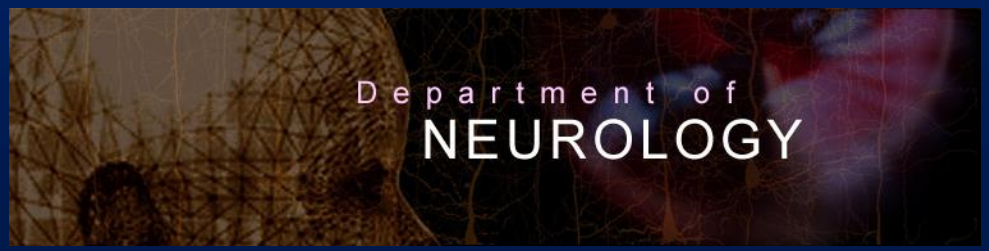
Brain Oxygen Optimization in Severe TBI—Phase 3 (BOOST-3)

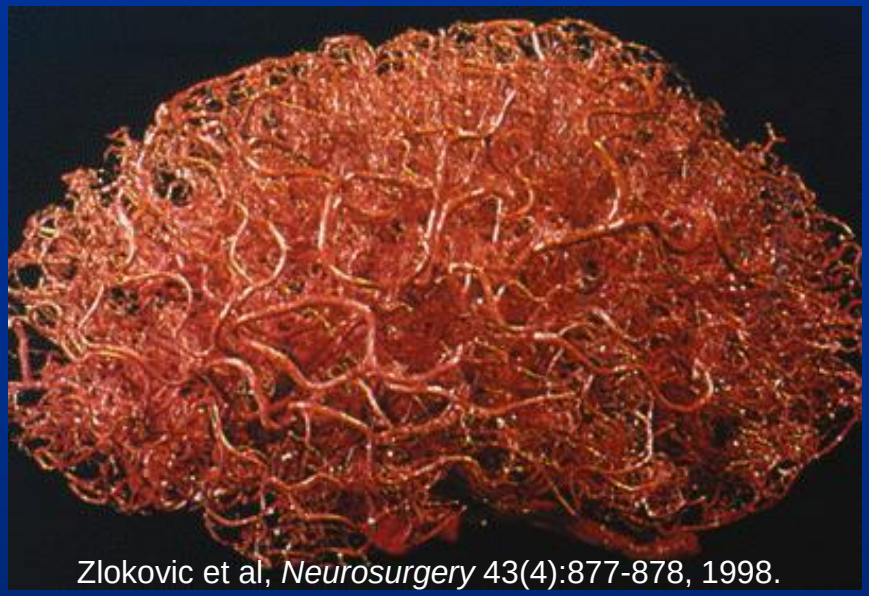
Ramon Diaz-Arrastia, MD, PhD

Professor, Department of Neurology

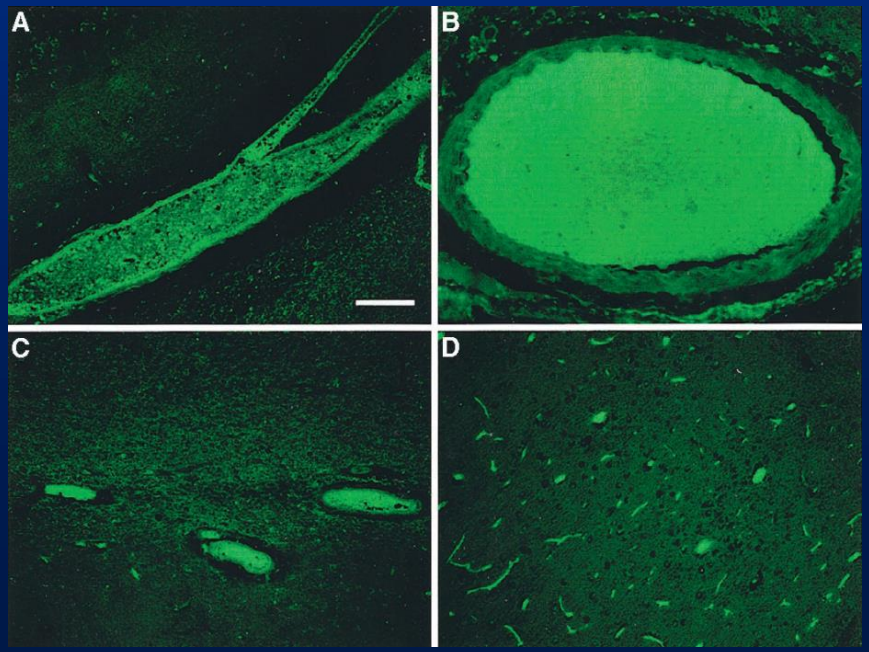
University of Pennsylvania Perelman School of Medicine



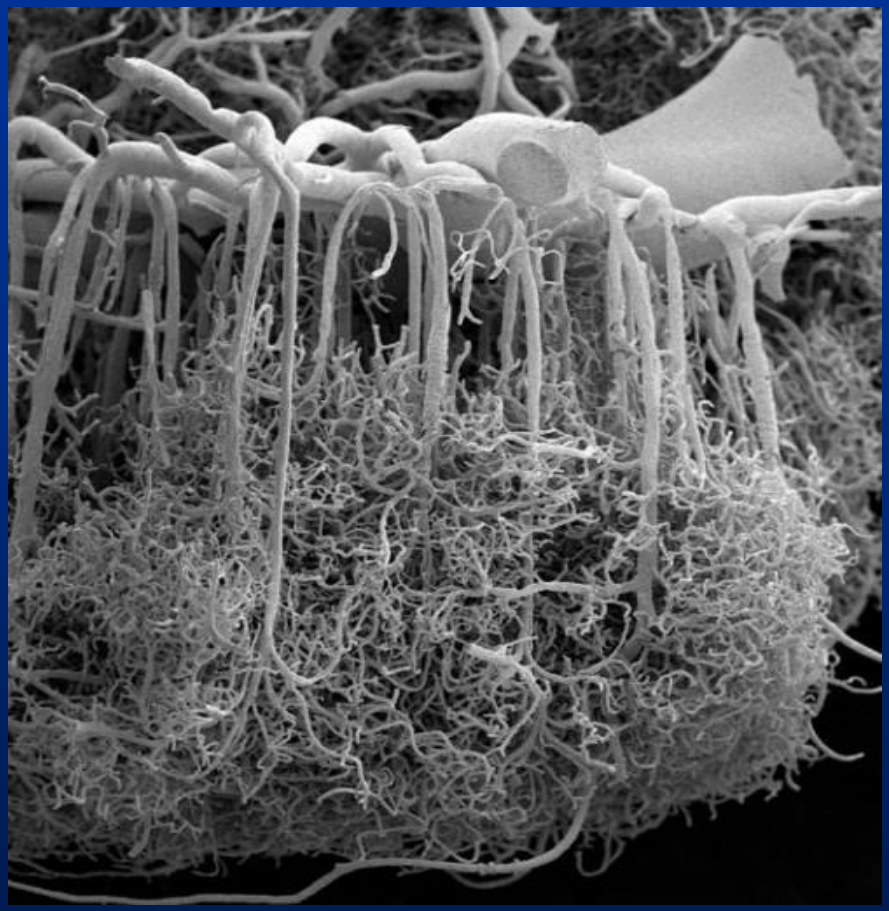
Anatomy of Cerebral Microvasculature



Zlokovic et al, *Neurosurgery* 43(4):877-878, 1998.

