.81], p = 0.029) and showed a significant reduction in mean hospital length of stay by -9.26 days (95% CI [-13.10 to -5.42], p <0.001). However, similarly to the study by Alali, et al., the treatment protocol informed by ICP monitoring was not controlled for or documented and was based on physician discretion, which introduces selection and information bias. Additionally, the study's external validity suffers due to the fact that it was conducted at a single medical center.[14]

Additional retrospective cohort studies by Farahvar, et al. in 2012 and Gerber, et al. in 2015 examined the relationship of ICP monitoring in TBI and 2-week in-hospital mortality rates.[15,16] Although both studies found a significant relationship to reduced 2-week in-hospital mortality rates with ICP monitoring, there are concerns with both designs. Farahvar, et al. identified their population retrospectively based on patients who received ICP lowering treatments based on their clinical presentation, and then followed their course from that point on to determine benefit.[15] This design is problematic in that they examined outcomes, but did not offer insight into how the monitoring itself, if initiated at baseline, would guide treatment.[15] Although the mortality rate for those treated with an ICP monitor was 19.6% (n=212), compared with 33.2% (n=74) in those treated without an ICP monitor, the question remains whether or not physicians decided

not to monitor those patients whose condition was considered more severe and potentially not salvageable, introducing bias.[15]

Although the findings were similar for Gerber, et al., their primary outcome was mortality based on adherence to guidelines for ICP monitoring, which varied among institutions and included guidelines for other factors. They studied severe TBI patients in New York State from 2001-2009 and found that based on guideline adherence, 55.6% of patients from 2001-2003 had ICP monitoring, which increased to 75.2% between 2007 and 2009 ($p < 0.0001$). There was also a significant association between mortality and ICP monitoring compliance such that mortality in the noncompliance group was 25.8% versus 18.6% in the compliance group ($p=0.0002$). However, it is difficult to establish causality in this relationship due to the advances in other aspects of TBI monitoring and care over that time period, and significant variability among patient demographics.[16]

Considering that ICP monitoring has been the standard of care in the BTF guidelines for management of severe TBI, most evidence in support of ICP monitoring has been observational in nature.[10,13-16] A 2012 multicenter RCT by Chesnut, et al. challenged this evidence by randomizing patients to protocols to treat intracranial hypertension (ICH) (pathologically elevated ICP) based on either an invasive ICP monitor or by clinical/radiological examination alone. 324 patients aged 13 or older in Bolivia and Ecuador were randomized to receive either invasive ICP monitors or imaging and clinical examination alone. Randomization was stratified according to study site, severity of injury, and age, and was conducted at 6 hospitals throughout Bolivia and Ecuador that received a high volume of trauma patients. Their primary hypothesis was that a management protocol based on ICP monitoring would result in reduced mortality

and improved functional outcome as measured by GOS-E at 6 months compared to management based on clinical/radiological evidence alone. Primary outcome was survival and functional outcome as assessed by GOS-E at 6 months, and secondary outcome was hospital length of stay.[17]

In contrast to findings by prior observational studies, the authors found that there was no significant between-group difference in the functional and cognitive status based on GOS-E (score of 56 in the ICP monitoring group vs. 53 in the imaging/clinical examination group; p=0.49). Additionally, 6-month mortality was similar at 39% in the ICP monitoring group and 41% in the imaging/clinical examination group (p=0.60), and median length of stay in the ICU was similar in the two groups (12 days in the ICP monitoring group and 9 days in the imaging/clinical examination group (p=0.25))[17]

As the only standardized, class 1 RCT providing evidence for ICP monitoring, this study had excellent internal validity. The results were not significant to refute the use of ICP monitoring and will not change the current recommended guidelines. However, this contributes to the uncertainty of multimodal monitoring strategies in TBI care and calls for additional research into a standardized algorithm of multimodal monitoring that is proven beneficial to TBI management.

2.3.2 Cerebral Perfusion Pressure Monitoring

Over the past decade, emphasis has been placed on optimizing CPP in addition to ICP in TBI. CPP is a surrogate for CBF and is the difference between systemic MAP and ICP.[10-12,18] CPP is directly influenced by ICP and MAP and can change based on alterations in either physiologic variable. Ensuring CPP is adequate in an injured brain is integral to maintaining sufficient blood flow and reducing secondary brain injury.

Decreased MAP, elevated ICP, and the resulting decreased CBF can result in tissue ischemia and infarction, supporting the importance of CPP in monitoring.[19] However, the question remains whether CPP monitoring alone, or in combination with other modalities can provide the optimal guidelines for management of severe TBI.

The first assessment of CPP monitoring in the management of TBI was a 1990 prospective study by Rosner, et al. in 34 patients with severe TBI (defined here as GCS ≤ 7). Their primary hypothesis was that CPP actively maintained between 70-80 mmHg would improve mortality and outcomes based on the GOS. Their results showed a mortality rate of 21%, and "good recovery rate" of 68%, based on their categorical scale informed by GOS.[20] Although the study had a small sample size and was conducted at a single institution, it was the first study examining CPP as a physiological monitoring parameter, established a reference range, and provided a necessary outline for management protocols going forward.

A more recent retrospective cohort by Gerber, et al. in 2013 evaluated CPP monitoring in severe TBI, whose findings were previously discussed in the analysis of ICP monitoring. Not only did they analyze guideline adherence and mortality rates for ICP monitoring, but for independent CPP monitoring as well. In New York State from 2001 to 2009, adherence to CPP treatment thresholds increased significantly from 14.6% in 2001-2003 to 48.2% in 2009 ($p<0.0001$). CPP monitoring compliance was associated with decreases in ICH (10.1% in the CPP noncompliance group in 2007-2009 versus 40.9% in 2007-2009 compliance group, $p<0.0001$). As mentioned previously, mortality rates dropped significantly over this time period and correlated with significantly increased adherence to CPP monitoring, as well as ICP monitoring.[16]

These results suggest a role in CPP monitoring in the reduction of mortality in TBI management. Not only did CPP monitoring adherence independently improve mortality rates, but the fact that ICH improved when CPP was elevated indicates that ICP and CPP monitoring together can contribute to mortality benefit. Strengths of the study include its large sample size, multiple sites and duration. However, the study took place only in New York, which reduces its generalizability to a larger population, and the authors admit that variability among sites and patient demographics is significant. As discussed previously, although there is a strong correlation with CPP monitoring and reduction of ICH and mortality, it is difficult to prove causality.

A 2006 retrospective analysis by Huang, et al. studied 376 patients with severe TBI over a 12-year period in Taiwan. Their main goal was to evaluate the efficacy of management based on: a) ICP monitoring, b) CPP monitoring (CPP target >70 mmHg), and c) CPP modified monitoring (mCPP) (CPP target >60 mmHg). Primary outcome was functional status as assessed by GOS at 6 months, in which favorable was defined as good recovery or moderate disability and unfavorable was defined as severe disability or vegetative state. Among the sample, 77 were in the CPP targeted group and each group was well balanced based on injury severity and demographics.

Results showed that mortality rates in the ICP only group were significantly higher than in the CPP or mCPP groups (28.6% in ICP, 14.3% in CPP, and 13.5% in mCPP, $p=0.02$ and $p=0.03$ respectively). In the CPP directed group, the percentage of unfavorable outcomes was 22.1% and the percentage of favorable outcomes was 63.6%, while in the ICP group the percentage of unfavorable outcomes was 22.7% and the percentage of favorable outcomes was 48.8%. Not only was there a statistically

significant reduction in mortality in both CPP groups versus the ICP group, but favorable outcome in the ICP group was also significantly lower than in the CPP and mCPP groups ($p=0.04$ and $p=0.01$, respectively). There was no significant difference between the two CPP directed groups, but both showed significant benefit versus the ICP only group.[21] These results suggest that a CPP targeted regimen is actually preferable over an ICP only regimen in the guidance of treatment for TBI.

Although the results of Huang, et al. are initially convincing, the study lacks internal validity due to its retrospective nature and lacks generalizability to the US population. The authors also admit that poor outcomes in the ICP group may have been attributed to poor clinical management strategies to lower ICP during this time period, which have been modernized and improved in the time since. Ultimately, the question of whether management should be directed towards CPP or ICP is still a matter of debate, as directing management towards one parameter may be minimizing the importance of the other.[12]

2.3.3 Brain Tissue Hypoxia

BTH is a common cause of secondary brain injury after severe TBI.[22,23] Increased BTH incidence, duration, and extent is associated with poor outcomes, and may result even when ICP and CPP are maintained within targeted thresholds.[22,24-26] Efforts to maintain adequate cerebral oxygenation is therefore an important aspect of TBI management and has been a topic recently addressed in the literature.

A systematic review conducted by Maloney-Wilensky, et al. in 2009 examined three prior prospective observational studies that evaluated BTH and outcome based on mortality and GOS scores at 6 months.[27] Collectively, 71 out of 150 (47%) patients met

the criteria for BTH, which was defined as brain tissue oxygen (BtO2) <10 mmHg (measured regionally by a direct brain oxygen probe) and was standardized across all three studies. Among those patients with BTH, 52 (73%) had an unfavorable outcome as determined by GOS, and 39 (55%) died. In the absence of BTH, only 34 (43%) had unfavorable outcome, and 17 patients died (22%). Overall, in patients who experienced BTH (BtO2 <10 mmHg for >15 minutes), the odds ratio (OR) of unfavorable outcome (death and disability) at 6 months was 4.00 (95% CI [1.9 – 8.2]), and the OR of death at 6 months was 4.6 (95% CI [2.2–9.6]), suggesting that BTH is significantly associated with poor outcome after severe TBI.[26,28,29]

However, there are limitations to conclusions drawn from this data based on the studies included. Considering that these studies were observational in nature, internal validity suffers. The authors also admit that these studies may have been subject to bias based on how risk factors for outcome were controlled. Additionally, differences in where monitors were placed, when the GCS was recorded, or how frequently data were obtained varied and may bias the results. But ultimately, the two major variables of concern, outcome and GCS, were similar across studies and the findings are consistent among the literature.[27]

2.3.4 Invasive Cerebral Oxygenation Monitoring

An attempt to establish a relationship between BTH, invasive cerebral oxygenation monitoring and outcome was conducted in a 2009 retrospective cohort study by Martini, et al. between 2004 and 2007. The study included 629 patients admitted with diagnosis of severe TBI at a single Level 1 Trauma Center in Seattle, WA. Their primary goal was to determine how clinical management based on PbtO2 monitoring affected

mortality rates, neurological outcome (as measured by Functional Independence Measure [FIM]), and resource utilization in this population. The entire population received ICP monitoring, but 506 received ICP monitoring alone, while 123 received ICP monitoring plus invasive cerebral oxygenation monitoring with PbtO2. The study found that there was no observed reduction in hospital mortality rate with management guided by the ICP/PbtO2 monitored group (29%) versus the ICP only group (23%). Even more surprising is that in patients who survived, the likelihood of a good neurological outcome (FIM≥ 7, which is defined as some level of independence) was actually smaller in the ICP/PbtO2 monitored group (7.6 ± 3.0) versus 8.6 ± 2.8 in the ICP monitored group ($p < 0.01$). After adjustment, there was a significant, -0.75 (95% CI -1.41 to -0.09) point reduction in mean FIM scores in patients with PbtO2 monitors versus ICP monitors alone.[30]

Although this data seemingly contradicts earlier observations in the literature regarding BTH and neurological and functional outcomes, there are significant flaws in the study design and protocol that reduce its applicability. The observational nature of the study and its single location had limitations on internal validity, and there was an additional possibility that patients in the PbtO2/ICP group had a different initial prognosis than those in the ICP group. In fact, patients in the ICP/PbtO2 group on average were younger (35.7± 16.9 years) and had more severe brain injuries (GCS 5.1 ±2.2) than in the ICP only group (40.7±19.6 years, GCS 5.6 ±2.3). The study reported that as a result, patients in the PbtO2/ICP group received more aggressive management and may have experienced serious adverse events. Finally, authors admit that the sample size of each group was significantly different (n=506 in ICP monitoring group, n=123 in

the ICP/PbtO2 monitoring group) and may have influenced results, and that the residual confounding that was possible in their study warrants an RCT to better investigate the relationship.[30]

