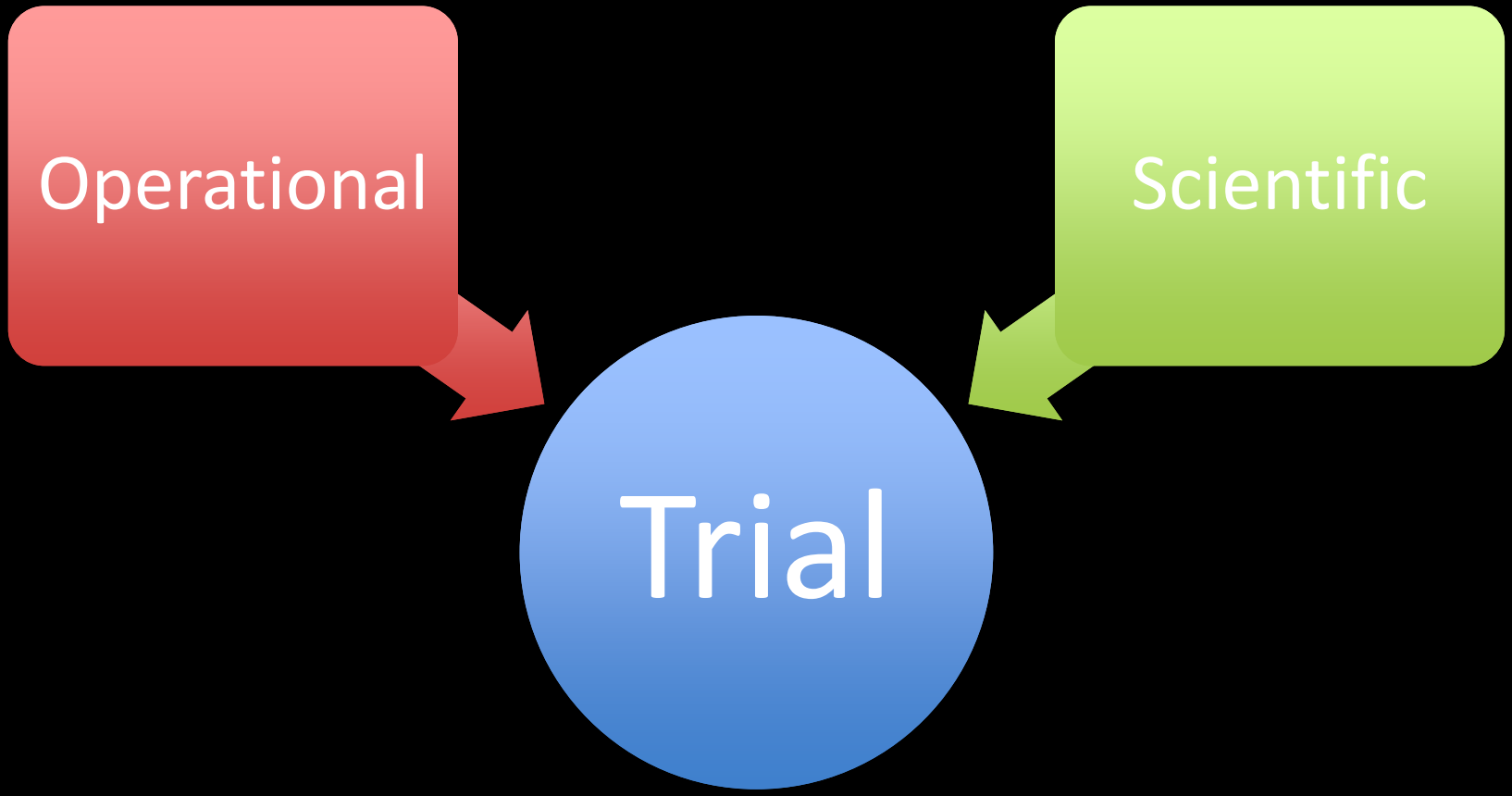
"More people would learn from their mistakes if they weren't so busy denying them"

LESSONS LEARNED



Failure of past TBI clinical Trials

- "None of the available medical therapies provide substantial relief from oedema and raised ICP, or at best, they are temporizing in most cases." *Ayata C and Ropper A, J Clin Neurosci 9, 2002.*
- Hypothermia trials have been inconclusive (Interagency meeting on TBI, Washington, DC 2003).
- 50 compounds in 30 TBI trials over 30 years—all failed. Most recently:
- Methylprednisolone (CRASH trial) Failed
- Magnesium Sulfate Failed
- Dexanabinol Failed
- Tirilizad Failed