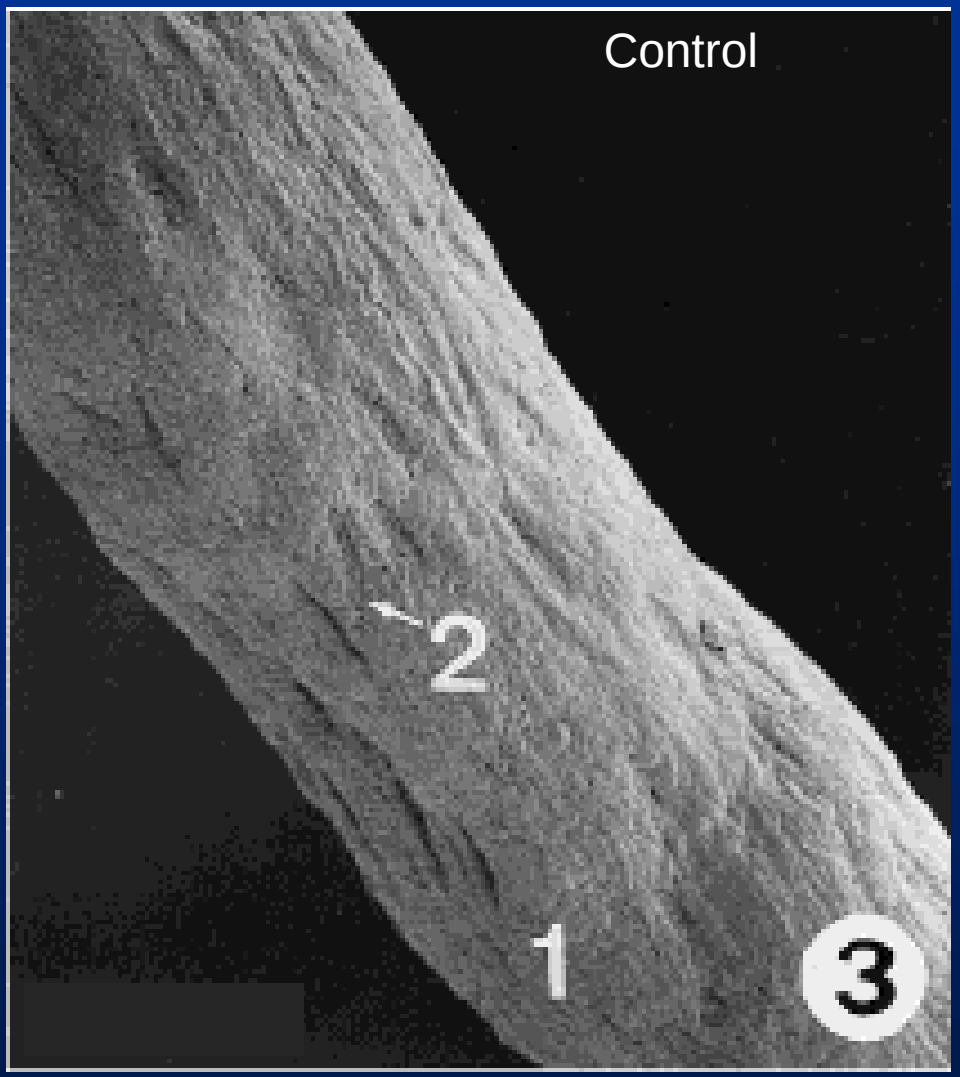


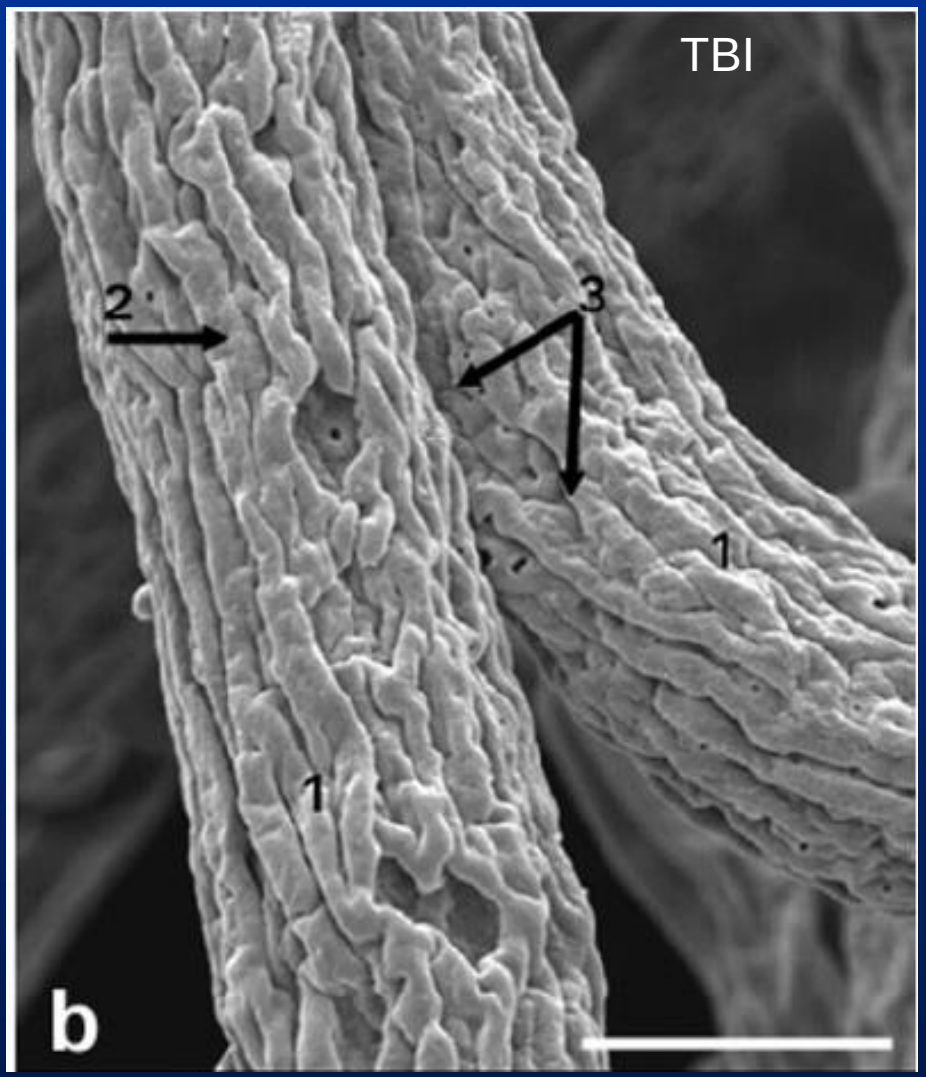
Stein et al, *Neurosurg* 54:687-691 (2004)