In opposition to results concluded by Martini, et al., two retrospective analyses by Oddo, et al. in 2011 and Narotam, et al. in 2009 found a significant reduction in BTH and improved functional outcomes with management protocols guided by PbtO2.[23,31] When 30-day outcomes were assessed, Oddo, et al. found that BTH (defined as PbtO2<15 mmHg) was longer in duration in patients with unfavorable outcomes (GOS 1-3, 8.3±15.19 hours) than in those with favorable outcomes (GOS 4-5, 1.7 ±3.7 hours, $p<0.01$).[23] When compared to an ICP plus CPP monitoring group, Narotam, et al. found that management based on PbtO2 alone showed a significant reduction in BTH, mortality rate and better long-term outcomes when evaluating GOS at 6 months. There was a 44% improvement in mean BTH in the PbtO2 group (23.65 mmHg ± 14.40 mmHg) versus the ICP/CPP group (16.21 mmHg ± 12.30; $p < 0.001$). Results also supported better functional outcomes at 6 months in the PbtO2 group (GOS of 3.55 ± 1.75 versus 2.71 ± 1.65, $p < 0.01$; OR for good outcome 2.09, 95% CI [1.031- 4.24]). [31] Each of these studies concluded that functional outcomes were better and mortality rates were lower with decreased burden of BTH. Additionally, they reported that BTH was possible even in the presence of normal ICP and CPP; and in the case of Oddo, et al., determined that a management strategy based on PbtO2 alone was actually superior in preventing BTH than in a protocol based on CPP and ICP in combination.[23,31]

In 2017, a two-arm, single blind, prospective randomized controlled multicenter trial by Okonkwo, et al. (BOOST-II) evaluated the relationship of management guided by

PbtO2 monitoring in severe TBI and functional outcome and mortality. Their main hypothesis was that in patients with severe TBI, a management protocol informed by PbtO2 and ICP values would reduce the total burden of BTH. 119 severe TBI patients who met the BTF criteria for ICP monitoring were randomized to ICP monitoring only (n=62) or ICP plus PbtO2 monitoring (n= 57), with patient demographics and injury severity remaining similar among groups. Each patient enrolled, regardless of randomization, was treated based on a tiered management protocol derived from the *Guidelines for the Management of Severe Traumatic Brain Injury* and informed by values indicated by their monitoring modalities.[10]

Results opposed Martini, et al. in that management for episodes of hypoxia based on PbtO2 resulted in significantly less BTH (as measured by median proportion of time below 20 mmHg) in the ICP+PbtO2 group (median .07) versus median .45 in the ICP only group (p= 0.0000147). Additionally, 6-month GOS-E scores trended towards lower mortality and better functional outcome in the ICP+ PbtO2 group with 25% mortality versus 34% mortality in the ICP only group, although those results were not significant due to limitations of sample size. At the 6-month evaluation checkpoint, 11% more patients in the ICP+PbtO2 group achieved favorable outcomes (GOS-E of 5-8) than in the ICP group, indicating improved recovery and return to functional status. In conclusion, we can reasonably state that these results confirm the safety and feasibility of a management protocol based on PbtO2 monitoring. BOOST-II also refutes Martini, et al. and supports the hypothesis that PbtO2 directed therapy can mitigate secondary brain injury by reducing BTH in severe TBI and can serve as a framework for future RCTs to examine this association.

Although the results of BOOST-II are convincing in their support of PbtO2 plus ICP monitoring as an optimal strategy in guiding TBI management, there are still limitations to the study design. Most significantly, the study did not recruit a sample size sufficient to power results for clinical efficacy, but rather for a safety and feasibility outcome. This was intentional by the authors, indicating that BOOST-II was a Phase II trial confirming the safety and feasibility of their clinical protocol. Additionally, the results trended towards lower mortality and better GOS-E scores at 6 months, but were not significant due to limitations of sample size.[25] Both of these flaws are the result of being insufficiently powered, which can be addressed in a future RCT examining this relationship. BOOST-III, which is now underway, will examine the impact of ICP monitoring vs. ICP+PbtO2 monitoring on outcome in a study powered for clinical efficacy.

2.3.5 Near Infrared Spectroscopy in Cerebral Oxygenation Monitoring

Cerebral NIRS measures cerebral oxygenation by indirectly measuring the metabolic state of the brain tissue.[6] It represents an exciting and novel approach to noninvasive measurement of cerebral oxygenation across many spectrums, including TBI.

Considering the current lack of clinical evidence for NIRS in adults with TBI, correlation with existing modalities of cerebral oxygenation monitoring, such as PbtO2, is necessary. In a 2012 retrospective analysis by Budohoski, et al., NIRS based parameters of cerebral oxygenation were shown to have a significant temporal relationship to PbtO2 and ICP. The goal of the study was to observe and categorize cerebral oxygenation and perfusion in 42 TBI patients with PbtO2 and NIRS monitoring

across a range of ICP and arterial blood pressures. The authors hypothesized that PbtO2 and NIRS could reliably monitor cerebral oxygenation but differed in their reaction times to patterns of change in arterial pressure and ICP.

Results indicated that the direction of change of each modality was similar, but NIRS reacted first to arterial pressure and ICP fluctuations, while PbtO2 showed a delayed response. These results indicate that the modalities both reliably measure changes in cerebral oxygenation but react on a different temporal scale. Among 25 occurrences of ICP fluctuation, there was a significant difference in latencies of detection of events between PbtO2 and NIRS ($p=0.04$), but a consistent direction of change between the two modalities. In arterial pressure fluctuations (96 events), there were significant temporal differences between NIRS and PbtO2 detection ($p<0.001$), but again, the majority in the same direction.

Overall, results indicate that with impaired cerebrovascular reactivity (ICP and arterial pressure fluctuations), NIRS parameters and PbtO2 were concordant in 77% of events.[32] However, the retrospective and observational nature of the study limits its internal validity. Although there is significant correlation between arterial pressure, ICP and cerebral oxygenation (measured by NIRS and PbtO2), it does not provide proof of causality. These results are important in establishing the relationship between PbtO2 and NIRS and provide evidence that NIRS can be utilized in cerebral oxygenation monitoring in TBI similarly to the way PbtO2 has been in previous trials, but the need for a large RCT establishing this relationship is clear.

In addition to cerebral oxygenation, NIRS can be used as a noninvasive method for continuous detection of cerebral blood volume as a marker of cerebral autoregulation.

Cerebrovascular pressure reactivity (PRx) is the capability of cerebrovascular smooth muscle to react to changes in transmural pressure. Autoregulation is the maintenance of cerebral blood flow over a wide range of arterial blood pressure, based on changes in resistance to cerebral vasculature.[10] PRx, therefore, is the index by which autoregulation can be measured, and is calculated using CPP (MAP-ICP), which requires invasive ICP monitoring and continuous assessment of arterial blood pressure. Alternatively, using a noninvasive NIRS based index of cerebrovascular reactivity called total hemoglobin reactivity (THx), one study hypothesized that continuous recording would correlate with PRx and provide similar information about optimal arterial blood pressure and CPP in ensuring adequate autoregulatory status in TBI.

In this prospective observational study by Zweifel, et al., 40 patients with TBI were recorded 120 times daily using either NIRS to determine THx or invasive ICP monitoring to derive PRx. Authors found a significant correlation between PRx and THx indices ($r=0.49$, $p<0.0001$) across averaged individual recordings, which increased to $r=0.65$, $p<0.0001$ when patients with possible confounding factors were excluded.[33] These results indicate that NIRS derived indices of autoregulation (THx) can be used as a noninvasive alternative to determine optimal CPP and MAP in TBI patients. Although significant, data was obtained from a single site with limited sample size, which limits external validity. In their review, Davies, et al. mentioned that only events where changes in ICP resulted in a significant change in THx were considered for analysis. It is possible then that there were significant events of elevations in ICP that evoked no change in NIRS parameters.[34] Additionally, correlation increased between the two techniques when patients with frontal contusions were excluded, indicating the possibility that superficial

contusions or hematomas on the scalp may interfere with NIRS signal acquisition, a major limitation in TBI patients. However, this method may be particularly beneficial in patients whom invasive monitoring is contraindicated, unavailable or poses unacceptable risk. This study adds clinical significance to the utility of NIRS for measurement of autoregulation in addition to cerebral oxygenation.

A 2015 Phase II RCT by Hyttel-Sorensen, et al. evaluated the influence of NIRS monitoring on treatment guidelines in 166 preterm infants. Their primary hypothesis was that the burden of BTH could be reduced by a treatment guideline informed by cerebral NIRS monitoring.[35] During the first 72 hours of life, infants were randomized to cerebral oxygenation monitoring with NIRS (n=86) or blinded monitoring (n=80), in which their treatment would be dependent upon. Their primary outcome measure was BTH as measured by time spent outside of a defined target cerebral oxygen range and expressed in percent hours; and secondary outcome was defined as all-cause mortality.

Results concluded that the 86 infants randomized to NIRS monitoring had a significantly reduced median duration of BTH (16.6% hours [IQR 5.4-68.1%]) compared to the blinded group (53.6% hours [IQR 17.4-171.3]; p=0.0012), and a trend towards reduced all-cause mortality, although results were not significant. These results indicate that NIRS cerebral oxygenation monitoring can be successfully utilized to guide a treatment protocol to significantly reduce burden of BTH without the risk of serious adverse events.[35]

A major limitation of this study was clearly the population of interest and lack of generalizability, in that these patients were premature infants and did not suffer a TBI. The authors also admit that there was variability in the delivery of treatment protocols

due to inconsistent clinical discretion of the healthcare team among different sites, and that complete blinding of group allocation to the staff was not possible. Although there are limitations to the study, this was the first multicenter RCT in analysis of NIRS in a human population and showed promising results in its applicability for clinical use. While results indicate that this technology can be successfully utilized in human patients, a review by Davies, et al. pointed out that cerebral NIRS is a more established modality in neonatal intensive care due to favorable anatomical factors in the population such as decreased skull thickness.[34,36] Reflecting the opinions of other authors, Davies, et al. call for large cohort prospective clinical trials to demonstrate the optimal use and clinical efficacy of NIRS monitoring in the adult TBI population.

2.4 Review of Prognostic Indicators

In order to predict the risk of unfavorable outcomes or death in patients with severe TBI, baseline prognostic models have been created that correlate significantly with 6-month GOS-E scores. The International Mission on Prognosis and Analysis of Clinical Trials (IMPACT) study gathered data from 9,205 patients with moderate and severe TBI (defined as GCS ≤12) from eight RCTs and three observational studies between 1984 and 1997.[37] Prognostic scoring algorithms were then derived from the IMPACT study by Steyerberg, et al., and were found to have individual statistical significance in correlating to GOS-E 6-month outcome scores. The baseline characteristics used in calculating prognosis are obtained at initial presentation, which allows for application of the model before in-hospital therapeutic interventions.[38] Baseline characteristics in the IMPACT prognostic lab model include: demographics (age, sex, race), indicators of clinical severity (cause of injury, GCS components, pupillary reactivity), secondary insults

(hypoxia, hypotension, hypothermia), blood pressure, Marshall CT classification,[39] presence of intracranial hematomas, glucose, and hemoglobin at time of admission.[38] The IMPACT core model is an abbreviated adaptation of the lab model that is composed of age, GCS motor score, and pupillary reactivity and has been utilized in studies such as BOOST-II to control for prognostic indicators of clinical severity between control and intervention groups.[25,38]

Table 2. *IMPACT Core Model Prognostic Indicator*[37,38]

Characteristics	Value	Score
Age (years)	≤ 30	0
	30-39	1
	40-49	2
	50-59	3
	60-69	4
	70+	5
Motor Score	None/extension	6
	Abnormal flexion	4
	Normal flexion	2
	Localizes/obeys commands	0
	Untestable/missing	3
Pupillary reactivity	Both pupils reactive	0
	One pupil reactive	2
	No pupil reactive	4
Sum Score Core Model		

A 2012 external validation study by Roozenbeek, et al. confirmed that the IMPACT prognostic model was generalizable and can be reasonably applicable to classify TBI patient populations based on prognostic risk, which may be ultimately indicative of GOS-E outcome scores.[40] In our proposed study, IMPACT core model scores will be obtained and matched between groups in order to reduce the imbalance of important prognostic indicators, and then compared to GOS-E outcome at the completion of the trial.

