

# The BRAIN OXYGEN AND OUTCOME IN SEVERE TRAUMATIC BRAIN INJURY (BOOST) STUDY

R34 NS063636-01A1

A MULTI-CENTER, PROSPECTIVE, PHASE III RANDOMIZED,  
CLINICAL TRIAL TO COMPARE  
BRAIN OXYGEN BASED THERAPY  
TO CONVENTIONAL ICP/ CPP THERAPY  
FOR SEVERE TRAUMATIC BRAIN INJURY

PI: Peter Le Roux MD FACS

# Impact of TBI?

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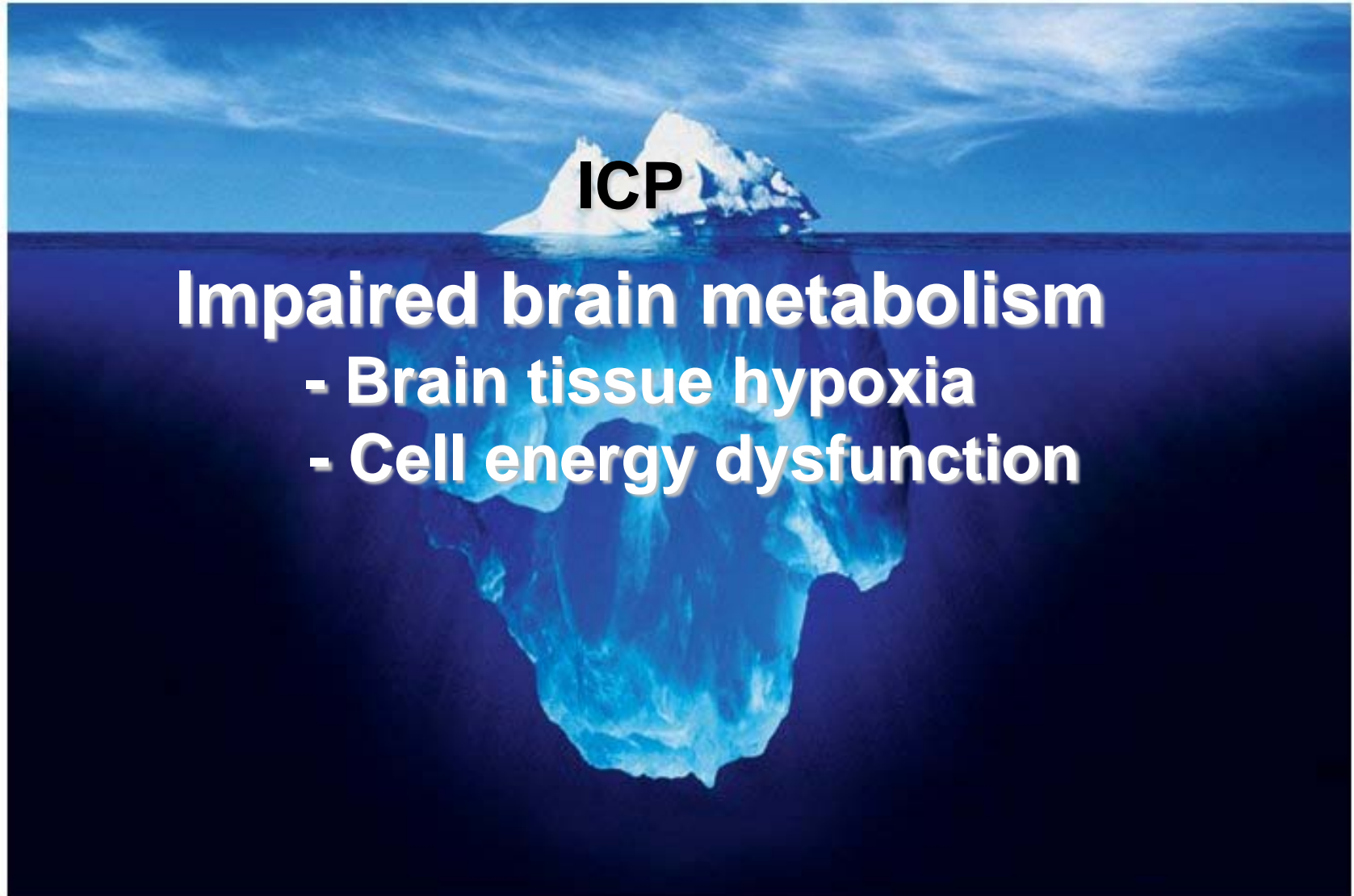
- Every 15 seconds in the USA someone suffers a TBI.
- Causes more deaths in men under 35 than all other diseases combined.
- 2% of US population lives with TBI related disability
- Leading cause of death and disability children age 1-15 worldwide
- EBIC - 40% severe TBI dead at 6 mths, 20% vegetative or severely disabled
- Costs for long term care estimated ~ \$50 billion each year.
- Signature Injury of the Iraq/Afghanistan War