Reina de la Torre, et al *Anat Record* 1998;251:87-96

Cerebral Microvasculature in TBI





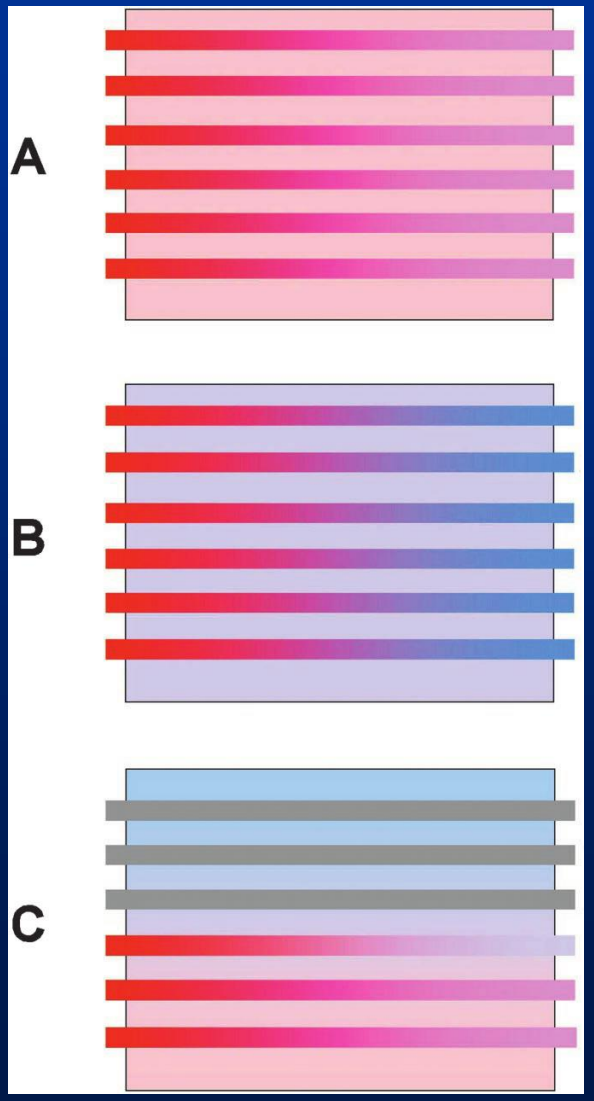
Rodriguez-Baeza, et al *Anat Record* 1998;252:176-184
Rodriguez-Baeza, et al *Anat Record* 2003;273A:583-593

Macrocirculatory vs. Microcirculatory Hypoxia

A. Normal condition. Oxygenated blood delivers O_2 to tissue. PaO2 and PtO2 equilibrated

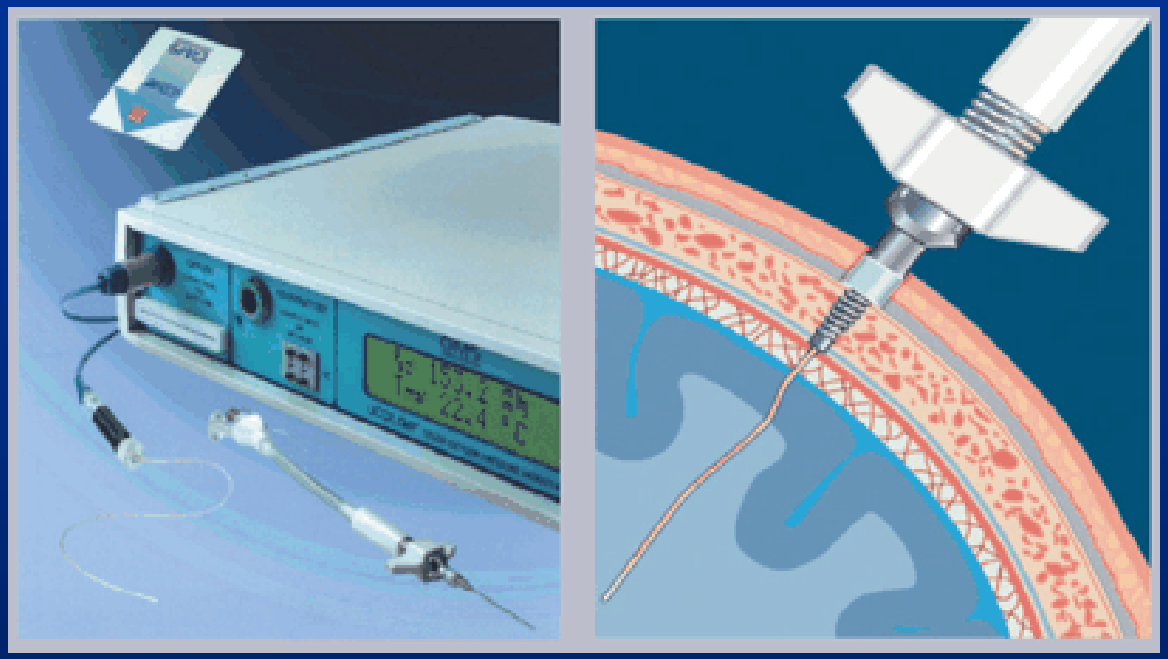
B. Macrocirculatory ischemia (classical ischemia). Hypotension of large vessel stenosis reduces blood entering capillaries. Tissue extracts higher fraction of O_2 from blood, but remains ischemic

C. Microcirculatory ischemia (diffusion hypoxia). Patchy microvascular collapse or occlusion results in increased gradient between blood O_2 and tissue O_2



Menon et al, *Crit Care Med* 2004;32:1384-1390

Brain Tissue Oxygen Monitors



- FDA-approved November, 2000
- Measures $PbtO_2$ in mm^3 region around tip of catheter
- No Class I data that it improves outcome
- Variable penetrance of utilization in NICU