At Present There Are No Effective Drug Treatments For Traumatic Brain Injury

Progesterone

Potential mechanisms in TBI

Remyelina

Increases Bcl2
AkT-P

Reduce Apoptosis

Mitochondrial
Recoupling

**Decreases free
radicals & lipi
peroxidation**

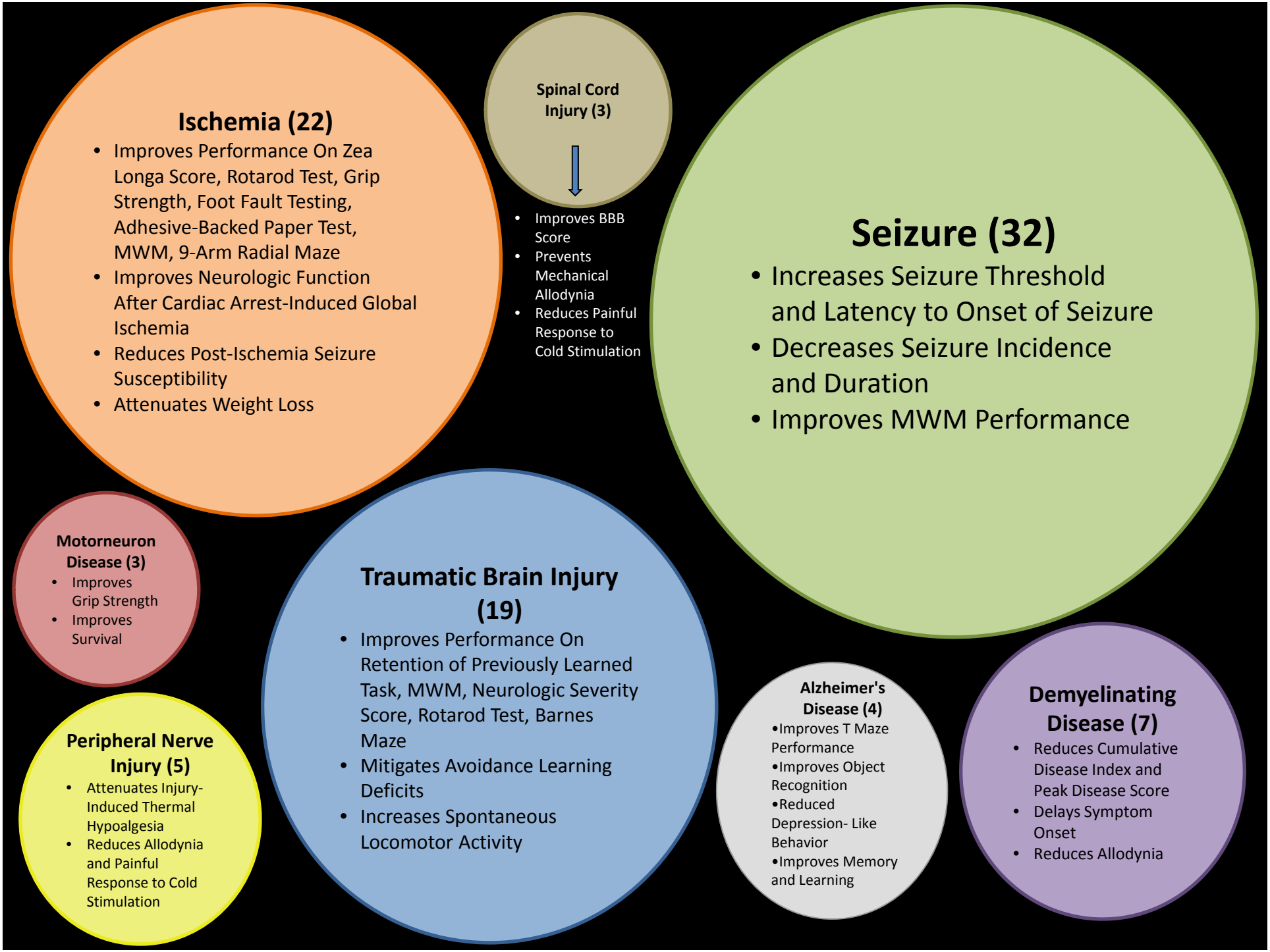
gonizes
Receptor

Vasogenic
Edema

**luces Cerebral
Edema**

Cytotoxic
Edema

ances
ABA


Ischemia (22)
• Improves Performance On Zea Longa Score, Rotarod Test, Grip Strength, Foot Fault Testing, Adhesive-Backed Paper Test, MWM, 9-Arm Radial Maze
• Improves Neurologic Function After Cardiac Arrest-Induced Global Ischemia
• Reduces Post-Ischemia Seizure Susceptibility
• Attenuates Weight Loss
Spinal Cord Injury (3)
• Improves BBB Score
• Prevents Mechanical Allodynia
• Reduces Painful Response to Cold Stimulation
Seizure (32)
• Increases Seizure Threshold and Latency to Onset of Seizure
• Decreases Seizure Incidence and Duration
• Improves MWM Performance
Motorneuron Disease (3)
• Improves Grip Strength
• Improves Survival
Traumatic Brain Injury (19)
• Improves Performance On Retention of Previously Learned Task, MWM, Neurologic Severity Score, Rotarod Test, Barnes Maze
• Mitigates Avoidance Learning Deficits
• Increases Spontaneous Locomotor Activity
Alzheimer's Disease (4)
•Improves T Maze Performance
•Improves Object Recognition
•Reduced Depression- Like Behavior
•Improves Memory and Learning
Demyelinating Disease (7)
• Reduces Cumulative Disease Index and Peak Disease Score
• Delays Symptom Onset
• Reduces Allodynia
Peripheral Nerve Injury (5)
• Attenuates Injury-Induced Thermal Hypoalgesia
• Reduces Allodynia and Painful Response to Cold Stimulation