# Successful clinical treatment of TBI?

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- There are greater than 200 randomized trials for TBI published in the literature
- **BUT NO THERAPY HAS BEEN SHOWN TO BE EFFECTIVE!!!!**
- Current care is centered on timely evacuation of mass lesions and prevention of secondary brain injury

# Standard Monitoring - Tip of the Iceberg



# Why monitor brain oxygen?

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- David K. Menon, PhD; Jonathan P. Coles, PhD; Arun K. Gupta, FRCA; Tim D. Fryer, PhD; Peter Smielewski, PhD; Doris A. Chatfield, BSc; Franklin Aigbirhio, PhD; Jeremy N. Skepper, PhD; Pawan S. Minhas, FRCS; Peter J. Hutchinson, PhD; T. Adrian Carpenter, PhD; John C. Clark, DSc; John D. Pickard, FRCS **Diffusion limited oxygen delivery following head injury. Crit Care Med 2004; 32:1384 –1390**
- Anthony Marmarou, Stefano Signoretti, Panos P. Fatouros, Gina Portella, Gunes A. Aygok, M. Ross Bullock. **Predominance of cellular edema in traumatic brain swelling in patients with severe head injuries J Neurosurg 104:720–730, 2006**
- Paul M. Vespa, MD; Kristine O’Phelan; David McArthur; Chad Miller; Matthew Eliseo; Daniel Hirt; Thomas Glenn, PhD; David A. Hovda, PhD. **Pericontusional brain tissue exhibits persistent elevation of lactate/pyruvate ratio independent of cerebral perfusion pressure\* Crit Care Med, 2007; 35:1153–1160**
- Panayiotis N. Varelas, Dan Eastwood, Hyun Yun, Marianna Spanaki, Lotfi Hacein Bey, Christos Kessaris, Thomas A. Gennarelli. **Impact of a neurointensivist on outcomes in patients with head trauma treated in a neurosciences intensive care unit J Neurosurg 104:713–719, 2006**

# Brain oxygen and outcome: a systematic review

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- Medline, Biosis, Dissertation Abstracts, Index Medicus search
- Inclusion: >10 pts; direct brain O<sub>2</sub> monitor; brain hypoxia defined; 6 month outcome data; clear report of outcome and brain oxygen. For systematic review - data to determine RR
- 13 studies, 3 for systematic review
- 158 patients
- Outcome - 71 favorable, 87 unfavorable
- Brain oxygen <10mmHg
  - Favorable outcome 26%
  - Unfavorable outcome 64%
- Brain hypoxia (<10mmHg)
  - Worse outcome RR 2.00 (95% CI 1.5-2.67)
  - Increased mortality RR 2.34 (95% CI 1.48-3.7)

# Predictors of outcome by multivariable analysis

Variable	Adjusted OR for favorable outcome	95% CI	Adjusted <i>P</i>
Marshall CT score	0.41	0.24-0.70	<b>&lt;0.01</b>
APACHE II score	0.83	0.71-0.96	<b>0.01</b>
Brain tissue hypoxia <sup>#</sup>	0.88	0.78-0.99	<b>0.04</b>
Intracranial hypertension	0.99	0.98-1.01	0.11

Retrospective analysis of prospective database of 103 patients with severe TBI  
Multivariable logistic regression controlling for age, admission Glasgow Coma Scale, Marshall CT, APACHE II