Rationale for $PbtO_2$ monitoring

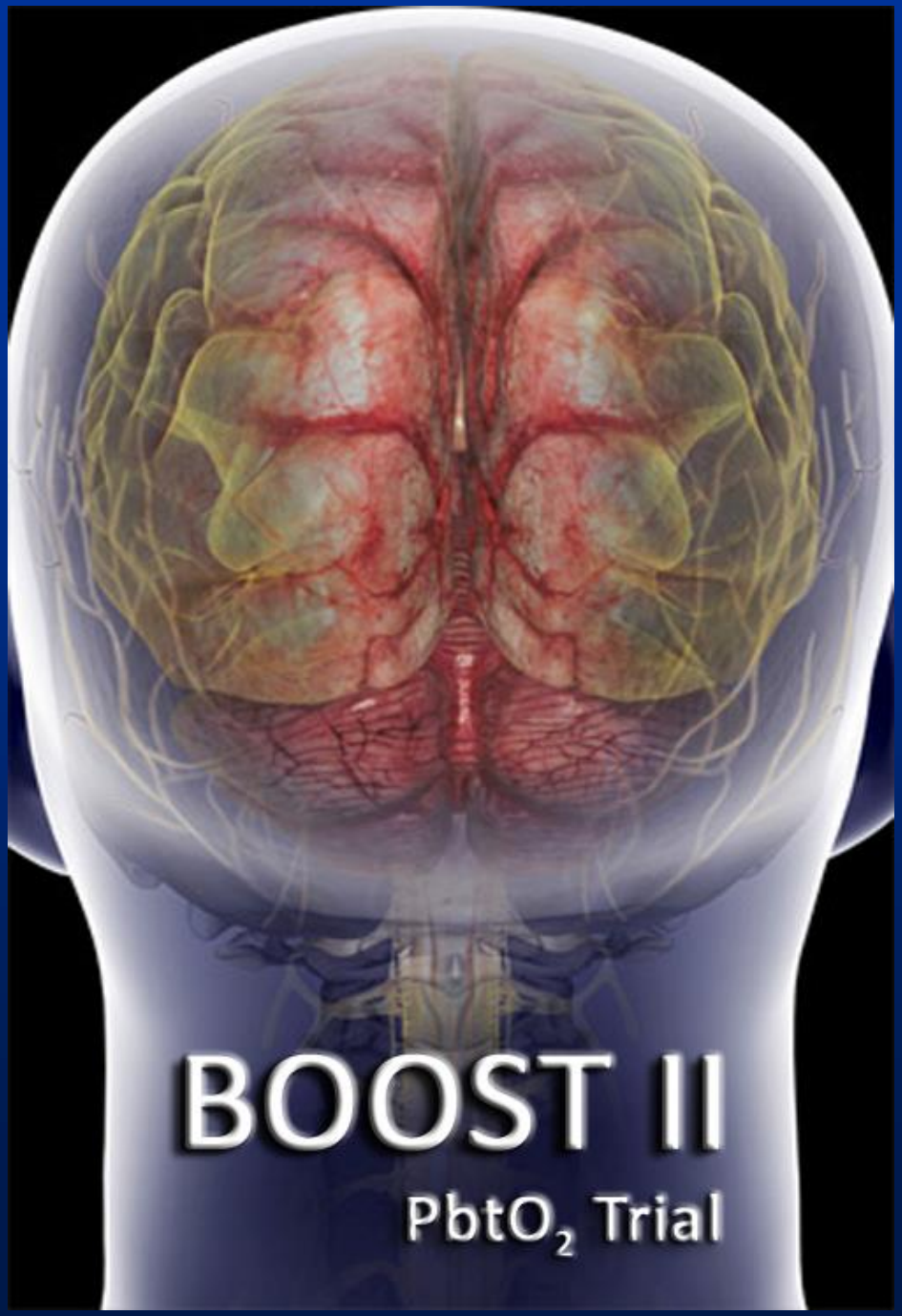
- Low $PbtO_2$ is associated with poor neurological outcome

Study (First Author, # of patients evaluable)	Hypoxia		No Hypoxia		Odds Ratio (95% C.I.)
	Unfavorable Outcome (n)	Favorable Outcome (n)	Unfavorable Outcome (n)	Favorable Outcome (n)	
Van den Brink 2000 (n = 99)	29	14	24	32	3.8 (1.6 – 8.4)
Bardt et al 1998 (n = 35)	18	5	3	9	10.8 (2.1 – 55.7)
Chang et al 2009 (n = 25)	6	1	7	11	9.43 (1.1 – 95.9)

1. van den Brink WA, etr al *Neurosurgery* 2000; 46:868-878
2. Bardt TF, et al, *Acta Neurochir* 1998; Suppl. 71:153-156
3. Chang J, et al, *Crit Care Med* 2009;37:283-290

Published Clinical Trials

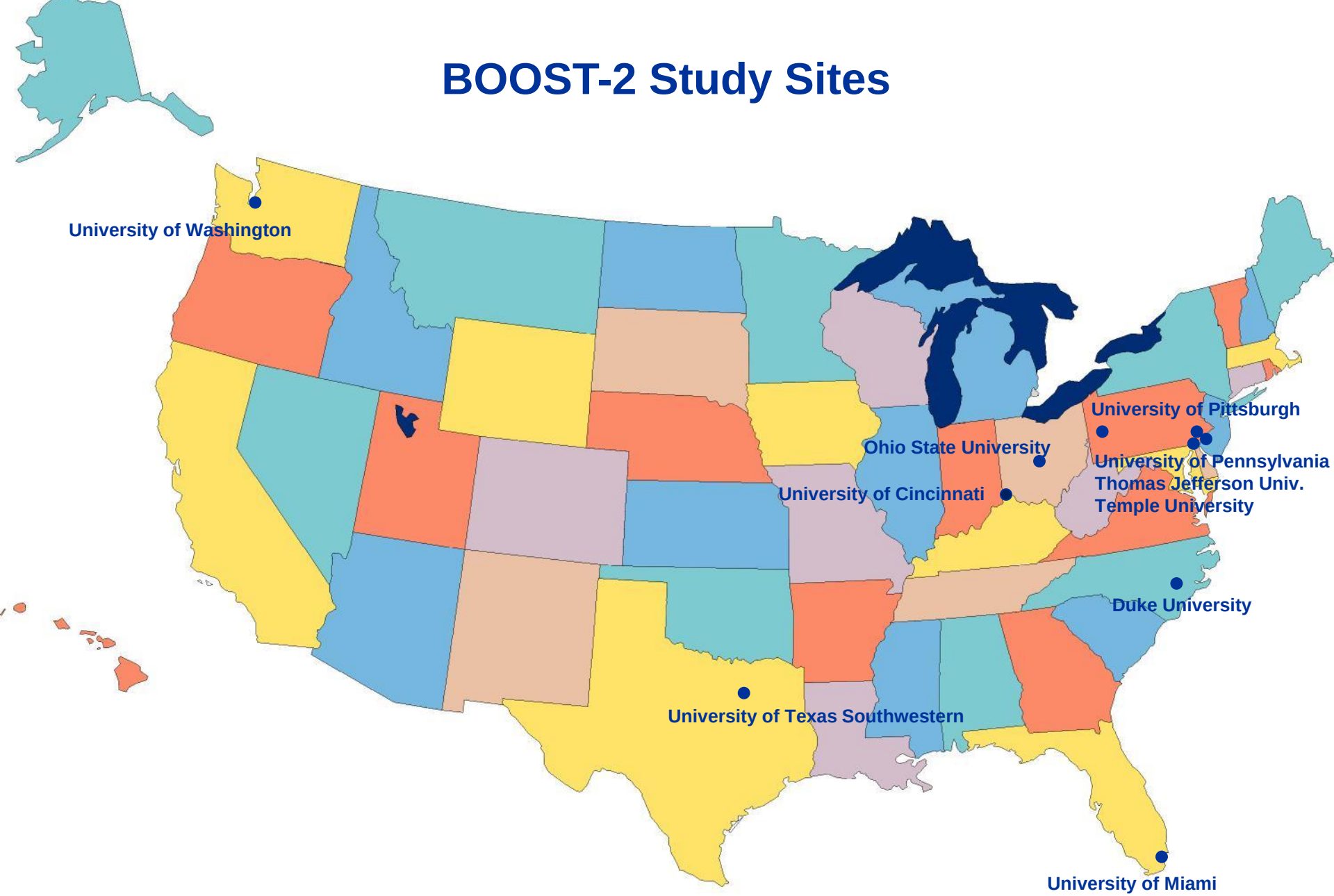
- No randomized clinical trials available
- Four studies have been published
  - Stiefel et al (2001) Univ. Pennsylvania
  - Narotam et al (2009) Creighton Univ.
  - McCarthy et al (2009) Wright State Univ.
  - Martini et al (2009) Univ. Washington
- All used historical or concurrent (physician choice) controls