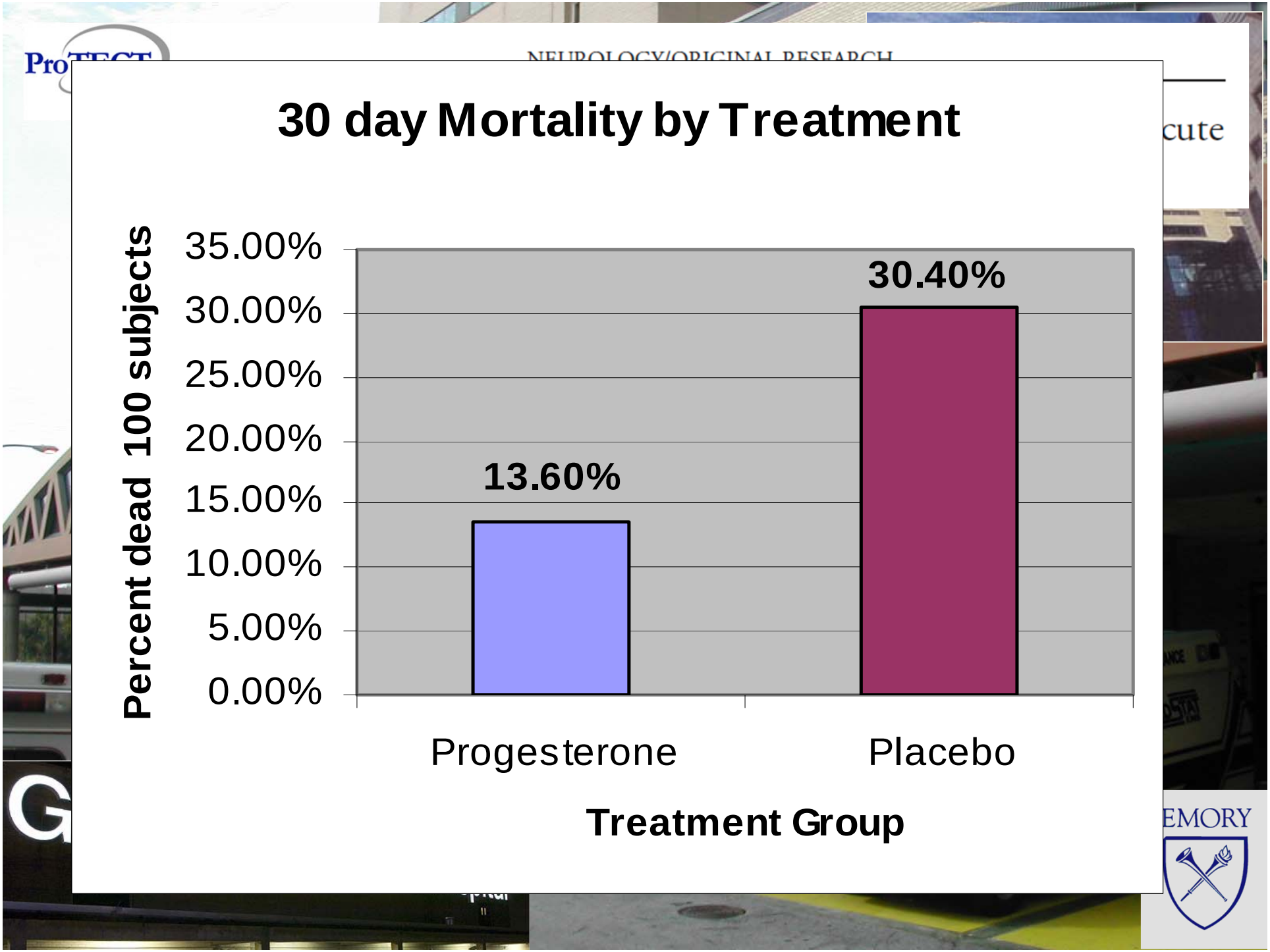
STAIR Rubric

STAIR Criteria	TBI	Ischemia	SCI	Peripheral Nerve Injury	Motorneuron Disease	Demyelinating Disease	Seizures
Dose Comparison	4	5	1	1	--	2	16
Timing Comparison (Initiation or Duration)	6	4	1	2	--	--	2
Histologic Outcomes	57	47	16	8	7	10	12
Functional Outcome	19	22	3	5	3	7	33
Long Term Outcomes (≥ 18 Days)	9	5	5	4	4	4	--
Species	64 Rodent	45 Rodent, 2 Cat	16 Rodent, 1 Rabbit	8 Rodent	7 Rodent	10 Rodent	38 Rodent, 1 Cat
Aged Animals	6	3	--	1	--	1	--
Comorbidities Studied	Hyperthermia, Vit D Deficiency	Hypertension, Infection	--	--	--	--	--
Male and Female	53 Male, 25 Female	38 Male, 14 Female	16 Male, 3 Female	6 Male, 1 Female	7 Male, 7 Female	5 Male, 5 Female	18 Male, 26 Female

Stroke Therapy Academic Industry Roundtable (STAIR)
(Feinklestein et al. 1999; updated Fisher et al. 2009)

Corroborative Research