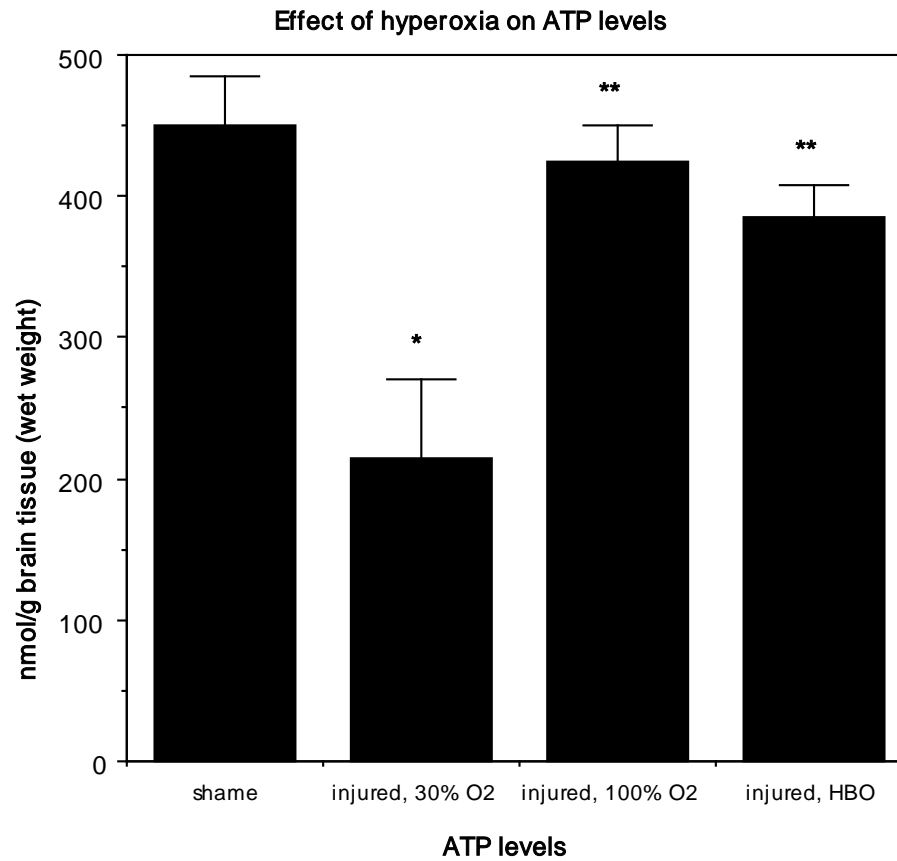
<sup>#</sup>duration of PbtO<sub>2</sub> < 15 mm Hg; <sup>†</sup>AUC of ICP > 20 mm Hg

# Brain oxygen based care is biologically plausible

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- 1) The brain depends on the delivery of oxygen and glucose i.e aerobic metabolism, for normal function.
- 2) There is considerable evidence both from experimental and clinical studies that traumatic brain injury (TBI) is associated with reduced aerobic metabolism.
- 3) The vast majority of patients (80-90%) who die after TBI have histopathologic evidence for ischemic injury.
- 4) Decreases in PbrO<sub>2</sub> are not benign and are associated with independent neurochemical markers of brain ischemia.
- 5) Cerebral hypoxia is a well-known independent predictor of outcome in multiple TBI prognosis studies.
- 5) An increase in PbrO<sub>2</sub> is associated with an improvement in brain metabolism in clinical TBI studies,
- 6) Improved brain oxygen is associated with reduced severity and extent of secondary brain damage in experimental TBI models and reduced stroke volumes in animal models of both global and focal cerebral ischemia.
- 7) A small randomized trial recently demonstrated that high-flow oxygen therapy was associated with a transient improvement of clinical deficits and MRI abnormalities in patients with acute ischemic stroke (Singhal et al 2005).

# Increased brain oxygen: Mechanism of effect



# PbtO<sub>2</sub> based care and outcome

Study (First Author)	Number of Patients	PbtO <sub>2</sub>		ICP-CPP		Odds Ratio (95% CI)	Odds Ratio (95% CI)
		Unfavorable Outcome	Favorable Outcome	Unfavorable Outcome	Favorable Outcome		
		(# patients)	(# patients)	(# patients)	(# patients)		
Spiotta J NSX in press 2009	123	25	45	32	21	2.7	2.1 (1.4-3.1)
Meixensberger JNNP 2003	91	18	34	18	21	1.6	
Narota m JNSX 2009	166	44	83	22	17	2.4	
McCarthy Surgery 2009	145 (111)	34	29	32	16	1.7	

Stiefel et al JNSX 2005: 53 patients, historical controls; significant reduction in mortality (44 v 25%; p<0.05) in PbtO<sub>2</sub> group

Martini et al JNSX 2009; 629 patients, (123 had PbtO<sub>2</sub> care), trend to higher hospital mortality in PbtO<sub>2</sub> care group (adjusted mortality difference 4.4%, 95% CI -3.9 to 13%).