BRAIN OXYGEN AND OUTCOME IN SEVERE TRAUMATIC BRAIN INJURY: PHASE 2

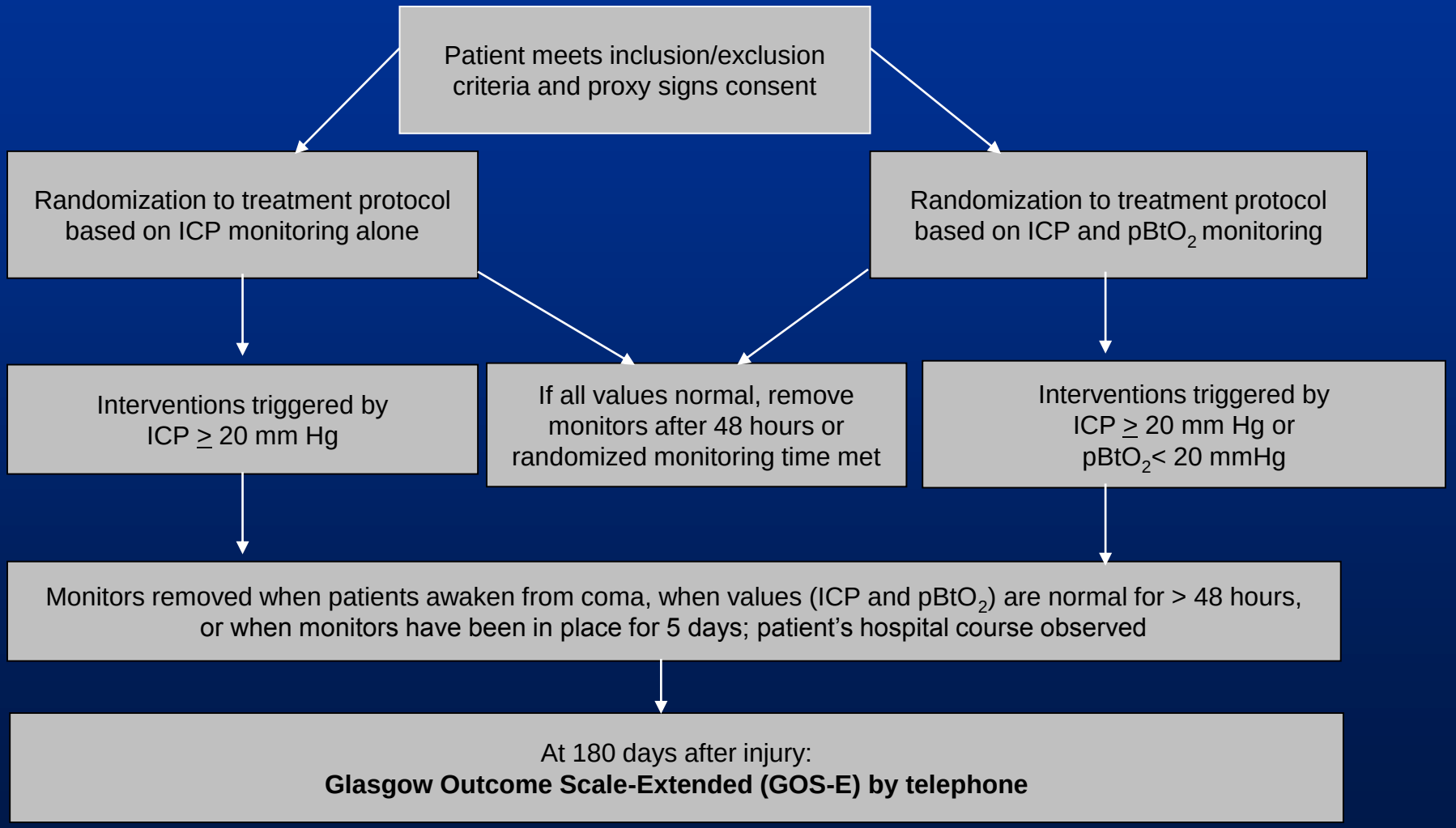
BOOST 2

BOOST-2 Study Sites



Produced by the Cartographic Research Lab
University of Alabama

Study Schematic



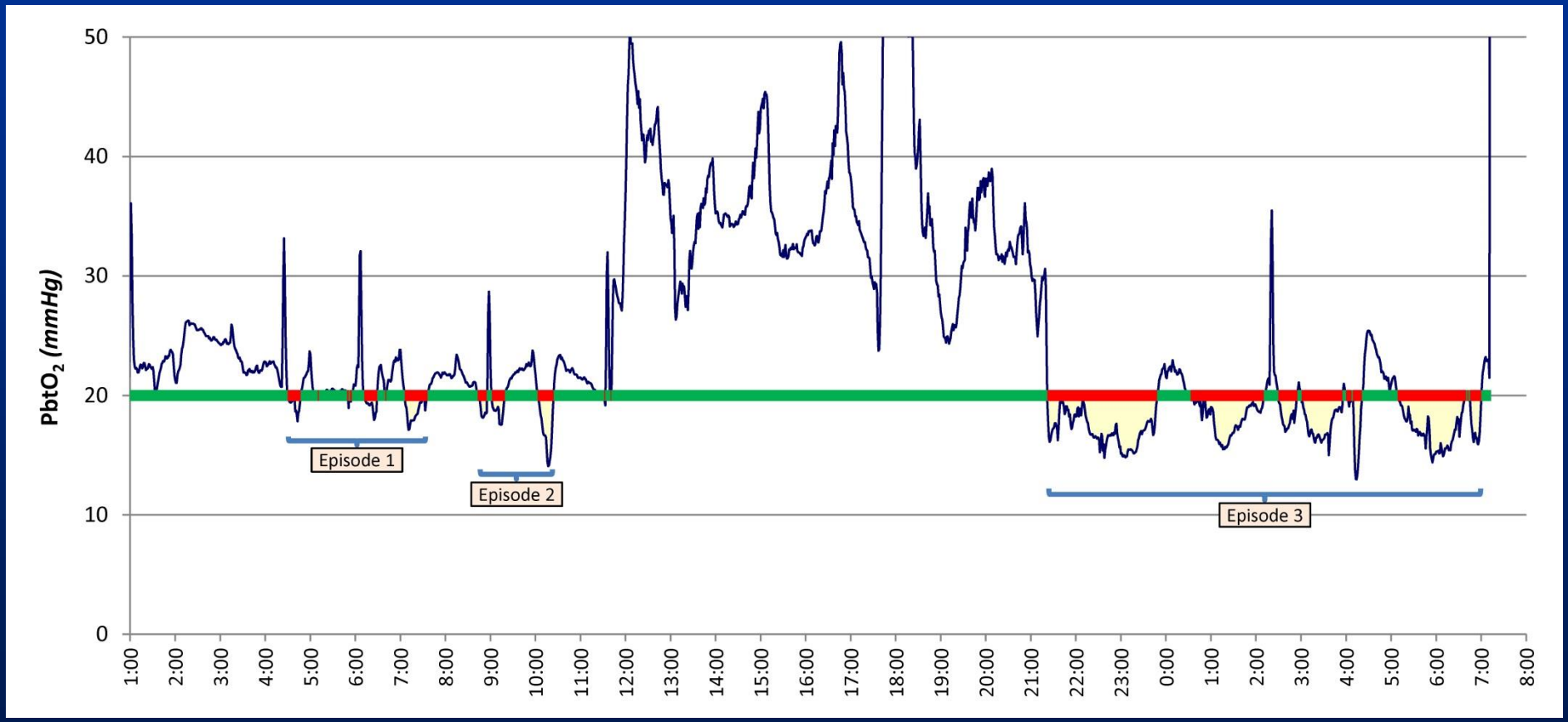
Types of events		ICP < 20	ICP ≥ 20
$PbtO_2 \geq 20$		Type A No interventions directed at $PbtO_2$ or ICP needed	Type B Interventions directed at lowering ICP
$PbtO_2 < 20$		Type C Interventions directed at increasing pBtO2	Type D Interventions directed at lowering ICP and increasing pBtO2