- **>200 publications showing positive results with progesterone in neurological injury**
  - 24 different laboratories
  - 4 animal species
  - 22 different animal models


30 day Mortality by Treatment
Percent dead 100 subjects
35.00%
30.00%
25.00%
20.00%
15.00%
10.00%
5.00%
0.00%
13.60%
30.40%
Progesterone
Placebo
Treatment Group

Two Human Pilot Trials

Progesterone clinical trial designs:

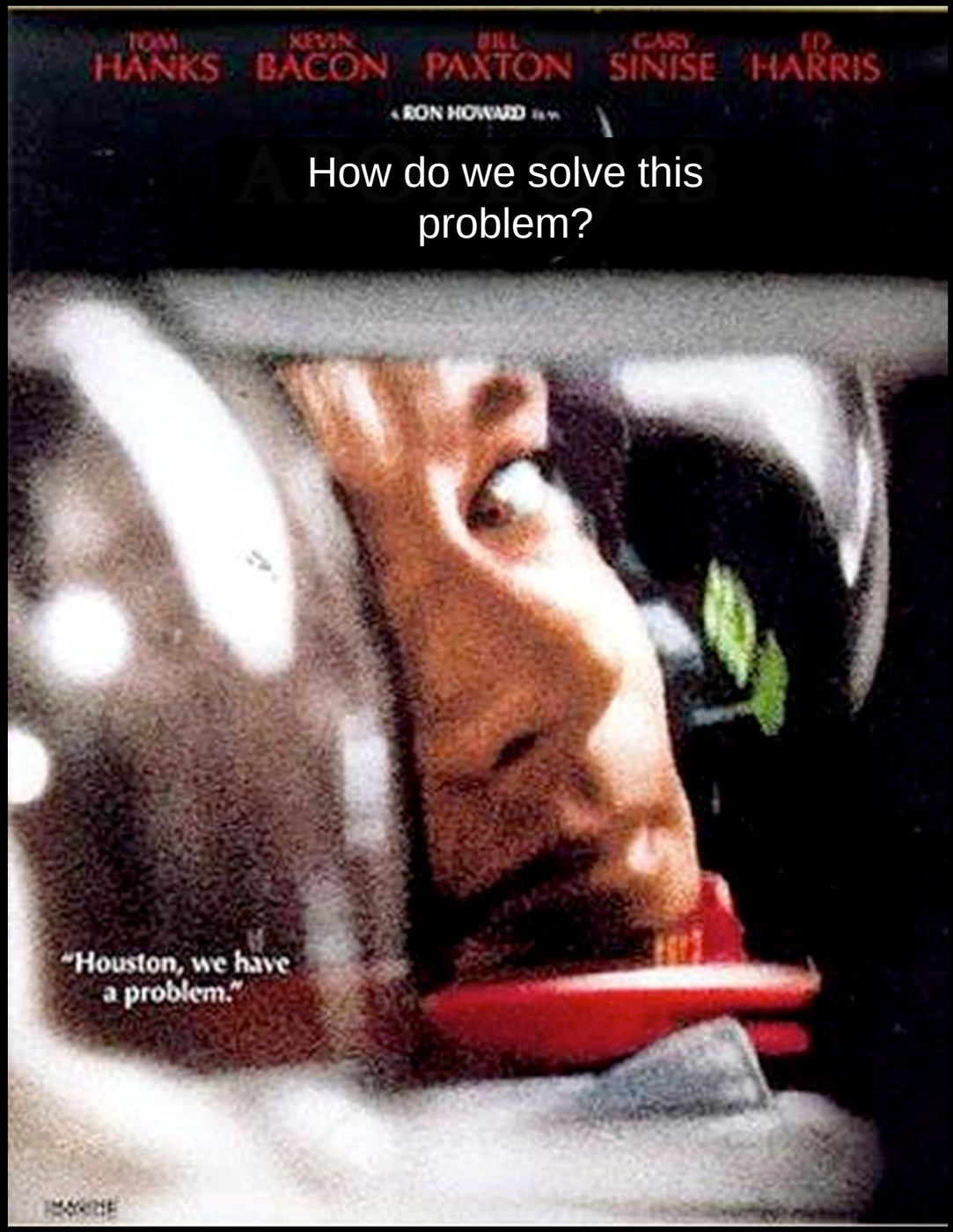
	Wright et al.	***Xiao et al.***
Publication Year	2007	2008
Country	USA	China
Sites	Single-Center	Single-Center
Blinding	Double	Double
Randomization Scheme	4:1 (Tx:Pl)	1:1
Primary Goal	Safety	Efficacy
N	100	159
GCS Included	4 – 12	≤ 8
Treatment Window	<11 hours post-injury	<8 hours post-injury
Medication Administration	Loading: 0.71 mg/kg IV @ 14 mL/h x 1h Maintenance: 0.5 mg/kg IV @ 10 mL/h q12h x 3 days	1 mg/kg IM q12h x 5 days