Adamides et al Acta Neurochir 2009; 50 patients, contemporary control; trend toward better outcome in PbtO<sub>2</sub> group

# Therapies to treat compromised brain oxygen

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Frequently used therapy	Less frequently used therapy
Adjust ventilator parameters to increase paO <sub>2</sub> Increase FiO <sub>2</sub> (e.g. 50 to 60%) Increase PEEP	Ventriculostomy continuous or intermittent CSF drainage
Transient Hyperoxia 100% FiO <sub>2</sub>	Blood transfusion
Augment CPP colloid bolus neosynephrine, dopamine	Neuromuscular paralysis Pancuronium, vecuronium
Pharmacologic analgesia and sedation Propofol, versed, ativan fentanyl, morphine	Adjust ventilator rate Increase to lower paCO <sub>2</sub> (ICP) Decrease to increase EtCO <sub>2</sub> , paCO <sub>2</sub>
Head position or avoid turning, certain positions	Pulmoary toilette and suction
ICP control sedation, mannitol, IV lidocaine	Penthothal
Insure Temperature < 38°C	DCH (or other cranial surgery)
	Labetalol

# Phase II, randomized controlled trial of PbtO<sub>2</sub> monitoring (BOOST II)

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- NIH/NINDS R01 NS061860
- Unrestricted NGA October 2009
- Recruitment starts January 2009
- 182 patients, 2 years
- Four centers:
  - UT Southwestern - Diaz - Arrastia
  - U Miami - Bullock
  - U. Washington - Temkin, Chesnut
  - PENN - Le Roux
- Medical Monitor: Lori Shutter

# Phase II, randomized controlled trial of PbtO<sub>2</sub> monitoring (BOOST II)

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- Primary Hypothesis: Treatment protocol is effective in reducing the fraction of time that p<sub>Br</sub>O<sub>2</sub> values are below the critical threshold of 20mm Hg.
- Secondary Hypotheses:
  - Safety hypotheses: Adverse events associated with p<sub>Br</sub>O<sub>2</sub> monitoring are rare (< 3% for combination of infectious, hemorrhagic, or other monitoring-related adverse events) and p<sub>Br</sub>O<sub>2</sub> directed therapy does not result in increased risk of pulmonary or systemic complications (such as acute lung injury/Adult Respiratory Distress Syndrome (ALI/ARDS)).
  - Feasibility hypotheses: Episodes of decreased p<sub>Br</sub>O<sub>2</sub> can be identified and treatment protocol instituted comparably across 3 Clinical sites, and protocol violations will be low (<10% and uniform across different clinical sites).
  - Non-futility hypothesis. A relative risk of good outcome measured by the Glasgow Outcome Scale-Extended (GOS-E) at 6 months post-injury of 2.0 in those randomized to management guided by p<sub>Br</sub>O<sub>2</sub> monitoring is compatible with the outcome of this Phase II study.

# The BRAIN OXYGEN AND OUTCOME IN SEVERE TRAUMATIC BRAIN INJURY (BOOST) STUDY

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- **Investigators:**

- Le Roux, Diaz-Arrastia, Bullock, Dikmen, Biester
- Ellenberg, Yang, Temkin
- Melhem, Hurst, Siman, Culler, Gupta

- **Sites:**

- Penn, Tennessee, UCSF, U. Iowa, Boston University, Wayne State -Detroit, U. Miami, U. Maryland, Emory, U Texas Southwestern, U. Cincinnati, U Florida, UMASS, U Washington, U Calgary - Canada, U. Lausanne - Switzerland, NTRI - Australia, Cambridge -UK, U. Cape Town RSA, Queens Square (UK), U. Milan (Italy), U. Newcastle (UK)