Type B	Type C	Type D
TIER 1 (1). Adjust head of the bed to lower ICP (2). Ensure Temperature < 38 oC. (3). Adjust pharmacologic analgesia and sedation: Titrate to effect. (4). CSF drainage (if EVD available) Titrate to effect. (5). Standard dose Mannitol (0.25 – 1.0 g/kg), to be administered as bolus infusion. (6). Hypertonic saline. Titrate to ICP control and maintain serum Na+ 155-160).	**TIER 1** (1). Adjust head of the bed to improve brain oxygen level (2). Ensure Temperature < 38 oC. (3). Increase CPP to 70 mm Hg with fluid bolus. (4). Optimize hemodynamics. (5). Increase PaO2 by increasing FiO2 to 60%. (6) Increase PaO2 by adjusting PEEP (7) Add EEG monitoring (8) Consider adding AED's, either Dilantin or Keppra, for 1 week only.	**TIER 1** (1). Adjust head of the bed to lower ICP (2). Ensure Temperature < 38 oC. (3). Pharmacologic analgesia and sedation (4). CSF drainage (if EVD available). (5). Increase CPP up to a maximum >70 mm Hg with fluid bolus. (6). Standard dose Mannitol, to be administered as bolus infusion. (0.25 – 0.5 mg/kg). (7). Hypertonic saline (8). Adjust ventilator parameters to increase paO2 by increasing FiO2 to 60%. (9). Increase FiO2 by increasing PEEP. (10) Consider EEG monitoring 11) Consider AED's, either Dilantin or Keppra, for 1 week only.
TIER 2 (1). Adjust ventilatory rate to lower paCO2 to 32 – 35 mm Hg. (2). High dose Mannitol > 1 g/kg. (3). Repeat CT to determine if increased size of intracranial mass lesions. (4).Treat surgically remediable lesions with craniotomy according to guidelines. (5). Adjust temperature to 35 – 37o C, using active cooling measures.	**TIER 2** (1). Adjust ventilator parameters to increase paO2. by increasing FiO2 to 100%. (2). Increase paO2 by adjusting PEEP (3). Increase CPP up to a maximum of 70 mmHg with vasopressors. (4). Adjust ventilatory rate to increase paCO2 to 45 – 50 mm Hg. (5). Transfuse pRBCs to reach Hgb > 10 g/dL. (6). Decrease ICP to < 10 mm Hg. 6a. CSF drainage. 6b. Increased sedation.	**TIER 2.** (1). High dose Mannitol 1 g/kg, or frequent boluses standard dose Mannitol (2). Increase CPP up to maximum of 70 mm Hg with vasopressors. (3). Adjust ventilator parameters to increase paO2 by increasing FiO2 to 100%. (4). Increase FiO2 by increasing PEEP (5). Transfuse to Hgb $\geq$ 10 g/dL. (6). Repeat CT to determine if increased size of intracranial mass lesions. (7). Treat surgically remediable lesions with craniotomy according to guidelines (8). Induced hypothermia to 35 - 37o C, using active cooling measures.
TIER 3 (Tier 3 therapies are optional). (1). Pentobarbital coma, according to local protocol. (2). Decompressive craniectomy. (3). Adjust temperature to 32 – 34.5o C, using active cooling measures. (4). Neuromuscular paralysis		**TIER 3.** (Tier 3 therapies are optional). (1). Pentobarbital coma: (2). Decompressive craniectomy. (3). Induced hypothermia. hypothermia to 32 – 34.5o C. (4). Neuromuscular paralysis

Primary and Secondary Objectives

1. *Primary Objective:* The prescribed treatment protocol, based on $PbtO_2$ monitoring, results in reduction of the fraction of time that brain oxygen levels are below the critical threshold of 20 mm Hg in patients with severe traumatic brain injury
2. *Secondary Objectives:*
   a. *Safety hypotheses:* Adverse events associated with $PbtO_2$ monitoring are rare.
   b. *Feasibility hypotheses:* Episodes of decreased $PbtO_2$ can be identified and treatment protocol instituted comparably across clinical sites, and protocol violations will be low and uniform across different clinical sites.
   c. *Non-futility hypothesis:* The odds of good outcome measured by the Glasgow Outcome Scale-Extended 6 months after injury of 2.0 is consistent with the results of this phase II study.