Lower DRS = Better outcome


PROTECT III

Outcome - Mortality

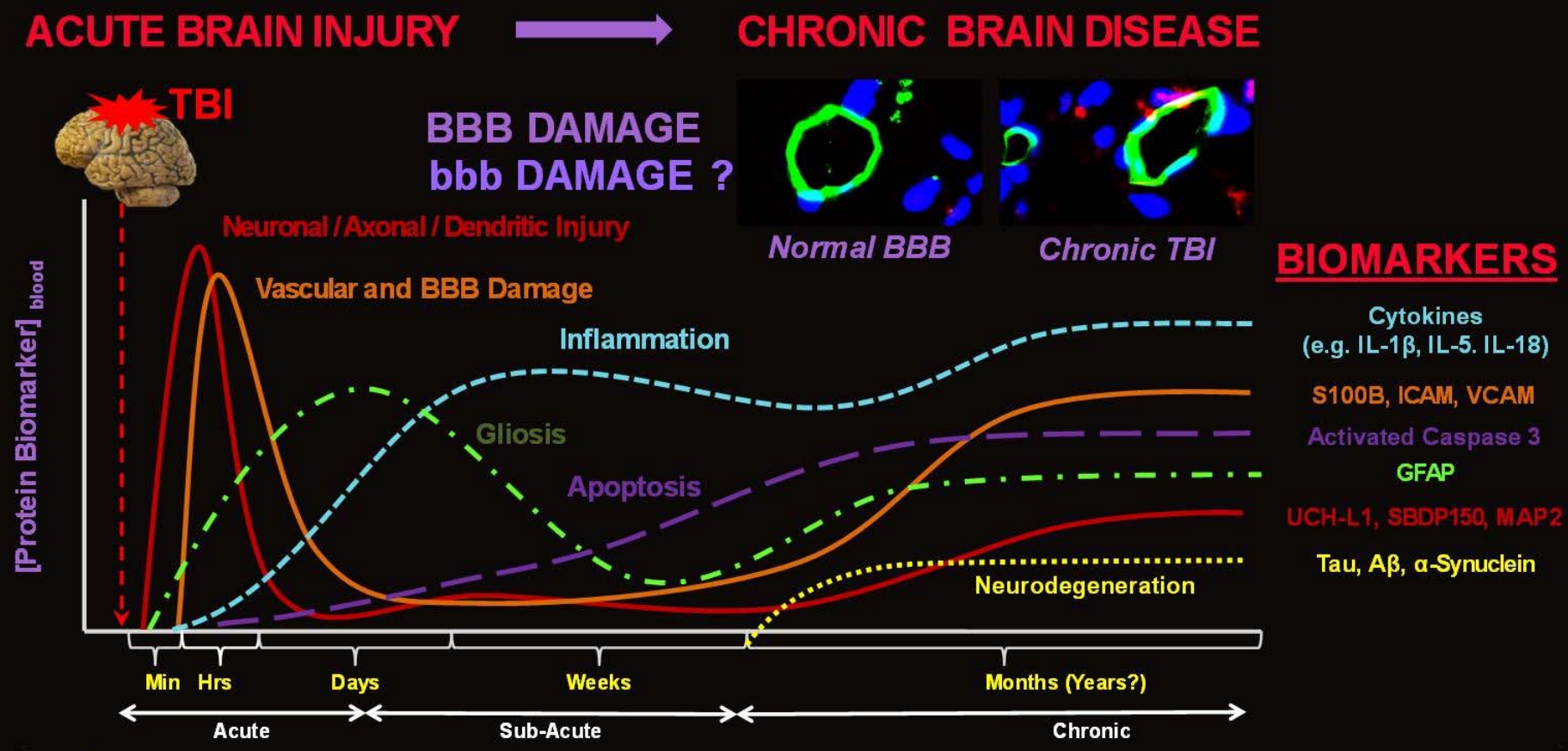
	Progesterone	Placebo	Overall
Mortality	83 (18.8)	69 (15.7)	152 (17.2)
Cause of Death: n (% of deaths)			
Neurological	53 (63.9)	49 (71.0)	102 (67.1)
Not Neurological	28 (33.7)	20 (29.0)	48 (31.6)
Other	2 (2.4)	0 (0.0)	2 (1.3)
Mortality by initial injury severity			
Moderate (iGCS 9-12)	19 (14.7)	14 (11.2)	33 (13.0)
Mod Severe (iGCS 6-8/iMotor 4-5)	37 (15.8)	39 (16.4)	76 (16.1)
Most Severe (iGCS 4-5/iMotor 2-3)	27 (34.2)	16 (20.8)	43 (27.6)