- **1394 patients, 8% absolute difference, ?start 2011, 5 year duration**

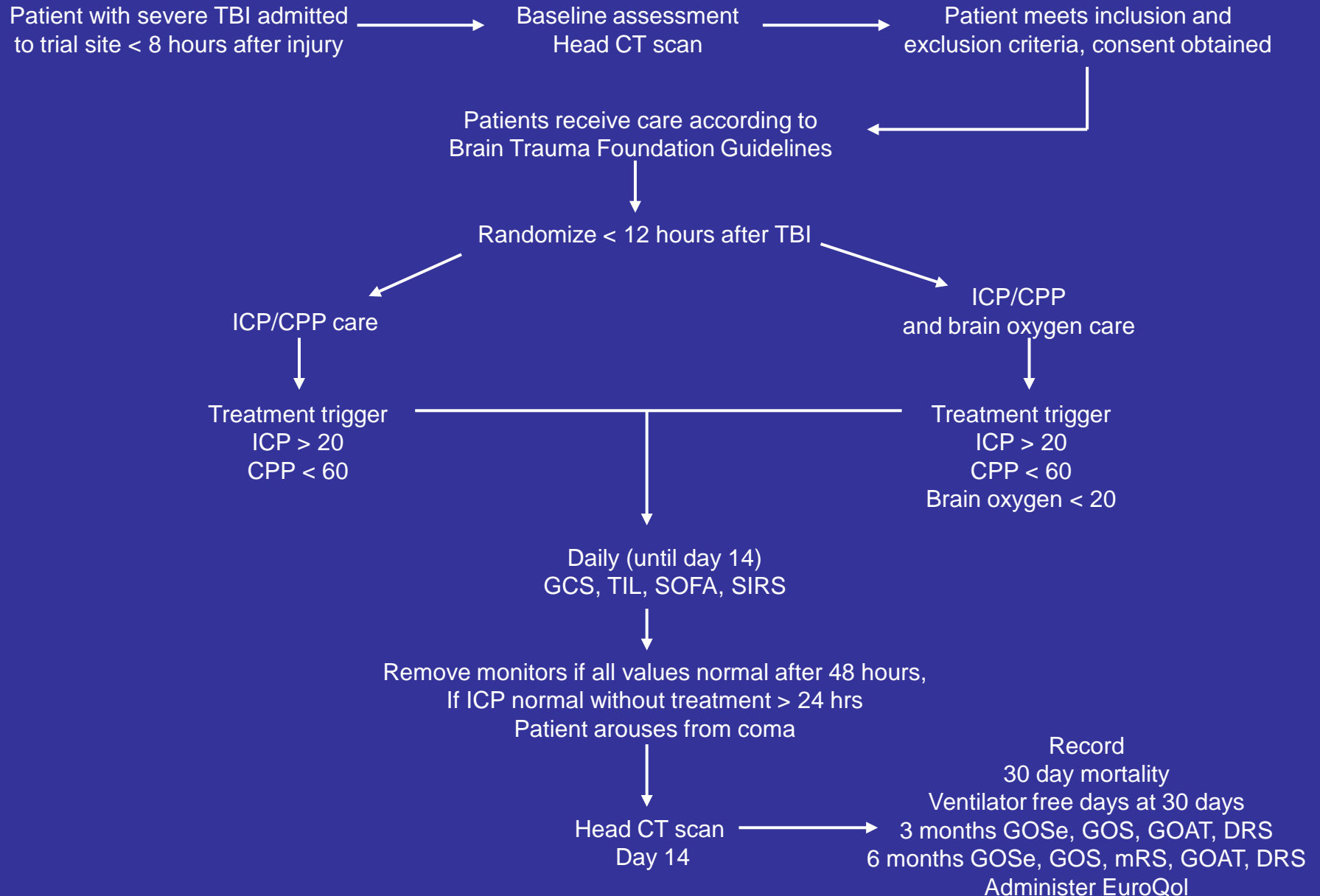
- **Medical Monitors: Stephan Mayer, Vicente Gracias**

- **Protocol Monitors: David Warner, Andrew Kofke**

- **External advisors: Claudia Robertson, Tom Bleck, H. Richard Winn, Jose Suarez, Gordon Murray**

- **Data management and statistics: CRCU and CCEB and UPENN**

# The BRAIN OXYGEN AND OUTCOME IN SEVERE TRAUMATIC BRAIN INJURY (BOOST) STUDY



# BOOST: primary objective

- The primary objective of BOOST is to determine whether a PbrO<sub>2</sub> -based TBI management policy compared with a conventional ICP/CPP policy, reduces the proportion of patients dependent or dead (Glasgow Outcome Score [GOS] of dead, vegetative or severe disability). We expect a PbrO<sub>2</sub> protocol to be associated with a greater proportion of patients with a favorable outcome (GOS of good or moderate disability).
- The treatment effect to be detected is an absolute risk reduction in unfavorable outcome of 8%.

# BOOST: Sample Size

Sample size calculations assuming 50% unfavorable outcome in ICP arm (alpha=0.05).					
% Subjects with unfavorable outcome		Power	Sample size per arm		Total sample size
ICP arm	PbrO <sub>2</sub> arm		Unadjusted	Adjusted	
0.5	0.35	0.9	240	264	528
0.5	0.35	0.8	183	202	404
0.5	0.4	0.9	538	592	1184
0.5	0.4	0.8	407	448	896
0.5	0.42	0.9	838	922	1844
0.5	0.42	0.8	633	697	1394
0.5	0.45	0.9	2134	2348	4696
0.5	0.45	0.8	1604	1765	3530

# BOOST: Secondary objectives

- PbrO<sub>2</sub>-directed therapy will be associated with:
  - a) reduced mortality, and
  - b) better functional outcome.
- We will assess outcome using the:
  - GOS extended (GOSe)
  - Galveston Orientation and Amnesia Test (GOAT)
  - Disability Rating Scale (DRS)
  - modified Rankin Scale (mRs)
  - EuroQol to assess quality of life.
  - Surviving patients will undergo 6-month neuropsychological evaluation.