BOOST-2 Primary Outcome



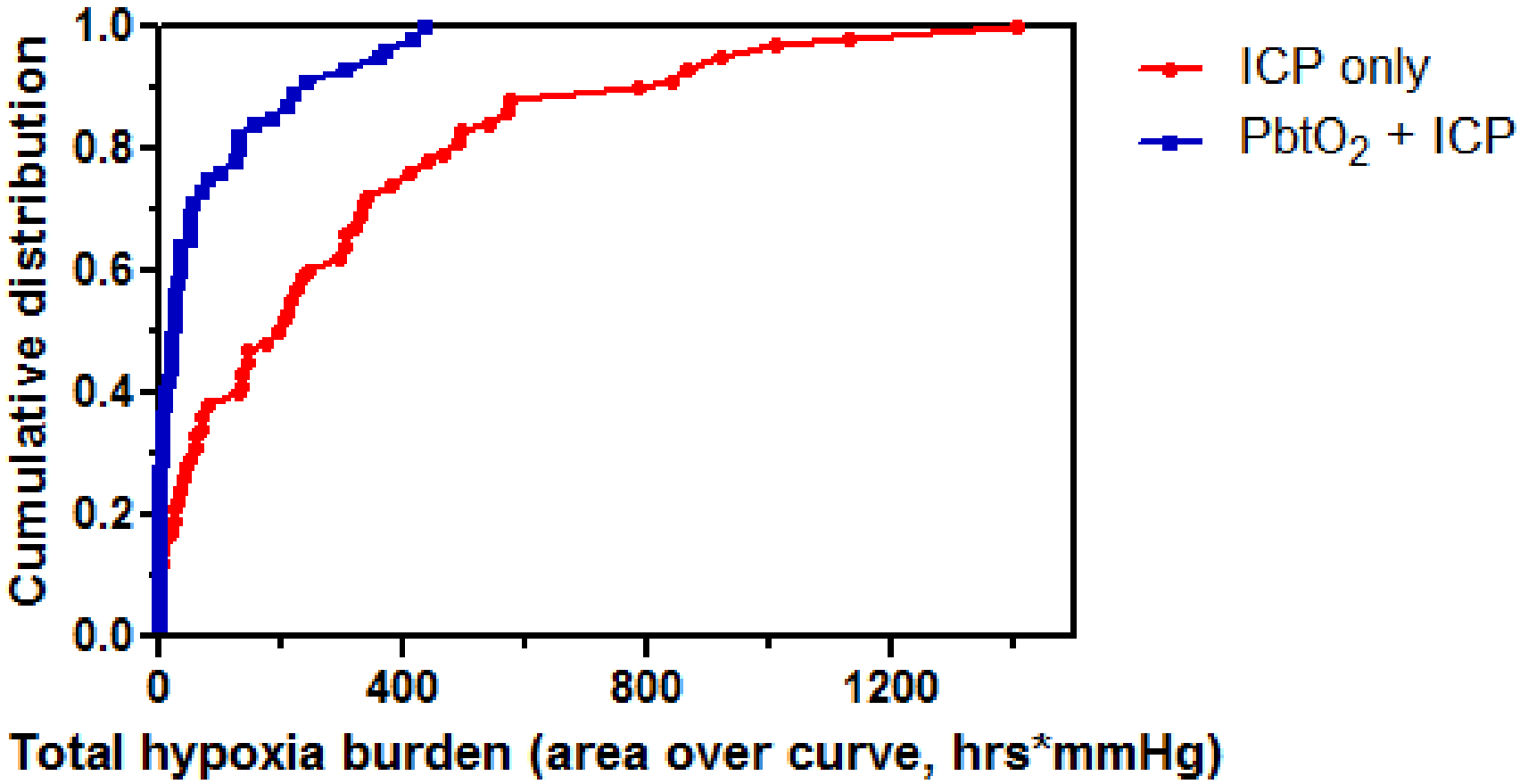
Okonkwo et al, *Critical Care Med* 2017

BOOST-2 Primary Outcome

$PbtO_2$ metric	ICP Only (N=57)	$PbtO_2$ + ICP (N=53)	p
Proportion of time below 20 mm Hg	.45 (.31) Median .44	.16 (.21) Median .14	<.00001
Average amount below 20 mm Hg	4.0 (4.0) Median 2.7	1.3 (2.2) Median 0.4	<.00001
Area [over] the curve (mm Hg*hrs)	287 (297) Median 196	94 (145) Median 28	<.00001

Okonkwo et al, *Critical Care Med* 2017

BOOST-2 Primary Outcome



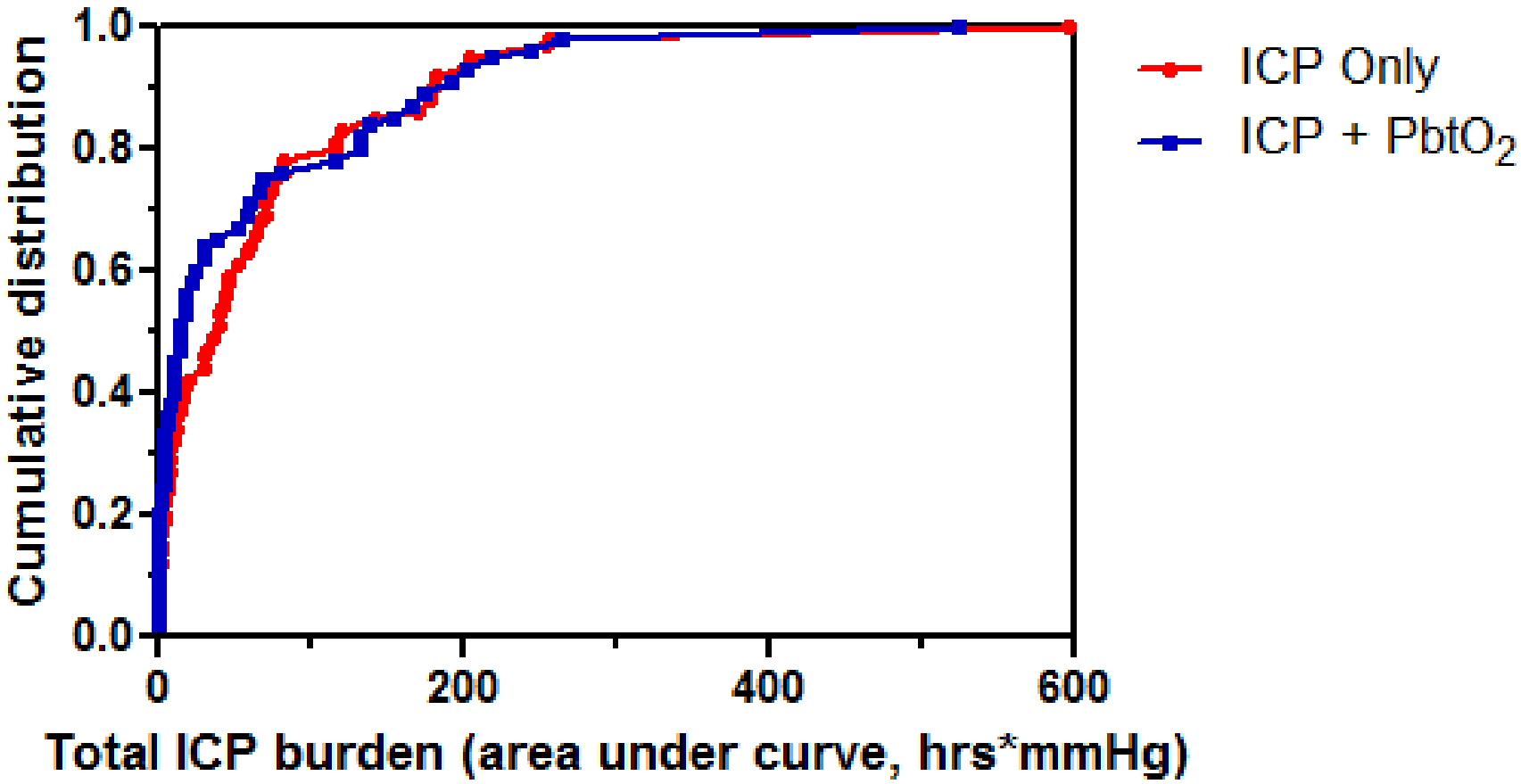
Okonkwo et al, *Critical Care Med* 2017

BOOST-2 Primary Outcome

ICP metric	ICP Only (N=55)	$PbtO_2$ + ICP (N=50)	p
Proportion of time above 20 mm Hg	.15 (.19) Median .10	.13 (.19) Median .04	.149
Average amount above 20 mm Hg	1.6 (7.0)* Median 0.4	0.7 (1.3)* Median 0.2	.299
Average amount above 20 mm Hg (excluding the 2 extreme outliers)	0.6 (0.9)	0.6 (0.8)	.311
Area under the curve (mm Hg*hrs)	103 (108) Median 36	50 (88) Median 17	.113
Area under the curve (mm Hg*Hrs) (excluding the 2 extreme outliers)	50 (56) Median 34	41 (59) Median 15	.115