TOM HANKS
KEVIN BACON
BILL PAXTON
GARY SINISE
ED HARRIS
A RON HOWARD
How do we solve this problem?
"Houston, we have a problem."


To Save Time,
Let's Just Assume
I Know Everything

Timing - Window - Dose

What are we treating?



VCU

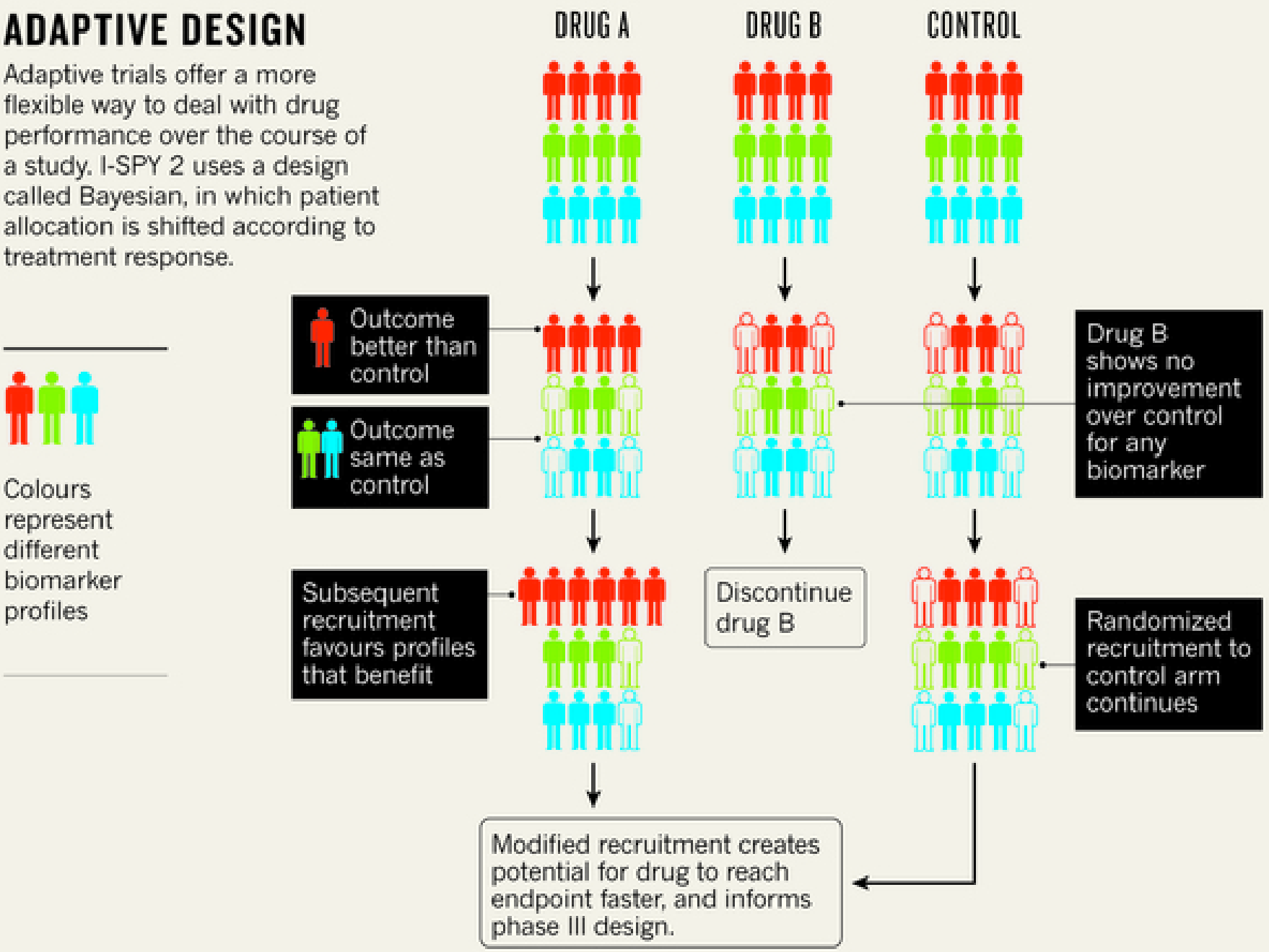
Make it real.