# BOOST: Secondary objectives

- PbrO<sub>2</sub>-directed therapy will be associated with better ICP control.
  - We will assess physiological data (ICP) and examine therapeutic intensity levels (TIL).
- PbrO<sub>2</sub> therapy is associated with less delayed brain injury (reduced incidence of secondary cerebral injury).  
To evaluate this we will examine:
  - low-density changes on day 14 or day closest to day 14 head CT scan
  - Short-term neurological function (14 days), using Glasgow Coma Scale (GCS) and GOAT.

# BOOST: Secondary objectives

- PbrO<sub>2</sub>-directed therapy will be associated with fewer extracranial complications and a reduced incidence of extracerebral organ dysfunction:
  - Major organ failure assessed using Sequential Organ Failure Assessment (SOFA) and adjusted for death.
  - Total ventilator days and ventilator free days at 30 days.
  - Presence and number of infections (urinary tract, pneumonia or ventilator associated pneumonia [VAP], blood stream, wound and central venous catheter as defined for Centers for Disease Control), Systemic inflammatory response syndrome (SIRS) and use of antibiotics for more than 10 days.
  - Cumulative Therapeutic Intervention Scoring System (TISS-28) scores
  - Daily therapeutic intensity levels.

# BOOST: Secondary objectives

- Neuropsychological outcome: A composite cognitive score (CCS) obtained at 6 months will be the primary outcome variable for neuropsychological outcome ( $\sum \text{DomZ}/8 = \text{CCS}$ ). Patients who die or are severely disabled and not able to undergo neuropsychological testing will be assigned worse scores than those observed in the trial.

<b>Domain</b>	<b>Test</b>	<b>Scores</b>	<b>Admin. Time (minutes)</b>
<b>INTELLIGENCE</b>			
Estimate of Verbal Intelligence	NART-R	Total Words	4
<b>COGNITIVE</b>			
Working Memory	WAIS-III: Letter-Number Sequencing	Total Score	4
Verbal Learning & Memory	Hopkins Verbal Learning Test (HVLТ)	Total Trial 1-3 Total Recall Recognition	5
Visual Learning & Memory	Brief Visuospatial Memory Test Š Revised (BVMT-R)	Total Trial 1-3 Delayed Recall Recognition	10
Motor Dexterity	Grooved Pegboard	Dom-Hand Time Non-Dom Hand Time	4
Processing Speed	1) WAIS-III: Digit Symbol 2) WAIS-III: Symbol Search	Processing Speed Index	5
Executive Functions	1) Trail Making Tests: Parts A&B 2) Controlled Oral Word Association	1)Trail A Time Trail B Time 2) Total Words	4 3
<b>MOOD</b>			
9 Psychological dimensions	Brief Symptom Inventory	9 Dimension Scores 3 Global Indices	10
<b>FUNCTION/QUALITY OF LIFE</b>			8
Functional Outcome Measure	SF-36	Scale Scores: 8 Summary Measures: 3	8

# BOOST: Safety

- The following safety measures will be examined in the two treatment groups:
  - Occurrence of death up to 30 days after TBI
  - Any severe adverse event (SAE)
  - Development of lung dysfunction (ALI/ARDS) according to established guidelines
  - Device related complications.

# BOOST: Economic analysis

- Health economic endpoints: The cost study will identify all hospital resources consumed by the patient during their index hospitalization using itemized Uniform Billing (UB-92) forms, and cost effectiveness will be explored.

# BOOST: Inclusion criteria

- Patients between 18 and 70 years of age
- Either gender and of any race.
- Patients with severe TBI who require an ICP monitor according to Brain Trauma Foundation guidelines (J Neurotrauma. 2007;24 Suppl 1). Severe TBI will be determined by a history of trauma, a clinical exam giving a post-resuscitation Glasgow Coma Scale (GCS) 3-8, and a head CT scan to confirm no other cause for coma.
  - If the CT scan is normal, patients with a motor GCS < 4 measured off paralytics will be considered to have a severe TBI.
  - If the patient has a witnessed seizure, the GCS will be evaluated 30 minutes after the seizure.
  - Intoxicated patients will be enrolled if they otherwise meet the BTF criteria for an ICP monitor.