2.5 Review of Relevant Methodology

This section will briefly review relevant methodology of the studies reviewed above to further validate our proposed study design and designation of methods.

2.5.1 Review of Studies to Identify Possible Confounding Variables

Most studies that investigate the clinical utility of monitoring modalities in TBI care employ observational studies to obtain their data. This type of study design is appropriate when there is a standard of care, such as ICP monitoring, which is being investigated or modified.[10] Most studies included in review, despite a select few seminal RCTs, have utilized observational studies to make conclusions about their hypothesized associations. Although almost all studies reach statistical significance in some outcome, potential confounding variables to their study designs will be reviewed.

Large retrospective observational cohorts are beneficial in analyzing a large sample with high external validity but are susceptible to confounding by uncontrolled variables. Several confounders were controlled for consistently among reviewed studies to reduce this effect, including gender, race, comorbid illnesses, injury mechanism and severity, type of intracranial lesion, and vital signs (including GCS) in the emergency department and during hospital stay. But authors admit that physician judgment, the course of the patient during the hospital stay, and the lack of availability of trained staff were all possible confounders that they could not reasonably control in this type of study design.[13] A widespread issue among observational studies included in review is the inability to control for physician biases or preferences, in that they may decide to place a particular monitor or not in patients because of an anticipated favorable or unfavorable outcome.[13-16] As Farahvar, et al. explain, to determine why some patients were treated or

not, and the decision behind it, is beyond the scope of their study and is a topic requiring investigation.[15]

A prospective, observational study by Talving, et al. attempted to reduce bias from confounding factors by utilizing propensity matching; a technique that tries to estimate the effect of a treatment by accounting for the covariates that predict receiving the treatment.[14] This technique specifically addressed the issue of physician bias in the decision to treat, or not. Regardless, a major issue in an observational design is that even when the decision is made to place a monitor or not, treatment regimens were largely dependent on clinical judgment. Physician discretion ultimately determined treatment plans, and it was possible that patients with ICP monitors were treated more aggressively than those without.[14] In fact, the retrospective cohort by Martini, et al. did collect information on patient demographics in each arm of their study (ICP monitoring alone versus ICP plus PbtO2 monitoring), and found that there was bias in decision to treat. Patients in the intervention group (ICP plus PbtO2 monitoring) on average were younger and had more severe brain injuries than in the control group (ICP monitoring only), and consequently received more aggressive management.[30] The opposite was observed in a single site retrospective analysis by Budohoski, et al., where treatment protocols were well established but patient characteristics varied. Although the treatment protocol was controlled for, sample size was small, and patient characteristics were significantly different (including injury type and severity based on GCS). Similarly to a study by Oddo, et al., the authors admit that confounding was possible based on the variable placement/location of devices, and the variable duration of monitoring among patients.[23,32] It is clear from the studies reviewed that management of severe TBI is

complex and multifaceted, and RCTs are necessary to control for patient demographics, monitoring protocols, and treatment algorithms within each study design.

In a review of RCTs, efforts were made to reduce confounding by creating guidelines for randomization and an established treatment protocol based on each treatment arm.[17,25,35] Despite this, a RCT by Hyttel-Sorensen, et al. still found that implementing treatment protocols based on NIRS monitoring was complex and difficult to apply across their entire sample size.[35] A tiered management protocol guided by PbtO2 and ICP monitoring was largely successful in BOOST-II; although they admit that treatment aimed at improving cerebral oxygenation had a small risk of significant adverse events, specifically respiratory events (4%), which may have confounded 6-month outcome measures.[25] In conclusion, the RCT design allows for implementation of specific interventions, treatment guidelines, elimination of physician bias, and minimizes the effects of inter-subject variability, and is a logical choice for our proposed study.

2.5.2 Study Design

As previously discussed, authors collectively agree that a large prospective RCT is necessary to establish the significance and clinical efficacy of a multimodal monitoring approach in TBI. Successive editions of the *Guidelines for the Management of Severe Traumatic Brain Injury* have noted that data from RCTs that have been conducted is lacking, and only a few high quality prospective cohort studies exist.[10] In our proposed two-arm single blind prospective, multicenter RCT, we will be able to control for confounding, reduce physician bias, and obtain high quality evidence to establish a relationship between a treatment protocol informed by cerebral oxygenation monitoring by NIRS and its effect on BTH and functional outcome.

2.5.3 Study Population and Selection Criteria

In accordance with the *Guidelines for the Management of Severe Traumatic Brain Injury*, observational studies, and adaptations from RCTs by Okonkwo, et al. and Chesnut, et al., the population selected will meet certain characteristics.[10,15-17,23,25] Patients will be 18 or older with severe TBI and meet clinical need for ICP monitoring. Selection will come from three academic, tertiary care, level I Trauma centers in the state of Connecticut with the appropriate resources to monitor and treat to the specifications of our protocol. Inclusion of three of the largest and most diverse medical centers in the state will allow for appropriate external validity. Like other studies in review, inclusion criteria will consist of severe TBI as defined by admission GCS and baseline demographic characteristics. Exclusion criteria will be similar to conditions established by previously reviewed studies, and include penetrating injury, GCS out of specified range, pregnancy, and age out of specified range, among others. Specific inclusion and exclusion criteria will be discussed in detail in Chapter 3.

2.5.4 Selection of Variables

Our proposed intervention will be cerebral oxygenation monitoring by NIRS plus ICP monitoring for 72 hours to guide a specified treatment regimen to determine efficacy of reducing burden of BTH and improving 6-month functional outcomes. Monitors will be placed within 12 hours of admission after confirming eligibility criteria based on inclusion and exclusion guidelines and consent agreement. Our proposed study design, timing and duration of monitor placement is comparative to previous RCTs that had analyzed the relationship of multimodal monitoring in TBI.[17,25] Although the trial by Chesnut, et al. found no significant improvement in functional outcomes with ICP

monitoring, its inability to refute its efficacy and the inclusion of ICP monitoring in the current guidelines is the primary factor for inclusion in our study as our control.[10,17] Additionally, safety and feasibility of regional brain tissue oxygen (PbtO2) monitoring was supported in BOOST-II, but was underpowered to show clinical significance, though there was a trend towards improved outcomes.[25] Well-documented limitations in PbtO2 monitoring, insufficient data, and promise for noninvasive strategies such as NIRS cerebral oxygenation monitoring is the primary determinant for including NIRS monitoring in our intervention arm instead of PbtO2.[12,25,35]

2.5.5 Treatment Protocol

The primary variable in our study design is the monitoring modality that each patient is randomized to; either NIRS plus ICP monitoring, or ICP monitoring alone, and how that approach influences treatment. Based on those physiological parameters and the treatment they guide, we will determine the efficacy of cerebral oxygenation monitoring by NIRS and ICP monitoring in reducing BTH and improving long-term functional outcome. A stepwise management protocol will be standardized across our study and adapted from the *Guidelines for the Management of Severe Traumatic Brain Injury* and BOOST-II.[10,25] A protocol based on ICP values and cerebral oxygenation values by PbtO2 was safely and feasibly implemented in BOOST-II.[25] We will use a similar protocol and adapt its thresholds based on NIRS criteria for BTH, instead of PbtO2, which will be described in greater detail in Chapter 3.

2.5.6 Primary and Secondary Outcomes

Our primary outcome is to determine if treatment guided by cerebral oxygenation monitoring with NIRS in addition to ICP monitoring can reduce the burden of BTH over

72 hours as compared to ICP monitoring alone. As previously discussed, BTH is a common cause of secondary brain injury after severe TBI and its extent, duration and depth is associated with negative outcomes in this population.[22,24-26] BTH has been analyzed as an outcome measure in a number of previously reviewed studies, and therefore it is reasonable to propose that median duration of BTH over both arms will be the primary measurement by which efficacy of both the intervention and control groups is determined in our study.[23,25,35]

Our secondary outcome is to determine the functional outcome in each of our groups at 6 months post initial injury utilizing the GOS-E 8-point rating system. Almost all of the studies reviewed utilize some measurement of outcome, whether it be in-hospital mortality,[13-16,30] overall mortality,[17,31,35] GOS,[23,31] or GOS-E.[17,25] GOS-E is an expanded 8-point ordinal outcome scale and provides increased sensitivity relative to the original 4-point GOS that was used in earlier studies. Using GOS-E allows for classification of a wider range of functional outcomes including death, and corresponds to a necessary sample size reduction on the order of 3-5%.[41] Additional outcomes will include number of interventions taken in each group, and incidence of serious adverse events throughout the entire study period.

2.5.7 Conclusion

The existing evidence supports the promise of cerebral oxygenation monitoring in guiding treatment regimens to lower BTH and improve functional outcomes in severe TBI. Clarifying its use in clinical practice alongside the current accepted standard of multimodal monitoring is essential to inform its efficacy and utility in treatment of this population. Exploring the possibility of monitoring cerebral oxygenation in a noninvasive

manner through NIRS is an exciting advancement in the field that has been shown to have preliminary success and is a logical choice for further investigation. Authors recognize that there are still inconsistent outcome measures, confounding, and inconclusive data regarding the utility and use of certain monitoring modalities in TBI care. Our proposed multicenter RCT will allow for control of confounding factors, a standardized outcome measure consistent with recent literature, and determination of clinical efficacy of multimodal monitoring in TBI.

2.6 References

1. Centers for Disease Control and Prevention. Report to Congress on Traumatic Brain Injury in the United States: Epidemiology and Rehabilitation. *National Center for Injury Prevention and Control; Division of Unintentional Injury Prevention.* 2015.
2. Marehbian J, Muehlschlegel S, Edlow BL, Hinson HE, Hwang DY. Medical Management of the Severe Traumatic Brain Injury Patient. *Neurocritical care.* 2017;27(3):430-446.
3. Prins M, Greco T, Alexander D, Giza CC. The pathophysiology of traumatic brain injury at a glance. *Dis Model Mech.* 2013;6(6):1307-1315.
4. Kinoshita K. Traumatic brain injury: pathophysiology for neurocritical care. *Journal of Intensive Care.* 2016;4(1):29.
5. Saatman KE, Duhaime A-C, Bullock R, et al. Classification of traumatic brain injury for targeted therapies. *Journal of neurotrauma.* 2008;25(7):719-738.
6. Al-Mufti F, Lander M, Smith B, et al. Multimodality Monitoring in Neurocritical Care: Decision-Making Utilizing Direct And Indirect Surrogate Markers. *Journal of Intensive Care Medicine.* 2018;34(6):449-463.
7. Nangunoori R, Maloney-Wilensky E, Stiefel M, et al. Brain tissue oxygen-based therapy and outcome after severe traumatic brain injury: a systematic literature review. *Neurocritical care.* 2012;17(1):131-138.
8. Chesnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. *The Journal of trauma.* 1993;34(2):216-222.
9. Robertson CS, Valadka AB, Hannay HJ, et al. Prevention of secondary ischemic insults after severe head injury. *Crit Care Med.* 1999;27(10):2086-2095.
10. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery.* 2017;80(1):6-15.
11. Tasneem N, Samaniego EA, Pieper C, et al. Brain Multimodality Monitoring: A New Tool in Neurocritical Care of Comatose Patients. *Critical care research and practice.* 2017;2017:6097265.