VIRGINIA COMMONWEALTH UNIVERSITY

Courtesy of Ron Hayes

ADAPTIVE DESIGN

Adaptive trials offer a more flexible way to deal with drug performance over the course of a study. I-SPY 2 uses a design called Bayesian, in which patient allocation is shifted according to treatment response.



Glasgow Coma Score

E

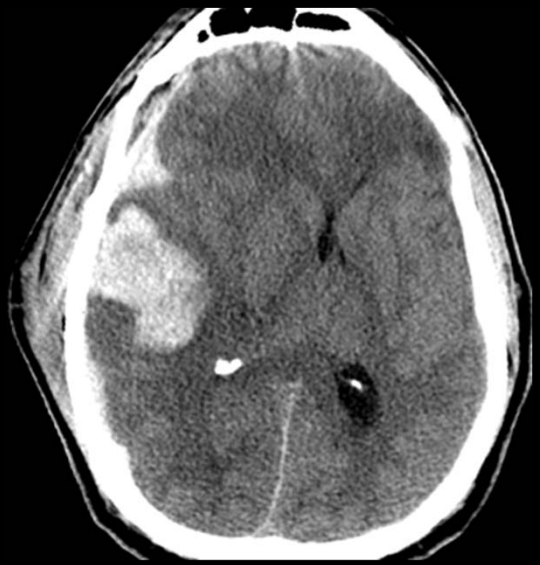
V

M

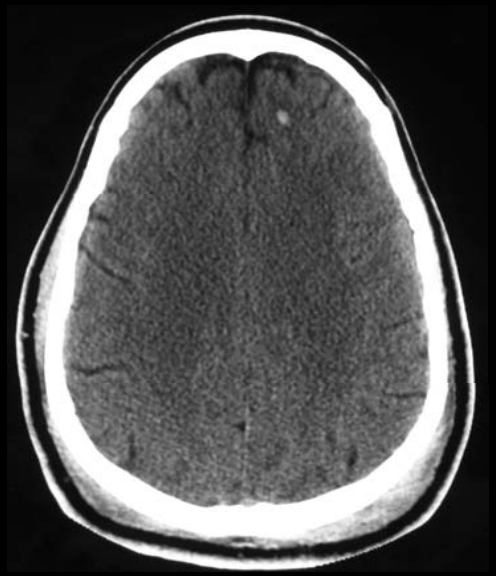
Finding	Pediatric Specific Score	
EYE OPENING		
Spontaneously		4
To speech		3
To pain		2
No response		1
VERBAL RESPONSE		
Alert & oriented	Smiles/Coos	5
Converses but disoriented	Inappropriate cries	4
Speaking nonsensical	Persistent scream	3
Moans, unintelligible sounds	Grunts	2
No response		1
MOTOR		
Follows commands	Spontaneous move	6
Localizes to pain		5
Movement or withdrawal to pain		4
Abnormal flexion (decorticate)		3
Abnormal extension (decerebrate)		2
No response		1
		15