# BOOST: Exclusion criteria

Exclusion Criteria	Measure	Rationale
Cannot speak any English	Family History	Outcome measures best validated in English
Prisoner or Ward of the State	History/Deputy present	Informed consent issues
Previous stroke, SAH, TBI, brain tumor, central nervous system infection, neurodegenerative disease	History	Affects outcome
Pregnancy	History and HCG test	Fetus may be at risk
Brain death or imminent (within 24 hours)	Glasgow Coma Score = 3 and criteria for brain death	No neurological activity; no treatment will be given.
Non-survivable injury	Bilaterally absent pupil response and SBP < 90mmHg	Treatment likely to be futile
Coma due to other causes or drug induced	Clinical, laboratory and radiographic assessment	Anatomical and physiologic differences
Clinical condition due to pharmacologic suppression	Intubated patients with GCS motor score $\geq 4$ with normal CT scan	Affects outcome
Penetrating head injury	History and clinical assessment	Different pathology
Terminal illness or receiving chemotherapy	History, Clinical and radiographic assessment	May interfere with outcome assessment
Refractory hypotension	SBP < 70 mm Hg for > 30 minutes	Affects outcome, treatment may be futile
Refractory systemic hypoxia	PaO <sub>2</sub> < 60 mm Hg on FiO <sub>2</sub> < 0.5	Affects outcome, treatment may be futile
Coagulopathy not corrected within 12 hours of injury	Platelets < 50,000/mL, INR > 1.4	Monitors cannot be placed

# BOOST: Schedule of events

Evaluation	Baseline	Day 1-7	Day 8-13	Day 14	30 days	3 months $\pm$ 7days	6 months $\pm$ 7 Days
Inclusion/Exclusion Criteria Review	X						
Informed Consent	X						
History & physical, GCS, ISS	X (SOC)						
GCS	X	X (Q 1hr)	X (Q 1hr)	X (Q 1hr)			
Standard scales (SOFA, SIRS)	X	X	X	X			
Process of care (TIL, TISS-28)		X	X	X			
Pregnancy Test (women of childbearing age)	X						
EKG	X (SOC)						
Chest X-Ray	X (SOC)						
Blood for banking and biomarkers	X	X*					
CSF analysis (if EVD placed) for banking	X	X*					
CT Scan (w/o contrast)	X (SOC)	X(SOC)	X (SOC)	X (SOC)			
CBC with Platelets	X (SOC)	X(SOC)	X (SOC)	X(SOC)			
Glucose / Electrolytes/LFT	X (SOC)	X(SOC)	X	X			
Arterial blood gas	X (SOC)	X	X	X			
Continuous physiological variables (PR, BP, ICP, CPP, CVP, FiO <sub>2</sub> , Sa O <sub>2</sub> , PbrO <sub>2</sub> )	X	X	X (if still monitored)	X (if still monitored)			
Telephone Call or Follow-Up Visit					X	X	X
GOS, GOSe					X	X	X
GOAT				X	X	X	X
DRS					X	X	X
Modified Rankin Scale	X						X
Euro Qol and SF-36 Questionnaires							X
Neurocognitive Assessment							X
Adverse Event Assessment	X	X	X	X	X	X	X

# BOOST: Structure

- **BOOST** is a collaboration between 25 different institutions, each with a site Neurosurgical and neurointensivist investigator
- There are 7 co - Principal Investigators:
  - Neurosurgery (**Peter Le Roux MD, Ross Bullock MD**)
  - Neurocritical care (**Ramon Diaz-Arrastia MD**)
  - Neuropsychology and TBI outcomes (**Rose Biester PhD, Sureyya Dikmen PhD**)
  - Epidemiology and biostatistics (**Jonas Ellenberg PhD, Nancy Temkin PhD**)
- Data management (the **CRCU at UPENN**).

# BOOST: Personnel

- Consultants:
  - Neuroradiology (**Robert Hurst MD, Elias Melhem MD**)
  - TBI trial design and statistics (**Gordon Murray PhD**)
  - Health economics (**Steven Culler PhD**)
  - Biomarkers (**Robert Siman PhD**)
- External Advisory Board: **Thomas Bleck MD, Claudia Robertson MD, Jose Suarez MD, H. Richard Winn MD**
- Independent medical monitors: **Stephan Mayer MD** and **Vicente Gracias MD**
- Physician Protocol Monitors: **David Warner MD** and **Andrew Kofke MD**
- International liaison: **Arun Gupta MD**