12. Prabhakar H, Sandhu K, Bhagat H, Durga P, Chawla R. Current concepts of optimal cerebral perfusion pressure in traumatic brain injury. *J Anaesthesiol Clin Pharmacol.* 2014;30(3):318-327.
13. Alali AS, Fowler RA, Mainprize TG, et al. Intracranial pressure monitoring in severe traumatic brain injury: results from the American College of Surgeons Trauma Quality Improvement Program. *Journal of neurotrauma.* 2013;30(20):1737-1746.
14. Talving P, Karamanos E, Teixeira PG, et al. Intracranial pressure monitoring in severe head injury: compliance with Brain Trauma Foundation guidelines and effect on outcomes: a prospective study. *Journal of neurosurgery.* 2013;119(5):1248-1254.
15. Farahvar A, Gerber LM, Chiu YL, Carney N, Hartl R, Ghajar J. Increased mortality in patients with severe traumatic brain injury treated without intracranial pressure monitoring. *Journal of neurosurgery.* 2012;117(4):729-734.
16. Gerber LM, Chiu YL, Carney N, Hartl R, Ghajar J. Marked reduction in mortality in patients with severe traumatic brain injury. *Journal of neurosurgery.* 2013;119(6):1583-1590.
17. Chesnut RM, Temkin N, Carney N, et al. A Trial of Intracranial-Pressure Monitoring in Traumatic Brain Injury. *New England Journal of Medicine.* 2012;367(26):2471-2481.
18. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. VIII. Intracranial pressure thresholds. *Journal of neurotrauma.* 2007;24 Suppl 1:S55-58.
19. Martini RP, Deem S, Treggiari MM. Targeting Brain Tissue Oxygenation in Traumatic Brain Injury. *Respiratory Care.* 2013;58(1):162.
20. Rosner MJ, Daughton S. Cerebral perfusion pressure management in head injury. *The Journal of trauma.* 1990;30(8):933-940; discussion 940-931.
21. Huang SJ, Hong WC, Han YY, et al. Clinical outcome of severe head injury using three different ICP and CPP protocol-driven therapies. *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia.* 2006;13(8):818-822.
22. Parmeet K, Saurabh S. Recent Advances in Pathophysiology of Traumatic Brain Injury. *Current Neuropharmacology.* 2018;16(8):1224-1238.
23. Oddo M, Levine JM, Mackenzie L, et al. Brain hypoxia is associated with short-term outcome after severe traumatic brain injury independently of intracranial hypertension and low cerebral perfusion pressure. *Neurosurgery.* 2011;69(5):1037-1045; discussion 1045.
24. Werner C, Engelhard K. Pathophysiology of traumatic brain injury. *Br J Anaesth.* 2007;99(1):4-9.
25. Okonkwo DO, Shutter LA, Moore C, et al. Brain Oxygen Optimization in Severe Traumatic Brain Injury Phase-II: A Phase II Randomized Trial. *Crit Care Med.* 2017;45(11):1907-1914.
26. van den Brink WA, van Santbrink H, Steyerberg EW, et al. Brain oxygen tension in severe head injury. *Neurosurgery.* 2000;46(4):868-876; discussion 876-868.

27. Maloney-Wilensky E, Gracias V, Itkin A, et al. Brain tissue oxygen and outcome after severe traumatic brain injury: a systematic review. *Crit Care Med.* 2009;37(6):2057-2063.
28. Bardt TF, Unterberg AW, Hartl R, Kiening KL, Schneider GH, Lanksch WR. Monitoring of brain tissue PO2 in traumatic brain injury: effect of cerebral hypoxia on outcome. *Acta neurochirurgica Supplement.* 1998;71:153-156.
29. Kiening KL, Hartl R, Unterberg AW, Schneider GH, Bardt T, Lanksch WR. Brain tissue pO2-monitoring in comatose patients: implications for therapy. *Neurological research.* 1997;19(3):233-240.
30. Martini RP, Deem S, Yanez ND, et al. Management guided by brain tissue oxygen monitoring and outcome following severe traumatic brain injury. *Journal of neurosurgery.* 2009;111(4):644-649.
31. Narotam PK, Morrison JF, Nathoo N. Brain tissue oxygen monitoring in traumatic brain injury and major trauma: outcome analysis of a brain tissue oxygen-directed therapy. *Journal of neurosurgery.* 2009;111(4):672-682.
32. Budohoski KP, Zweifel C, Kasprowicz M, et al. What comes first? The dynamics of cerebral oxygenation and blood flow in response to changes in arterial pressure and intracranial pressure after head injury. *Br J Anaesth.* 2012;108(1):89-99.
33. Zweifel C, Castellani G, Czosnyka M, et al. Noninvasive Monitoring of Cerebrovascular Reactivity with Near Infrared Spectroscopy in Head-Injured Patients. *Journal of neurotrauma.* 2010;27(11):1951-1958.
34. Davies DJ, Su Z, Clancy MT, et al. Near-Infrared Spectroscopy in the Monitoring of Adult Traumatic Brain Injury: A Review. *Journal of neurotrauma.* 2015;32(13):933-941.
35. Hyttel-Sorensen S, Pellicer A, Alderliesten T, et al. Cerebral near infrared spectroscopy oximetry in extremely preterm infants: phase II randomised clinical trial. *BMJ (Clinical research ed).* 2015;350:g7635.
36. Ghosh A, Elwell C, Smith M. Review article: cerebral near-infrared spectroscopy in adults: a work in progress. *Anesth Analg.* 2012;115(6):1373-1383.
37. Marmarou A, Lu J, Butcher I, et al. IMPACT database of traumatic brain injury: design and description. *Journal of neurotrauma.* 2007;24(2):239-250.
38. Steyerberg EW, Mushkudiani N, Perel P, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. *PLoS medicine.* 2008;5(8):e165; discussion e165.
39. Marshall LF, Marshall SB, Klauber MR, et al. The diagnosis of head injury requires a classification based on computed axial tomography. *Journal of neurotrauma.* 1992;9 Suppl 1:S287-292.
40. Roozenbeek B, Lingsma HF, Lecky FE, et al. Prediction of outcome after moderate and severe traumatic brain injury: external validation of the International Mission on Prognosis and Analysis of Clinical Trials (IMPACT) and Corticoid Randomisation After Significant Head injury (CRASH) prognostic models. *Crit Care Med.* 2012;40(5):1609-1617.
41. Weir J, Steyerberg EW, Butcher I, et al. Does the extended Glasgow Outcome Scale add value to the conventional Glasgow Outcome Scale? *Journal of neurotrauma.* 2012;29(1):53-58.

Chapter 3: Study Methods

3.1 Study Design

We will conduct a two-arm single blind prospective, multi-center RCT among adult hospitalized patients with severe TBI. We will compare the median time of BTH in TBI with patients being managed with a treatment protocol informed by ICP monitoring alone (control) against one informed by ICP monitoring plus cerebral oxygenation monitoring with NIRS (intervention).

3.2 Study Population and Sampling

Our source population will be derived from inpatient adults aged 18 and older with severe TBI and clinical need for ICP monitoring according to the *Guidelines for the Management of Severe Traumatic Brain Injury, 4th Edition*.[1] Eligible medical facilities include three academic, tertiary care, Level 1 trauma centers in the state of Connecticut: Yale New Haven Hospital, St. Francis Hospital and Hartford Hospital.

Inclusion criteria will consist of the following: male and female patients aged 18 and older admitted to eligible medical centers with severe TBI, not following commands after resuscitation and without influence of paralytics or sedation, clinical need for ICP monitoring according to the *Guidelines for the Management of Severe TBI, 4th edition,* and ICP monitor placement within 12 hours of presentation.

Exclusion criteria will include: penetrating brain injury, neurological exam suggestive of imminent brain death, uncertain neurologic exam, pregnancy, chest/lung injury evident on diagnostic imaging likely to produce hypoxia independent of brain injury, and inability to obtain authorized consent from subject or from legal authorized

representative (LAR). Presence of intracranial hematomas will not be excluded, and will be reported in participant baseline characteristics (Table 3).

3.3 Subject Protection and Confidentiality

This study will be reviewed by the Institutional Review Board (IRB), a commission of Yale University's Human Research Protection Program, in accordance with IRB Policy 100 PR.1. Based on the functional and cognitive status of our study population, we will act in accordance to IRB Policy 340: Participation of Individuals with Impaired Consent Capacity, which will employ additional safeguards in order to protect our participant's rights and welfare, including appropriateness and justification of inclusion, risk/benefit assessment, and the use of a surrogate or LAR for decision making on each subject's behalf. We will require written, informed consent (Appendix B) from each LAR before inclusion, which will outline the purpose of the research, study design and procedures, expected duration, risks, and potential scientific and personal benefit of their participation. In addition, the consent form will outline that each LAR has the right to withdraw from the study at any time if he/she feels unsatisfied with treatment. Continued participation consent will be obtained at or before the 6-month follow-up visit by LAR or participant if they regain cognitive capacity. All clinical information in this study will be kept confidential and research will be conducted in accordance to the Health Insurance Portability and Accountability Act (HIPAA). Additionally, all clinical and/or research staff involved in care of participants will be required to undergo HIPAA training prior to initiation of this study if they have not already done so.

3.4 Recruitment

Any patient over the age of 18 who presents to the emergency department of participating locations with mechanism of injury consistent with head trauma will be evaluated in conjunction with the trauma surgery/ neurocritical care team for inclusion criteria. Once a thorough trauma assessment has been completed, the patient is hemodynamically stable and diagnostic imaging is complete, they will be evaluated for inclusion criteria. If the patient is deemed a viable candidate, an LAR will be identified and given information and consent to enroll in the study. Since this protocol is time sensitive, it is imperative that an LAR is identified in a timely fashion, and that study guidelines, eligibility, and medical and scientific benefits of their enrollment are discussed before agreement.

3.5 Study Variables and Measures

The intervention group will include patients managed by a protocol determined by ICP and cerebral oxygenation monitoring with NIRS, while the control group will be patients managed by a protocol determined by ICP monitoring alone. Intraparenchymal ICP monitors and noninvasive NIRS monitors will be placed within 12 hours in each patient before they are subsequently randomized. In the intervention group, measurements of ICP, SctO2 (as measured by NIRS) and CPP will be monitored at 5-minute intervals, and treatment will be initiated in a stepwise fashion based on specific physiological thresholds. In the control group, the same protocol will be in place, but providers will be blinded to SctO2 and instructed to manage based on ICP and CPP alone.

The primary outcome will be to determine if treatment guided by cerebral oxygenation monitoring with NIRS plus ICP monitoring can reduce the burden of BTH

over a 72-hour period as compared to ICP monitoring alone. The secondary outcome will be functional outcome as defined by GOS-E at 6 months post initial injury, evaluated by a trained member of our research team who was blinded to the intervention group.[2] An additional secondary outcome will be number of interventions taken in each group.

3.5.1 Treatment Algorithm and Thresholds

Treatment protocols and thresholds will be adapted from the current *Guidelines for the Management of Severe Traumatic Brain Injury, 4th Edition*, as well as BOOST-II. Treatment protocol is directed at a set combination of physiological interventions that will address elevated ICP alone, or BTH and elevated ICP in conjunction. Our control and intervention groups will be managed based on specific thresholds for intervention, which include: ICP ≥ 22 mmHg; CPP ≤ 60 and ≥80 mmHg; unintentional hyperthermia or hypothermia; blood glucose <60 or >150 mg/dL; and standard hospital protocol involving correction of electrolyte abnormalities. The intervention group will be managed with the addition of a physiological threshold of BTH, defined as: SctO2 (as measured by NIRS) ≤ 50%. With utilization of medical management defined by these thresholds, the median duration of BTH over a 72-hour period will be determined among each group.

After initial stabilization, standard management will include early identification and evacuation of all traumatic hematomas and intubation and ventilation with goal of SaO_2 > 93% and $PaCO_2$ 30-40 mmHg. Increase in $PaCO_2$ is associated with an increase in cerebral blood flow, which in turn provides increased oxygenation to brain tissue, but may increase total brain volume and ICP as well.[1] Subsequent treatment protocols will be grouped based on which physiologic threshold is breached. The control group will trigger

intervention only with evidence of ICH, while our intervention group will trigger intervention if either variable is out of range.

1) *Group A:* ICP < 22mmHg, SctO2 > 50%, no treatment required.
2) *Group B:* ICP ≥ 22, SctO2 > 50%, will require treatment in both control and intervention group based on the presence of elevated ICP.
3) *Group C:* ICP < 22mmHg, SctO2 ≤ 50%, will require treatment from the intervention group based on BTH, but will not require treatment in the control group based on ICP within defined range.
4) *Group D:* ICP ≥ 22, SctO2 ≤ 50%, will require treatment from both the control and intervention groups, based on the presence of elevated ICP and BTH.

Brief physiologic elevations in ICP or reductions in SctO2 may occur throughout the 72-hour monitoring period, so our threshold to intervene will occur at 10 minutes (or two consecutive readings, measured 5 minutes apart) of continuous elevated ICP or BTH as defined by our values above. The following protocol will outline the specific interventions that will be taken to correct the variance in either ICP or SctO2, and will be taken in a stepwise approach as listed. If at any point during the protocol physiological variables return to normal range, clinicians should discontinue further intervention.