Okonkwo et al, *Critical Care Med* 2017

BOOST-2 Primary Outcome



Okonkwo et al, *Critical Care Med* 2017

BOOST-2 Secondary Outcome --Safety

Serious Adverse Events by Treatment Groups	Overall	ICP Only	$PbtO_2$ + ICP	p
Subjects	**119**	**62**	**57**	
A - Cardio-Vascular	14 (12%)	5 (8%)	9 (16%)	.257
B - Genito-Urinary	0 (0%)	0 (0%)	0 (0%)	---
C - Gastro-intestinal	2 (2%)	1 (2%)	1 (2%)	1.000
D - Laboratory abnormalities	0 (0%)	0 (0%)	0 (0%)	---
E - Metabolic Disorders	0 (0%)	0 (0%)	0 (0%)	---
F - Musculo-skeletal	0 (0%)	0 (0%)	0 (0%)	---
G - Neurological	15 (13%)	10 (16%)	5 (9%)	.276
H - Opthamologic	0 (0%)	0 (0%)	0 (0%)	---
I - Respiratory	5 (4%)	1 (2%)	4 (7%)	.192
J - Skin	0 (0%)	0 (0%)	0 (0%)	---
K - Other	25 (21%)	17 (27%)	8 (14%)	.114
Death following w/d of medical care	22 (18%)	14 (23%)	8 (14%)	.248
Other*	3 (3%)	3 (5%)	0 (0%)	.245

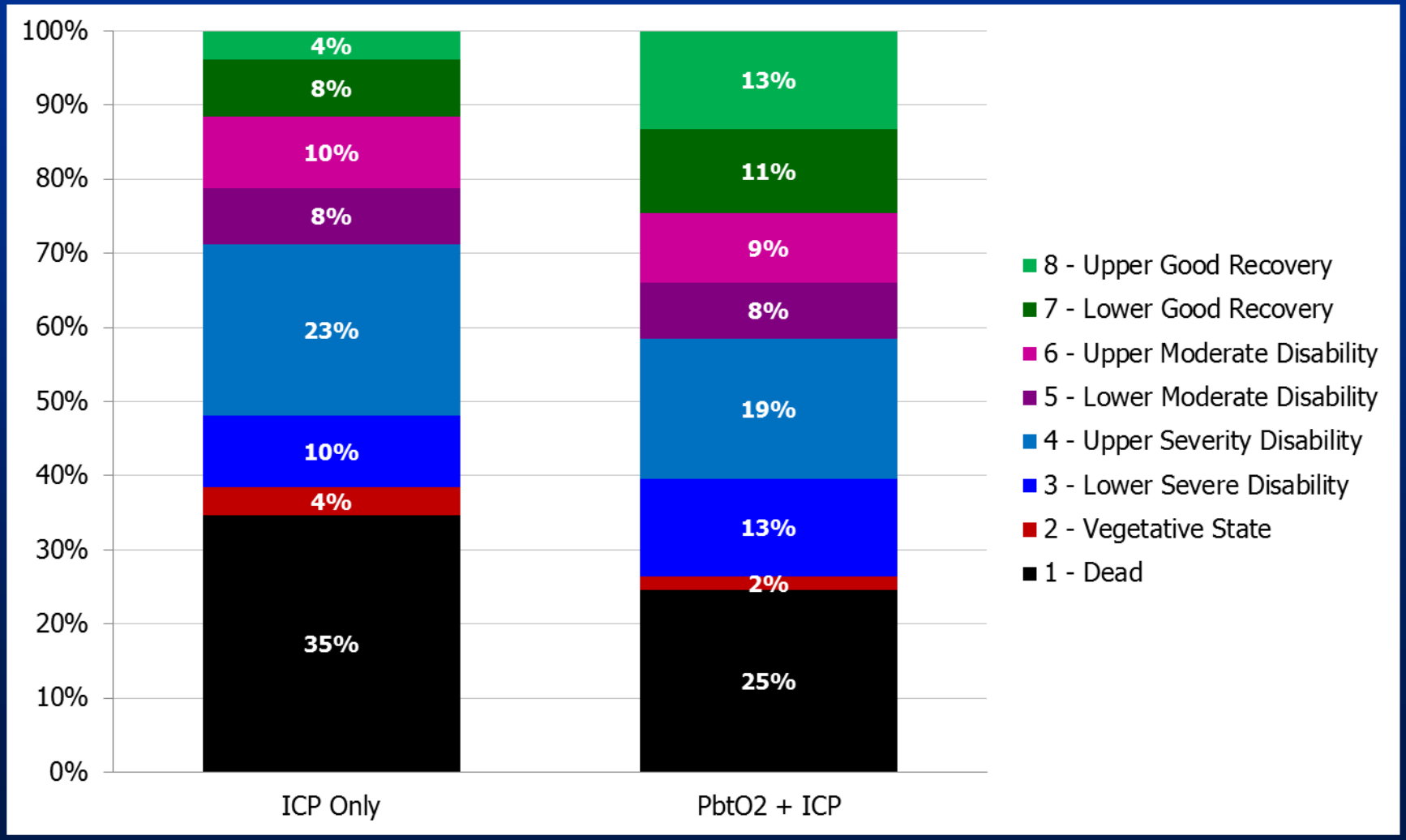
Okonkwo et al, *Critical Care Med* 2017

BOOST-2 Secondary Outcome --Feasibility

	Overall	ICP Only	$PbtO_2$ + ICP
Total	**166**	**71**	**95**
Deviation: ICP 20-25 for >30 min.	104	57	47
Deviation: pBtO2 15-19 for >30 min.	24	0	24
Violation: ICP >25 for >30 min.	21	14	7
Violation: pBtO2 <15 for >30 min.	17	0	17

Okonkwo et al, *Critical Care Med* 2017

BOOST-2 Secondary Outcome --Non-futility



Okonkwo et al, *Critical Care Med* 2017

BOOST-Phase 3

- Approved by NINDS Council 9/2017
- Target enrollment 1094
  - Sufficient to detect a 10% absolute improvement in good outcome
  - GOS-E Sliding Dichotomy
- Planned 45 sites
- In collaboration with SIREN Network

Bio-BOOST

- Invited to submit proposal by DoD/MRMC
- Goals
  - Collect blood from 300 participants in BOOST-3 (at 10 experienced clinical sites)
  - Samples obtained twice daily over 5 days, and again at day 7 and 14
  - Assay GFAP, UCHL-1, Tau, and NF-L
- Samples stored at BioSEND, Indiana Univ.
- Scientific outcomes:
  - Confirm relationship between tissue hypoxia and neurodegeneration
  - Assess efficacy of treatments reversing brain tissue hypoxia for preventing neurodegeneration