# BOOST: Participating centers, study personnel and severe TBI patient volume at each site during last 3 years

Hospital	University	Neurosurgeon	Intensivist	Study Coordinator	# TBI last 3 years
Hospital of the University of Pennsylvania	University of Pennsylvania	Jim Schuster	Joshua Levine	Eileen Maloney	382
Jackson Memorial Hospital	University of Miami	Ross Bullock	Stephen Olvey	Kimberly Fernandez	561
San Francisco General Hospital	UCSF	Geoff Manley	Claude Hemphill	Michelle Meeker	308
Elvis Presley Memorial Trauma Center	University of Tennessee Health Science Center	Shelley Timmons	Michael Muhlbauer	Inge Fine	570
R Adams Cowley Shock Trauma Center	University of Maryland	Bizhan Arabi	Deborah Stein	Christina Aldrich	939
University Hospital Grady Memorial	University of Cincinnati	Raj Narayan	Lori Shutter	Suzanne Kempisty	478
Parkland Memorial Hospital	Emory University	Dan Barrow	Owen Samuels	Kate Hanson	1200
Harborview Medical Center	University of Texas Southwestern	Christopher Madden	Ramon Diaz-Arrastia	Carol Moore	345
Harborview Medical Center	University of Washington	Randall Chesnut	MJ Souter	Sara Wellnitz	182
U Mass Memorial Medical Center	Massachusetts University	Frits Pennings	Wiley Hall	Shauneen Valliere	499
Shands Hospital	University of Florida	Steve Lewis	Andrea Gabrielli	Judith Wishin	120
University of Pittsburgh Medical Center	University of Pittsburgh	David O Okonkwo	Sam Tisherman	Ava Puccio	180
Detroit Receiving Hospital	Wayne State	Ken Casey	William Coplin	Kelly Evans	281
Boston Medical Center	Boston University	James Hosapple	Deborah Green	Helena Lau	478
University of Iowa Hospitals and Clinics	University of Iowa	Matthew Howard	Brent Haddler	Marge Rodgers	310
Foothills Medical Center	University of Calgary	Clare Gallagher	David Zygun	Linda Knox	300
The Alfred	Monash University	Jeffrey Rosenfeld	Jamie Cooper	Lynne Murray	288
Cambridge University Hospitals NHS Foundation Trust	Cambridge University	Peter Hutchinson	Arun Gupta	Dot Chatfield	267
Centre Hospitalier Universitaire Vaudois	University of Lausanne	Marc Levivier	Mauro Oddo	Lucas Liaudet	150
Groote Schuur Hospital	University of Cape Town	Graham Fieggan	Patrick Semple	TBN	468
The National Hospital for Neurosurgery	University College London	Neil Kitchen	Martin Smith	Tina Stephen	120
Newcastle General Hospital	Newcastle University	Patrick Mitchell	Gus Vincent	Gus Vincent	312
					<b>8738</b>

Since NIH submission added Royal London, UMDNJ and Stanford

# BOOST III: Site surveys

- Standardization of care:
  - [http://www.surveymonkey.com/s.aspx?sm=KJzl9ZiJ2laNeP9WSd dcxA\\_3d\\_3d](http://www.surveymonkey.com/s.aspx?sm=KJzl9ZiJ2laNeP9WSd dcxA_3d_3d)
- Site and research infrastructure, and likely recruitment of study subjects at the study sites:
  - Recruitment:  
[http://www.surveymonkey.com/s.aspx?sm=PQmFv9AUDYTsl71e4HwWCg\\_3d\\_3d](http://www.surveymonkey.com/s.aspx?sm=PQmFv9AUDYTsl71e4HwWCg_3d_3d)
  - Research Infrastructure:  
[http://www.surveymonkey.com/s.aspx?sm=luM\\_2b8E8Arg\\_2bwdYr\\_2b6BgSGQ\\_3d\\_3d](http://www.surveymonkey.com/s.aspx?sm=luM_2b8E8Arg_2bwdYr_2b6BgSGQ_3d_3d)
  - Site Infrastructure:  
[http://www.surveymonkey.com/s.aspx?sm=Mf8ZKkefu1laXfqismZJCg\\_3d\\_3d](http://www.surveymonkey.com/s.aspx?sm=Mf8ZKkefu1laXfqismZJCg_3d_3d)

# BOOST III: 2010

- Gather Phase II data (recruitment and compliance)
- Finalize sample size
- Recruit and certify additional centers
- Patient trial eligibility
- Standardize management
- Prepare Training Schedules and Materials
- Establish Membership of Trial Committees
- Develop IRB protocol, consent template
- Continue to Analyze data for Phase III Planning
- BOOST Trial Investigator Meetings
- Prepare Budget and cooperative agreements
- Finalize research proposal
- Develop manual of procedures (MOP), Investigators Brochure, Regulatory Binders and case report forms
- Begin to develop tools for data collection and management
- Create a webpage for trial use and public access