Group B Intervention: (1) elevate head of bed, (2) ensure sufficient sedation of the patient with propofol at 0.3 mg/kg/hour, titrating by 5 to 10 mcg/kg/minute every 5 to 10 minutes until proper sedation is achieved,[3] (3) ensure T <38° C, control with IV acetaminophen as needed, as fever increases metabolic demand and can increase ICP with elevated CBF, (4) transfuse 1 U pRBCs until Hgb ≥ 7 mg/dL, (5) hypertonic saline 250 mL IV bolus titrated to control ICP, while maintaining serum Na^+ 155-160 mEq/L,

(6) IV Mannitol 1g/kg 20% solution, with repeat dosing every 6-8 hours as needed at 0.25-1 g/kg and maintaining systolic BP > 90 mmHg, (7) therapeutically adjust ventilatory rate to lower $PaCO_2$ to 32-35 mmHg. If refractory, (8) repeat CT Head non-contrast to evaluate for bleeding or mass effect, then (9) consider removal of CSF at 1-2 mL/min with external ventricular drain (EVD) into the lateral ventricle on least affected side, (10) pentobarbital bolus at 5-20 mg/kg, titrated at 1-4 mg/kg/hour to achieve induced coma, and finally (11) decompressive craniectomy.

Group C Intervention: (1) elevate head of bed, (2) ensure T <38° C, control with IV acetaminophen as needed, (3) transfuse 1 U pRBCs until Hgb ≥ 7 mg/dL, (4) increase PaO_2 by adjusting ventilator parameters to increase FiO_2 to 60% initially, increase until 100% as needed based on response, (5) increase PaO_2 by increasing Positive End Expiratory Pressure (PEEP) accordingly, (6) therapeutic hyperventilation to increase $PaCO_2$ to 45-50 mmHg, (7) transfuse pRBC to goal Hgb > 10 g/dL.

Group D Intervention: (1) elevate head of bed, (2) ensure T <38° C, control with IV acetaminophen as needed, (3) pharmacologic sedation as listed in Group B protocol above, titrated to effect, (4) transfuse pRBCs until Hgb ≥ 7 mg/dL, (5) hypertonic saline 250 mL IV bolus titrated to control ICP, while maintaining serum Na^+ 155-160 mEq/L, (6) IV Mannitol 1g/kg 20% solution, with repeat dosing every 6-8 hours as needed at 0.25-1 g/kg and maintaining systolic BP > 90 mmHg, (7) obtain arterial blood gas to determine if oxygenation is within desired range, if not, increase FiO_2 by increasing PEEP accordingly (increase to 60% and up to 100% as needed based on response), (8) remove CSF at 1-2 mL/min with EVD as listed in Group B protocol. If treatments are refractory, consider (9) high dose IV Mannitol >1 g/kg 20% solution, (10) transfuse

pRBCs until Hgb ≥ 10 mg/dL, (11) attempt to increase CPP >70 mmHg with IV normal saline fluid boluses, (12) repeat CT Head non-contrast to evaluate for bleeding or mass effect and then (13) treat surgically correctable lesions with craniotomy, (14) induced hypothermia to 35-37° C using active cooling measures, (15) pentobarbital bolus at 5-20 mg/kg, titrated at 1-4 mg/kg/hour to achieve induced coma, (16) induced hypothermia to 32-34.5° C, and finally (17) decompressive craniectomy.

3.6 Assignment of Intervention and Blinding

Participants who meet inclusion criteria will be randomly allocated by computer generation to either intervention or control group in a matched, one to one ratio until sample size in each arm is achieved. To reduce the likelihood of an imbalance of clinical severity factors between groups, a covariate-adjusted randomization scheme will be used in this study.[4] The goal of randomization is to create groups that are comparable with respect to prognosis and clinical site and without selection bias. Therefore, adjustment variables will include two factors: clinical site, and probability of a poor outcome as defined by the IMPACT core model. Matching based on prognosis will occur by separating subjects into three distinct categories as determined by IMPACT core model scores and distributed evenly among both control and intervention groups. Categories will be defined as: (a) IMPACT score 0-5, (b) IMPACT score 6-10, or (c) IMPACT score 11-15. Subjects will then be evenly distributed among these three categories and the three included clinical sites. This scheme will be utilized to prevent an imbalance of participant inclusion from any one particular site, and clinical severity imbalances among groups. Otherwise, as long as participants meet inclusion criteria no preference to either group will be given based on mechanism of injury, comorbidities, gender, or physician

determined prognosis of outcome. Therefore, nonbiased representation of each group will be maintained throughout our study.

Researchers involved in our study including those collecting data, any nonessential healthcare providers, and researchers evaluating GOS-E will be blinded to allocation group. Based on the nature of our study design, it is impossible to blind individual healthcare providers responsible for implementing treatment protocols once each monitor is in place. However, treatment protocols have been controlled for, which will eliminate physician biases and limit potential confounding. Additionally, LAR's and family members will be blinded to group assignment and treatment protocol, as will be outlined in their consent agreement.

Table 3. *Participant Baseline Characteristics*

Characteristic	Control	Intervention	P-Value
Subjects (n)			
Average Age			
Male Gender (%)			
Race (%)	-	-	-
- White			
- Black			
- Hispanic			
- Other			
Average GCS (3-15)			
Average Motor Score (0-6)			
Average IMPACT score (0-15)			
Evidence of Hematoma on CT (%)			
- Epidural Hematoma (%)			
- Subdural Hematoma (%)			
- Subarachnoid Hemorrhage (%)			

3.7 Adherence and Monitoring of Adverse Outcomes

In order to reduce drop out rates after our initial outcome is assessed, recruiters from the research study will be contacting subjects and LAR's once a month via telephone or electronic mail in order to maintain communication before their scheduled

6-month follow-up. They will be contacted again one week before their scheduled follow-up appointment to ensure their participation and coordinate logistics of their appointment. Participants will be reimbursed for any travel expenses pertaining to in-person follow-up at their 6-month appointment.

During communication, participants will be asked to provide information on serious adverse events (SAE), which will be defined in our study as any medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability or incapacity.[5]

3.8 Data Collection

Once an LAR has signed consent and the subject is hemodynamically stable, an ICP monitor will be inserted 1.5-2 cm into brain parenchyma through a burr hole, with positioning close to, but not directly in the area most at risk. Subjects will then undergo a non-contrast CT Head to evaluate for proper placement of each monitor. CASMED-Foresight NIRS monitors will subsequently be placed and each respective modality will record ICP and SctO2 continuously. These values will be transmitted at 5-minute intervals over the 72-hour span and sent to a private laptop for data compilation that will be analyzed at the completion of each individual trial. Attending clinical staff will also be responsible for routine monitoring and charting of significant events, repositioning, vital signs, routine lab work, ventilator settings and arterial blood gas values when available (pH, $PaCO_2$, and PaO_2).

As described in section 3.7, research staff will maintain communication with subjects and LARs at specified intervals after the initial 72-hour monitoring period is

complete. Six months after initial presentation each subject will be evaluated by a trained researcher for functional status as outlined by GOS-E. Evaluation will be done at a private site in New Haven, CT by a single evaluator, and coordination of logistics will be done previously to ensure each subjects attendance. If a subject is in the hospital or rehabilitation facility at the time of their session and is not safe to leave, additional measures will be taken so that the evaluator can conduct the evaluation at their current location. Each session will consist of a standardized interview and physical exam focused on each subject's ability to carry out activities of daily living. A more detailed description of the assessment is included in Appendix A.

3.9 Sample Size Calculation

Sample size was calculated to detect a difference in median duration of BTH over 72 hours of continuous monitoring. Sample size was based on an adaptation of BOOST-II, an RCT that analyzed a similar outcome and population. Using this study, calculation was made using sample size statistics in Power and Precision 4. For a given effect size (population means of 0.440 vs 0.150), SD (0.310), sample sizes of 36 and 36, and alpha (0.010, 2 tailed), power is 0.903. This means that 90% of studies would be expected to yield a significant effect, rejecting the null hypothesis that the two-population means are equal. In order to properly power our study to compare medians, we will add a 15% correction (10 or more patients) to account for comparison of medians and correction for losses to follow up. Therefore, in order to achieve an alpha of 0.050 and maintain power, we estimate that we will need a sample size of 50 subjects in each study group, with a final sample size of 100 patients. The sample size calculation will be included in Appendix C.

Table 4. *Prevalence of BTH, ICH, or low CPP over 72-hour duration of trial*

Variable	Measurement of Variable
Subjects with BTH ($SctO_2$ <50%), (n)	
-Median Duration of BTH, (t)	
Subjects with ICH (ICP ≥ 22), (n)	
-Median duration of ICH, (t)	
Subjects with reduced CPP (<60 mmHg)	
- Median duration of reduced CPP, (t)	

Table 5. *Glasgow Outcome Scale- Extended (GOS-E**),** evaluated at 6 months*

Score	Interpretation
1= Dead	Dead
2= Vegetative State	Absence of awareness of self and environment
3= Lower Severe Disability	Needs full assistance in ADLs
4= Upper Severe Disability	Needs partial assistance in ADLs
5= Lower Moderate Disability	Independent, but cannot resume work/school or all previous social activities
6= Upper Moderate Disability	Some disability exists, but can partly resume work or previous activities
7= Lower Good Recovery	Minor physical or mental deficits that affect daily life
8= Upper Good Recovery	Full recovery or minor deficits that do not affect daily life

Table 6. *Number of interventions required in each group throughout 72-hour period*

Assignment Group and Type of Intervention	Number of Interventions (total, average per subject in group)
Control	-
- Group B protocol	
- Group D protocol	
Intervention	-
- Group B protocol	
- Group C protocol	
- Group D protocol	

3.10 Analysis

Statistical analysis will occur with an intention-to-treat principle and be performed using Mann-Whitney U for nonparametric variables for both our primary and secondary outcomes. This statistical analysis is supported by previously reviewed studies that have analyzed similar associations. Primary outcome will be to determine if

treatment guided by cerebral oxygenation monitoring with NIRS in addition to ICP monitoring can reduce the median duration of BTH burden over 72 hours as compared to ICP monitoring alone. SctO2 values will be recorded continuously and logged every 5 minutes in order to obtain cerebral oxygenation data over a 72-hour span.

Our secondary outcome will be to determine functional outcome of each subject in each of our groups at 6 months post initial injury utilizing the GOS-E on an 8-point rating system. Each subject will receive a score by a trained researcher who will be blinded to group allocation and interventions taken throughout the study. Additional outcomes that will be evaluated include frequency and type of interventions by assignment group and occurrence and type of SAE.

3.11 Timeline and Resources

Our study will be performed over a two-year time period beginning on July 1, 2020. This time frame includes recruitment and training of clinical staff, patient enrollment and data collection, and outpatient follow-up. Anticipated timeline consists of: recruitment and training of appropriate clinical staff across three locations (months 0-2); phase 1 (and phase 2 dependent on timing of subject recruitment) of study protocol with rolling recruitment until sample size is reached (months 2-18); completion of phase 2 of study protocol (months 18-24). Phase 1 refers to the initial study protocol including inpatient management and 72-hour monitoring and treatment period, while phase 2 refers to the time period after 72 hours and the 6-month follow up visit. The last subject must be enrolled no later than month 18 to ensure that each subject has a full 6 months before follow up. Statistical analysis will occur immediately after the 6-month follow-up appointments are completed following month 24 and are anticipated to take 1-2 months.

Study protocol will be initiated immediately after each subject is hemodynamically stable and consent is obtained from an LAR and will be complete after a total of 6 months and 3 days. Sufficient supply of monitors, ventilators and support equipment at each location must be confirmed before any subject is enrolled. An outpatient exam site will be confirmed in New Haven, CT for 6-month follow-up appointments provided by the Yale New Haven Hospital Department of Neurology.

Study personnel at each site will include: one attending physician, two advanced practice practitioners (physician assistants or nurse practitioners) and four nurses among both trauma and intensive care units that will be recruited and trained in our study protocol to ensure 24-hour coverage. Additionally, a research assistant for data collection, a statistician and a GOS-E evaluator will be trained in pertinent aspects of our study.

3.12 References

1. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery.* 2017;80(1):6-15.
2. Olsen A. *Cognitive Control Function and Moderate-to-Severe Traumatic Brain Injury: Functional and Structural Brain Correlates* 2014.
3. Lassen NA, Christensen MS. PHYSIOLOGY OF CEREBRAL BLOOD FLOW. *Br J Anaesth.* 1976;48(8):719-734.
4. Okonkwo DO, Shutter LA, Moore C, et al. Brain Oxygen Optimization in Severe Traumatic Brain Injury Phase-II: A Phase II Randomized Trial. *Crit Care Med.* 2017;45(11):1907-1914.
5. Dewan Y, Komolafe EO, Mejia-Mantilla JH, Perel P, Roberts I, Shakur H. CRASH-3 - tranexamic acid for the treatment of significant traumatic brain injury: study protocol for an international randomized, double-blind, placebo-controlled trial. *Trials.* 2012;13:87.

Chapter 4: Conclusion

4.1 Study Advantages

The major advantages of our proposed study lie primarily in its design, methodology, and specific predetermined evidence-based treatment protocol.[1,2] To date there have been no large, prospective clinical trials examining noninvasive monitoring in severe TBI, and no RCTs specifically analyzing cerebral NIRS as a monitoring technique in adults within this population. Our proposed multicenter RCT aims to determine whether cerebral oxygenation monitoring with NIRS can reduce the burden of BTH and be incorporated into a standardized multimodal monitoring approach to guiding treatment of severe TBI.

Most relevant studies on this matter are observational in nature, are subject to physician biases,[3-6] and contain a high prevalence of confounding factors. By matching control and intervention groups among clinical sites and IMPACT prognostic scoring, our study will drastically reduce the potential for confounding. Additionally, providing proper training for clinical staff and implementing a fixed treatment protocol triggered by specific, predetermined physiological variables will limit variability in treatment among patients across multiple clinical locations. These measures will serve to increase our study's internal validity and reduce clinician biases.

Previous studies have been significantly limited by sample size, however with utilization of three large, Level I trauma centers in CT over a 16-month period we will ensure enrollment of an adequate sample size that will be generalizable to a larger population. Our study has feasibly proposed a high quality, evidence-based protocol that can potentially influence current guidelines and determine whether cerebral oxygenation

monitoring with NIRS is a justified addition to the current guidelines for multimodal monitoring of TBI.

4.2 Study Disadvantages

One major disadvantage of our study is the variability of injury. Although each subject will be enrolled based on satisfaction of inclusion criteria, each mechanism of injury, subsequent brain trauma, intracranial bleeding, and other sequelae of traumatic injury are inherently different and cannot reasonably be controlled for based on our ideal sample size and time restrictions. Importantly, significant scalp swelling and the presence of intracranial hematomas can contaminate the NIRS signal and lead to inconsistent measurements, and cannot be controlled for based on the nature of our population.[7]

Similar to a 2015 RCT by Hyttel-Sorensen, et al., a significant disadvantage of our study design is that blinding of group allocation to trained clinical staff is impossible.[8] To execute the treatment protocol as designed, clinicians must know to treat based on group allocation, and therefore cannot be blinded. However, since each protocol is predetermined and physician bias is minimal, this should not have a significant effect on our results. Additionally, in many cases the responsibility to maintain communication with researchers and coordinate 6-month follow-up visits is dependent on each subject's LAR. This introduces burden to these representatives who are not directly participating in the study and may potentially increase loss to follow-up or have a negative effect on maintaining communication with each subject during the follow-up period.

4.3 Clinical and Public Health Significance

TBI is a leading cause of death and disability in the United States, accounting for prolonged hospital admissions, financial stressors, and long-term reductions in functional

status and quality of life. Current guidelines are focused on monitoring and treating physiological variations in ICP and CPP in order to prevent secondary brain injury, but there is a lack of level I prospective clinical evidence proving their efficacy. Cerebral oxygenation monitoring with and without NIRS has also been examined in recent literature as an addition to a multimodal monitoring strategy in managing these patients, but research is inconclusive and techniques are imperfect. Considering the prevalence of TBI and its potentially devastating effects, there is a clinical need for consensus on monitoring techniques in management of these patients.

By proposing a prospective, multicenter RCT we aim to determine if cerebral oxygenation with NIRS is a suitable technique to reliably monitor cerebral oxygenation and reduce BTH in severe TBI patients. Its efficacy in this trial will potentially determine if it is a safe, noninvasive alternative to invasive cerebral oxygenation monitoring, and if it is of benefit in guiding management in our target population. Ultimately, our study will help to clarify the current guidelines for monitoring and managing patients with severe TBI and determine whether cerebral oxygenation monitoring with NIRS is suitable for inclusion into a multimodal management approach for these patients.

4.4 References

1. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery.* 2017;80(1):6-15.
2. Okonkwo DO, Shutter LA, Moore C, et al. Brain Oxygen Optimization in Severe Traumatic Brain Injury Phase-II: A Phase II Randomized Trial. *Crit Care Med.* 2017;45(11):1907-1914.
3. Farahvar A, Gerber LM, Chiu YL, Carney N, Hartl R, Ghajar J. Increased mortality in patients with severe traumatic brain injury treated without intracranial pressure monitoring. *Journal of neurosurgery.* 2012;117(4):729-734.
4. Talving P, Karamanos E, Teixeira PG, et al. Intracranial pressure monitoring in severe head injury: compliance with Brain Trauma Foundation guidelines and

effect on outcomes: a prospective study. *Journal of neurosurgery.* 2013;119(5):1248-1254.
5. Alali AS, Fowler RA, Mainprize TG, et al. Intracranial pressure monitoring in severe traumatic brain injury: results from the American College of Surgeons Trauma Quality Improvement Program. *Journal of neurotrauma.* 2013;30(20):1737-1746.
6. Gerber LM, Chiu YL, Carney N, Hartl R, Ghajar J. Marked reduction in mortality in patients with severe traumatic brain injury. *Journal of neurosurgery.* 2013;119(6):1583-1590.
7. Tasneem N, Samaniego EA, Pieper C, et al. Brain Multimodality Monitoring: A New Tool in Neurocritical Care of Comatose Patients. *Critical care research and practice.* 2017;2017:6097265.
8. Hyttel-Sorensen S, Pellicer A, Alderliesten T, et al. Cerebral near infrared spectroscopy oximetry in extremely preterm infants: phase II randomised clinical trial. *BMJ (Clinical research ed).* 2015;350:g7635.

Appendices

Appendix A. Glasgow Outcome Scale- Extended (GOS-E)

Score	Interpretation
1= Dead	Dead
2= Vegetative State	Absence of awareness of self and environment
3= Lower Severe Disability	Needs full assistance in ADLs
4= Upper Severe Disability	Needs partial assistance in ADLs
5= Lower Moderate Disability	Independent, but cannot resume work/school or all previous social activities
6= Upper Moderate Disability	Some disability exists, but can partly resume work or previous activities
7= Lower Good Recovery	Minor physical or mental deficits that affect daily life
8= Upper Good Recovery	Full recovery or minor deficits that do not affect daily life

Consisting of: (1) Detailed client interview (2) Collateral interviews (in person or questionnaires) (3) Functional Testing (4) Synthesis of Data

Expanded Description of Categories:
8 levels are in the scale: Minimum score = 1, maximum score = 8

Level 1: Dead

Level 2: Vegetative State- condition of unawareness with only reflex responses but with periods of spontaneous eye opening

Level 3 and 4: Lower and Upper Severe Disability – Patient who is dependent for daily support for mental or physical disability, or usually a combination of both. If the patient can be left alone for more than 8 hours at home, it is upper level of severe disability (4). If patient cannot be left at home for more than 8 hours, it is considered lower level of severe disability (3)

Level 5 and 6: Low and Moderate Disability- patients have some disability such as aphasia, hemiparesis or epilepsy and/or deficits of memory or personality but are able to care for themselves. They are independent at home but dependent outside. If they are able to return to work with or without special arrangement, they are categorized as upper moderate disability (6). If they are unable to return to work, they are categorized as lower moderate disability (5).

Level 7 and 8: Lower and Upper Good Recovery- Resumption of normal life with the capacity to work even if pre-injury status has not been achieved. Some patients have minor neurological or psychological deficits. If these deficits are not disabling, then they are categorized as upper good recovery (8). If these deficits are disabling, they are categorized as lower good recovery (7).

Appendix B. Sample HIC Consent Form
Created using 200 FR.7 HIC Consent For Participation in a Research Project Template

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

200 FR. 7 (2016-1)

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL
HARTFORD HEALTHCARE- HARTFORD HOSPITAL
TRINITY HEALTHCARE- ST. FRANCIS HOSPITAL AND MEDICAL CENTER

Study Title: Cerebral Oxygenation Monitoring by Near-Infrared Spectroscopy in Severe Traumatic Brain Injury
Principal Investigator: Emily J. Gilmore, MD
Co-Principal Investigator: Drew H. Zimmerman, PA-SII
Funding Source: The Brain Trauma Foundation

Invitation to Participate and Brief Description of the Project

You or the person you legally represent are invited to participate in a research study called Cerebral Oxygenation Monitoring by Near Infrared Spectroscopy in Severe Traumatic Brain Injury. This form is addressed to the person who will enroll in the study but should also be reviewed by a legally authorized representative for consent if applicable. This study is designed to determine the efficacy of a new monitoring technique employed in patients with severe traumatic brain injury that will help guide treatment and potentially improve functional outcomes. You have been invited to participate because you have been diagnosed with a severe traumatic brain injury and meet our study's inclusion criteria. About 100 persons will be asked to participate in the study over a 2-year time period.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits and possible alternative treatments. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

If you agree to participate in this study, you will be randomly assigned to one of two treatment groups: (a) control group that will monitor you based on current guidelines, and, (b) an experimental group that will monitor you based on current guidelines plus a noninvasive measurement tool to assess your brain's oxygen status. If placed in our control group, you will be monitored and then treated with a predetermined protocol

designed according to the current *Guidelines for Management of Severe Traumatic Brain Injury, 4th Edition*, if warranted. In our experimental group, the same procedures will apply, with addition of an extra monitoring strategy that will help guide a treatment protocol with additional steps based on those values.

At the time of reading this consent, you have been brought to one of three participating facilities included in this study (Yale-New Haven Hospital, Hartford Hospital, or St. Francis Hospital) for evaluation of a traumatic head injury. Your injury has been categorized as severe by our clinical staff and based on current guidelines you meet clinical criteria for intracranial pressure monitoring.

Regardless of which group you are randomized to, you will undergo a procedure that involves placing an intracranial pressure monitor, which is the standard of care for managing patients with severe traumatic brain injury. We will sedate you with general anesthesia and place a probe through a small hole into the skull. To insert the probe a small cut is made in the scalp and a hole is drilled into the skull beneath the cut. The probe is placed 1.5-2cm into the brain tissue and positioned close to, but not directly in, the area injured. The probe is connected to an electronic measuring device that monitors the brain pressure. You will then undergo a computed tomography (CT) scan to ensure proper placement of the monitor. The cut will be closed with sutures or staples after the trial and once it is no longer needed. You will not be aware of this procedure once under sedation and will not experience any pain or physical sensation. You will be intubated and placed on a ventilator before proceeding.

If you are randomly selected to participate in our experimental group, near infrared spectroscopy detectors will be placed on your skull for additional monitoring of your brain tissue oxygen levels. These detectors are stickers that are noninvasive and require no surgical intervention. They will have multiple wires attached to them that will transmit the information to our monitor for reading. If you are in our control group the same monitors will be placed, but clinical staff will be instructed not to use information from the near infrared spectroscopy detectors in determining your care. Throughout the study, you and your family will not be aware of which group you have been selected to.

All monitors will be placed within 12 hours of your initial presentation to the hospital, and once in place, information from them will be recorded for 72 hours. Over that time period, a predetermined, evidence-based treatment protocol will be implemented for any monitored value that is out of range. Treatment protocols are dependent on which group you will be randomized to but will be consistent among all participants in the study. After the 72-hour study period is complete, near infrared spectroscopy monitors will be removed, and your treatment and subsequent hospital course will be directed by individual hospital protocol.

After the 72-hour period is complete, investigators will contact you and/or your LAR at scheduled intervals each month via e-email or phone call. During these periods of communication, you will be asked to provide information on any location changes or moves, hospital discharge or readmission, significant adverse events, or death. If you

remain admitted or are readmitted to any of our participating hospitals, we will monitor your electronic medical record for updates.

6 months after your hospital admission you will be asked to be present for a follow up appointment with one of our researchers at our clinic in New Haven, Connecticut. One week before this meeting, an investigator will contact you and review logistics of travel and will reimburse you for any costs accrued while traveling to your appointment. At this appointment, you will be asked a series of questions that will indicate your functional ability to work and carry out activities of daily living, and then will undergo a physical exam.

A description of this study is available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. The purpose of this database is to allow everyone to see information on what studies are being done, and what studies have been done. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Risks and Inconveniences

(1) *Intracranial Pressure Monitoring:* There are risks and complications with this procedure. They include but are not limited to the following:

- Common risks and complications (more than 5%) include: minor pain, bruising and/or infection from IV cannula site. This may require treatment with antibiotics.
- Uncommon risks and complications (1-5%) include:
- Infection, requiring antibiotics and further treatment.
- Bleeding can occur and may require a return to the operating room. Bleeding is more common if you have been taking blood-thinning drugs such as Warfarin, Aspirin, Clopidogrel (Plavix) or Dipyridamole.
- Heart attack due to the strain on the heart.
- Stroke or stroke like complications may occur causing neurological deficits such as weakness in the face, arms and legs. This could be temporary or permanent.
- Fluid leakage from around the brain may occur through the wound after the operation. This may require further surgery.
- Inadequate placement or malfunction of the probe and/or device. This may require further surgery.
- Blood clot in the leg (DVT) causing pain and swelling. In rare cases part of the clot may break off and go to the lungs.
- Rare risks and complications (less than 1%) include:
- Seizure which may require medication
- Injury to the brain, important nerves or blood vessels. This can lead to stroke like complications.
- Death as a result of this procedure is very rare.

(2) *Near Infrared Spectroscopy Monitoring*: There are minimal to no risks involved in this monitoring technique. There is no need for injection of any medication, IV access or surgical intervention. Areas of hair may need to be shaved in order to place the detectors in proper position.

(3) *Treatment Protocols:* There are potential risks associated with each specific intervention outlined in our treatment protocol. You will only receive treatment if necessary, as outlined by our predetermined protocol.

- Medications given through IV cannula site may commonly result in minor pain, bruising and/or infection from IV cannula site, which may require treatment with antibiotics.
- Allergic reactions to medications are rare but possible, and allergies will be reviewed with you and your clinical team before proceeding with any treatment.
- Known risks of blood transfusions include but are not limited to: infection or irritation where the needle is placed, temporary reactions such as fever, chills, or skin rashes. Other rare but more serious complications may occur such as allergic reactions, heart failure due to fluid overload, acute pulmonary edema (fluid leaking into the lungs), shock, or death. Transfusions of blood or blood products involve a small risk of transmission of diseases such as Hepatitis B (~1 in 1,000,000), Hepatitis C (~1 in 1,200,000), and HIV/AIDS (~1 in 1,500,000). There is also a small risk of bacterial infection when blood products are transfused.
- Surgical intervention (placing an external ventricular drain (EVD), decompressive craniectomy, or evacuation or newly formed brain bleeding) will only be taken if absolutely necessary, and risks and benefits of these procedures will be discussed and consented before proceeding on an individual basis.

Benefits

There are potential benefits resulting from the study including better recovery from injury and faster return to baseline function, reduced length of hospital stay, reduced permanent disability, and improved long term functional outcomes. This study may also provide important clinical information that will help to clarify current guidelines for monitoring and management of severe traumatic brain injury.

Economic Considerations

No compensation will be provided to participants or LARs in this study. One free parking voucher will be provided for each LAR throughout the duration of the study, if applicable. Participants will be reimbursed for any travel expenses pertaining to in person follow up at their 6-month appointment.

Treatment Alternatives

If you choose not to participate in this study, treatment alternatives do exist. These alternatives include the use of an ICP monitor and physician clinical judgment in

treatment, however you will not have the opportunity to be managed based on cerebral oxygen levels with a NIRS monitor. You may choose not to participate.

Confidentiality and Privacy

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or state law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. Information will be kept confidential by using only identification numbers on study forms, storing signed forms in locked cabinets, and password protecting data stored on a computer. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific permission for this activity is obtained.

We understand that information about your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that identifies your personal health information. This may include information that might directly identify you, such as his or her name and address, telephone number, and email address, or mobile phone number. This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your identifying information with a code that does not directly identify you. The principal investigator will keep a link that identifies you and your coded information, and this link will be kept secure and available only to the principal investigator or selected members of the research team. Any information that can identify you will remain confidential. Information will be kept confidential by using only identification numbers on study forms, storing signed forms in locked cabinets, and password protecting data stored on a computer. The research team will only give this coded information to others to carry out this research study. The link to your personal information will be kept for 5 years, after which time the link will be destroyed and the data will become anonymous. The data will be kept in this anonymous form indefinitely.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staffs at the Yale School of Medicine, Hartford Hospital and St. Francis Hospital are required to comply with HIPAA and to ensure the confidentiality of your information.

Representatives from the Yale Human Research Protection Program, the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects) may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.

Voluntary Participation and Withdrawal

You are free to choose not to participate in this study. Your health care outside the study, the payment for your health care, and your health care benefits will not be affected if you

do not agree to participate. However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study. You do not give up any of your legal rights by signing this form.

Withdrawing from the Study

If you become a subject, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you or your LAR can call a member of the research team at any time and tell them that you no longer want to take part. This will cancel any future interventions or appointments.

The researchers may withdraw you from participating in the research if necessary. This will only occur if continuation is considered unsafe or if there is a breach of confidentiality or blinding. If you choose not to participate or if you withdraw it will not harm your relationship with your own doctors or with the Yale School of Medicine, Yale New-Haven Hospital, Hartford Hospital or St. Francis Hospital.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the permission form carefully – if you feel is necessary – before you make a decision.

Authorization

My LAR or I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

You do not give up any of your legal rights by signing this form.

Name of Subject:_____

Signature:_____

Date:_____

or

Name of Legally Authorized Representative:_____

Signature:_____

Date:_____

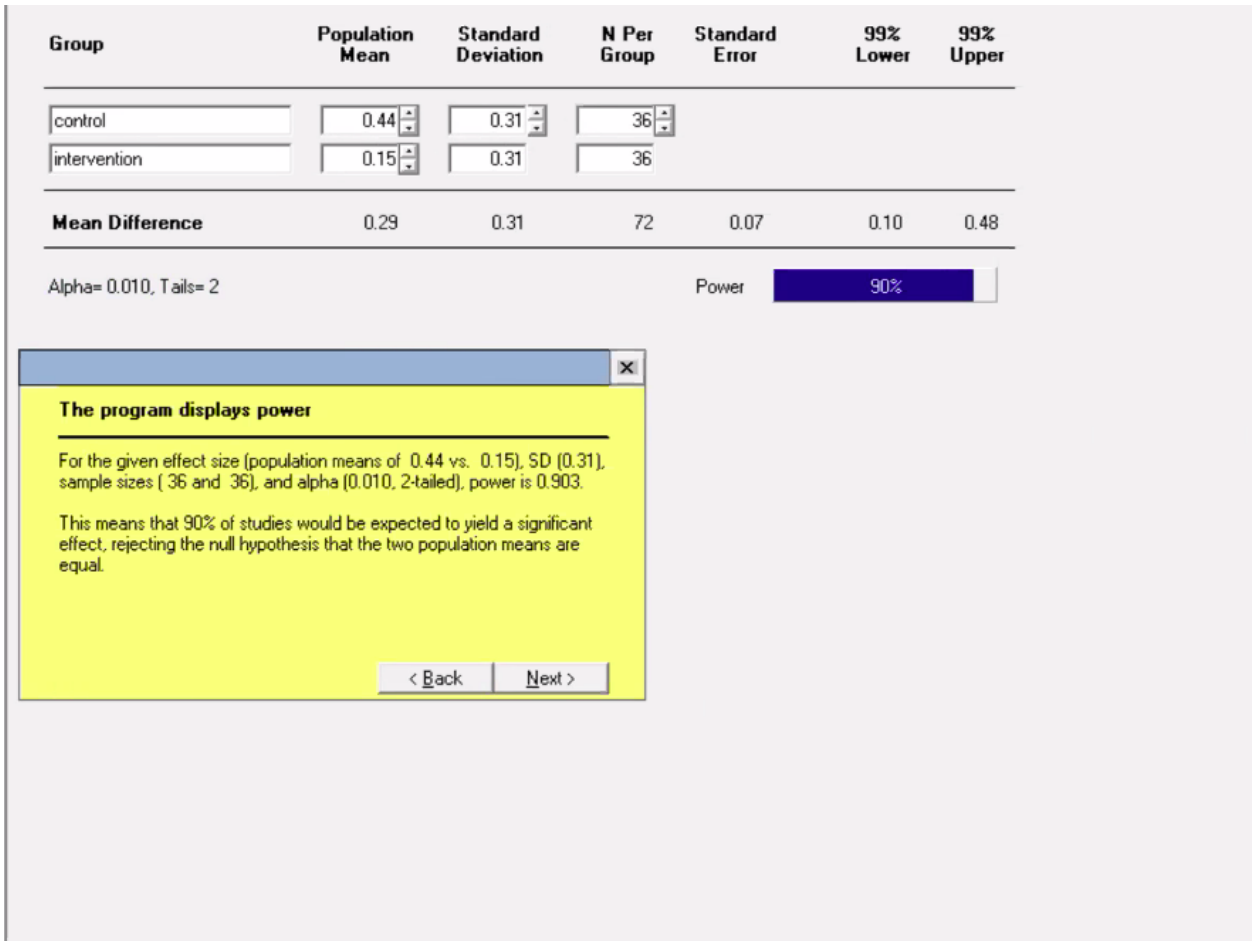
_____ _____

Signature of Person Obtaining Consent Date

If you have further questions about this project or if you have a research-related problem, you may contact the **Principal Investigator, Emily J. Gilmore, MD** at (***) ***-****or the Co-Principal Investigator, **Drew H. Zimmerman, PA-SII** at (***) ***-****.

If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions, offer input, discuss situations in the event that a member of the research team is not available, or if you have any questions concerning your rights as a research subject, you may contact the Human Investigation Committee at (203) 785-4688.

Appendix C. Sample Size Calculation



Calculated using:

Power and Precision. Version 4.0. Biostat, Inc. Englewood, New Jersey.

Bibliography

1. Al-Mufti F, Lander M, Smith B, et al. Multimodality Monitoring in Neurocritical Care: Decision-Making Utilizing Direct And Indirect Surrogate Markers. *Journal of Intensive Care Medicine.* 2018;34(6):449-463.
2. Al-Rawi PG, Kirkpatrick PJ. Tissue oxygen index: thresholds for cerebral ischemia using near-infrared spectroscopy. *Stroke.* 2006;37(11):2720-2725.
3. Alali AS, Fowler RA, Mainprize TG, et al. Intracranial pressure monitoring in severe traumatic brain injury: results from the American College of Surgeons Trauma Quality Improvement Program. *Journal of neurotrauma.* 2013;30(20):1737-1746.
4. Ayaz H, Izzetoglu M, Izzetoglu K, Onaral B. Chapter 3 - The Use of Functional Near-Infrared Spectroscopy in Neuroergonomics. In: Ayaz H, Dehais F, eds. *Neuroergonomics.* Academic Press; 2019:17-25.
5. Bardt TF, Unterberg AW, Hartl R, Kiening KL, Schneider GH, Lanksch WR. Monitoring of brain tissue PO2 in traumatic brain injury: effect of cerebral hypoxia on outcome. *Acta neurochirurgica Supplement.* 1998;71:153-156.
6. Bohman LE, Heuer GG, Macyszyn L, et al. Medical management of compromised brain oxygen in patients with severe traumatic brain injury. *Neurocritical care.* 2011;14(3):361-369.
7. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. VIII. Intracranial pressure thresholds. *Journal of neurotrauma.* 2007;24 Suppl 1:S55-58.
8. Budohoski KP, Zweifel C, Kasprowicz M, et al. What comes first? The dynamics of cerebral oxygenation and blood flow in response to changes in arterial pressure and intracranial pressure after head injury. *Br J Anaesth.* 2012;108(1):89-99.
9. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery.* 2017;80(1):6-15.
10. Centers for Disease Control and Prevention. Report to Congress on Traumatic Brain Injury in the United States: Epidemiology and Rehabilitation. *National Center for Injury Prevention and Control; Division of Unintentional Injury Prevention.* 2015.
11. Chesnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. *The Journal of trauma.* 1993;34(2):216-222.
12. Chesnut RM, Temkin N, Carney N, et al. A Trial of Intracranial-Pressure Monitoring in Traumatic Brain Injury. *New England Journal of Medicine.* 2012;367(26):2471-2481.
13. Davies DJ, Su Z, Clancy MT, et al. Near-Infrared Spectroscopy in the Monitoring of Adult Traumatic Brain Injury: A Review. *Journal of neurotrauma.* 2015;32(13):933-941.
14. Dewan Y, Komolafe EO, Mejia-Mantilla JH, Perel P, Roberts I, Shakur H. CRASH-3 - tranexamic acid for the treatment of significant traumatic brain injury: study protocol for an international randomized, double-blind, placebo-controlled trial. *Trials.* 2012;13:87.

15. Di Domenico SI, Rodrigo AH, Dong M, et al. Chapter 28 - Functional Near-Infrared Spectroscopy: Proof of Concept for Its Application in Social Neuroscience. In: Ayaz H, Dehais F, eds. *Neuroergonomics.* Academic Press; 2019:169-173.
16. Drenckhahn C, Koch SP, Dümmler J, Kohl-Bareis M, Steinbrink J, Dreier JP. A validation study of the use of near-infrared spectroscopy imaging in primary and secondary motor areas of the human brain. *Epilepsy & Behavior.* 2015;49:118-125.
17. Farahvar A, Gerber LM, Chiu YL, Carney N, Hartl R, Ghajar J. Increased mortality in patients with severe traumatic brain injury treated without intracranial pressure monitoring. *Journal of neurosurgery.* 2012;117(4):729-734.
18. Garvey AA, Kooi EMW, Smith A, Dempsey EM. Interpretation of Cerebral Oxygenation Changes in the Preterm Infant. *Children (Basel, Switzerland).* 2018;5(7).
19. Gerber LM, Chiu YL, Carney N, Hartl R, Ghajar J. Marked reduction in mortality in patients with severe traumatic brain injury. *Journal of neurosurgery.* 2013;119(6):1583-1590.
20. Ghosh A, Elwell C, Smith M. Review article: cerebral near-infrared spectroscopy in adults: a work in progress. *Anesth Analg.* 2012;115(6):1373-1383.
21. Godoy DA, Lubillo S, Rabinstein AA. Pathophysiology and Management of Intracranial Hypertension and Tissular Brain Hypoxia After Severe Traumatic Brain Injury: An Integrative Approach. *Neurosurgery Clinics of North America.* 2018;29(2):195-212.
22. Heuer GG, Smith MJ, Elliott JP, Winn HR, LeRoux PD. Relationship between intracranial pressure and other clinical variables in patients with aneurysmal subarachnoid hemorrhage. *Journal of neurosurgery.* 2004;101(3):408-416.
23. Huang SJ, Hong WC, Han YY, et al. Clinical outcome of severe head injury using three different ICP and CPP protocol-driven therapies. *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia.* 2006;13(8):818-822.
24. Hyttel-Sorensen S, Pellicer A, Alderliesten T, et al. Cerebral near infrared spectroscopy oximetry in extremely preterm infants: phase II randomised clinical trial. *BMJ (Clinical research ed).* 2015;350:g7635.
25. Jacobsson L, Lexell J. Functioning and disability from 10 to 16 years after traumatic brain injury. *Acta Neurologica Scandinavica.* 2019;n/a(n/a).
26. Jaeger M, Schuhmann MU, Soehle M, Nagel C, Meixensberger J. Continuous monitoring of cerebrovascular autoregulation after subarachnoid hemorrhage by brain tissue oxygen pressure reactivity and its relation to delayed cerebral infarction. *Stroke.* 2007;38(3):981-986.
27. Kiening KL, Hartl R, Unterberg AW, Schneider GH, Bardt T, Lanksch WR. Brain tissue pO2-monitoring in comatose patients: implications for therapy. *Neurological research.* 1997;19(3):233-240.
28. Kinoshita K. Traumatic brain injury: pathophysiology for neurocritical care. *Journal of Intensive Care.* 2016;4(1):29.
29. Klein SP, Depreitere B, Meyfroidt G. How I monitor cerebral autoregulation. *Critical care (London, England).* 2019;23(1):160-160.

30. Lassen NA, Christensen MS. PHYSIOLOGY OF CEREBRAL BLOOD FLOW. *Br J Anaesth.* 1976;48(8):719-734.
31. Lee JK, Kibler KK, Benni PB, et al. Cerebrovascular Reactivity Measured by Near-Infrared Spectroscopy. *Stroke.* 2009;40(5):1820-1826.
32. Maloney-Wilensky E, Gracias V, Itkin A, et al. Brain tissue oxygen and outcome after severe traumatic brain injury: a systematic review. *Crit Care Med.* 2009;37(6):2057-2063.
33. Marehbian J, Muehlschlegel S, Edlow BL, Hinson HE, Hwang DY. Medical Management of the Severe Traumatic Brain Injury Patient. *Neurocritical care.* 2017;27(3):430-446.
34. Martini RP, Deem S, Yanez ND, et al. Management guided by brain tissue oxygen monitoring and outcome following severe traumatic brain injury. *Journal of neurosurgery.* 2009;111(4):644-649.
35. Mokri B. The Monro-Kellie hypothesis: applications in CSF volume depletion. *Neurology.* 2001;56(12):1746-1748.
36. Nangunoori R, Maloney-Wilensky E, Stiefel M, et al. Brain tissue oxygen-based therapy and outcome after severe traumatic brain injury: a systematic literature review. *Neurocritical care.* 2012;17(1):131-138.
37. Narotam PK, Morrison JF, Nathoo N. Brain tissue oxygen monitoring in traumatic brain injury and major trauma: outcome analysis of a brain tissue oxygen-directed therapy. *Journal of neurosurgery.* 2009;111(4):672-682.
38. Oddo M, Levine JM, Mackenzie L, et al. Brain hypoxia is associated with short-term outcome after severe traumatic brain injury independently of intracranial hypertension and low cerebral perfusion pressure. *Neurosurgery.* 2011;69(5):1037-1045; discussion 1045.
39. Okonkwo DO, Shutter LA, Moore C, et al. Brain Oxygen Optimization in Severe Traumatic Brain Injury Phase-II: A Phase II Randomized Trial. *Crit Care Med.* 2017;45(11):1907-1914.
40. Olsen A. *Cognitive Control Function and Moderate-to-Severe Traumatic Brain Injury: Functional and Structural Brain Correlates* 2014.
41. Parmeet K, Saurabh S. Recent Advances in Pathophysiology of Traumatic Brain Injury. *Current Neuropharmacology.* 2018;16(8):1224-1238.
42. Pascual JL, Georgoff P, Maloney-Wilensky E, et al. Reduced brain tissue oxygen in traumatic brain injury: are most commonly used interventions successful? *The Journal of trauma.* 2011;70(3):535-546.
43. Prabhakar H, Sandhu K, Bhagat H, Durga P, Chawla R. Current concepts of optimal cerebral perfusion pressure in traumatic brain injury. *J Anaesthesiol Clin Pharmacol.* 2014;30(3):318-327.
44. Prins M, Greco T, Alexander D, Giza CC. The pathophysiology of traumatic brain injury at a glance. *Dis Model Mech.* 2013;6(6):1307-1315.
45. Robertson CS, Valadka AB, Hannay HJ, et al. Prevention of secondary ischemic insults after severe head injury. *Crit Care Med.* 1999;27(10):2086-2095.
46. Roh D, Park S. Brain Multimodality Monitoring: Updated Perspectives. *Curr Neurol Neurosci Rep.* 2016;16(6):56-56.
47. Rosner MJ, Daughton S. Cerebral perfusion pressure management in head injury. *The Journal of trauma.* 1990;30(8):933-940; discussion 940-931.

48. Rosner MJ, Rosner SD, Johnson AH. Cerebral perfusion pressure: Management protocol and clinical results. *Journal of neurosurgery.* 1995;83(6):949-962.
49. Saatman KE, Duhaime A-C, Bullock R, et al. Classification of traumatic brain injury for targeted therapies. *Journal of neurotrauma.* 2008;25(7):719-738.
50. Steiner LA, Pfister D, Strebel SP, Radolovich D, Smielewski P, Czosnyka M. Near-infrared spectroscopy can monitor dynamic cerebral autoregulation in adults. *Neurocritical care.* 2009;10(1):122-128.
51. Sternbach GL. The Glasgow coma scale. *The Journal of emergency medicine.* 2000;19(1):67-71.
52. Stewart C, Haitsma I, Zador Z, et al. The new Licox combined brain tissue oxygen and brain temperature monitor: assessment of in vitro accuracy and clinical experience in severe traumatic brain injury. *Neurosurgery.* 2008;63(6):1159-1164; discussion 1164-1155.
53. Steyerberg EW, Mushkudiani N, Perel P, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. *PLoS medicine.* 2008;5(8):e165; discussion e165.
54. Stiefel MF, Spiotta A, Gracias VH, et al. Reduced mortality rate in patients with severe traumatic brain injury treated with brain tissue oxygen monitoring. *Journal of neurosurgery.* 2005;103(5):805-811.
55. Stiefel MF, Udoetuk JD, Spiotta AM, et al. Conventional neurocritical care and cerebral oxygenation after traumatic brain injury. *Journal of neurosurgery.* 2006;105(4):568-575.
56. Suzuki S, Takasaki S, Ozaki T, Kobayashi Y. Tissue oxygenation monitor using NIR spatially resolved spectroscopy. Paper presented at: Proceedings of the 1999 Optical Tomography and Spectroscopy of Tissue III1999; Bellingham, WA, United States
San Jose, CA, USA.
57. Talving P, Karamanos E, Teixeira PG, et al. Intracranial pressure monitoring in severe head injury: compliance with Brain Trauma Foundation guidelines and effect on outcomes: a prospective study. *Journal of neurosurgery.* 2013;119(5):1248-1254.
58. Tasneem N, Samaniego EA, Pieper C, et al. Brain Multimodality Monitoring: A New Tool in Neurocritical Care of Comatose Patients. *Critical care research and practice.* 2017;2017:6097265.
59. Thurman DJ, Alverson C, Dunn KA, Guerrero J, Sniezek JE. Traumatic brain injury in the United States: A public health perspective. *The Journal of head trauma rehabilitation.* 1999;14(6):602-615.
60. van den Brink WA, van Santbrink H, Steyerberg EW, et al. Brain oxygen tension in severe head injury. *Neurosurgery.* 2000;46(4):868-876; discussion 876-868.
61. Weir J, Steyerberg EW, Butcher I, et al. Does the extended Glasgow Outcome Scale add value to the conventional Glasgow Outcome Scale? *Journal of neurotrauma.* 2012;29(1):53-58.
62. Werner C, Engelhard K. Pathophysiology of traumatic brain injury. *Br J Anaesth.* 2007;99(1):4-9.
63. Whiteneck GG, Cuthbert JP, Corrigan JD, Bogner JA. Prevalence of Self-Reported Lifetime History of Traumatic Brain Injury and Associated Disability: A

Statewide Population-Based Survey. *The Journal of head trauma rehabilitation.* 2016;31(1):E55-62.
64. Zoerle T, Lombardo A, Colombo A, et al. Intracranial pressure after subarachnoid hemorrhage. *Crit Care Med.* 2015;43(1):168-176.
65. Zweifel C, Castellani G, Czosnyka M, et al. Noninvasive Monitoring of Cerebrovascular Reactivity with Near Infrared Spectroscopy in Head-Injured Patients. *Journal of neurotrauma.* 2010;27(11):1951-1958.