6 Different Examples of Severe TBI

Epidural hematoma

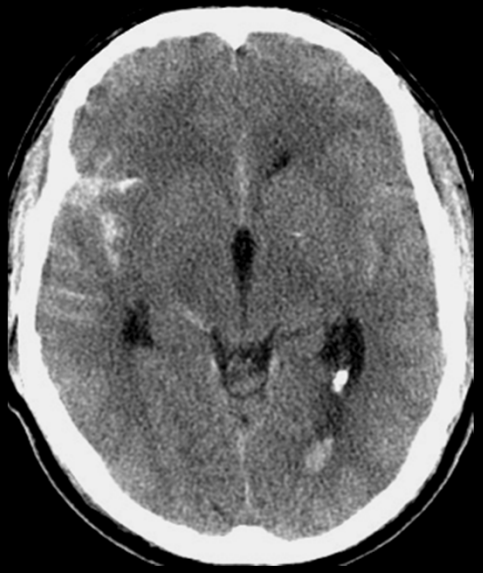


Contusion/Hematoma



Diffuse axonal injury

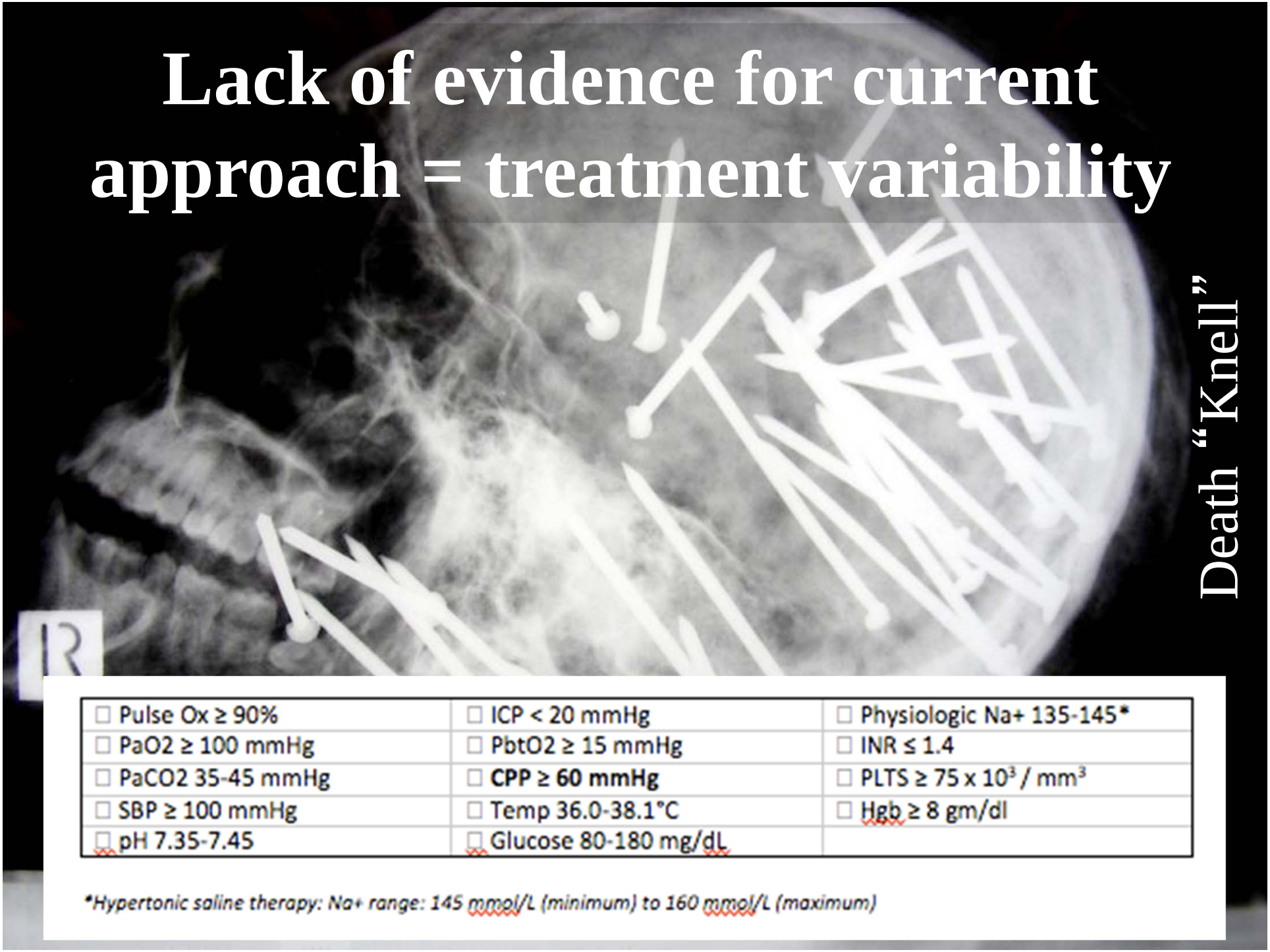
Subdural hematoma



Subarachnoid hemorrhage

Diffuse swelling

Lack of evidence for current approach = treatment variability



Death "Knell"

☐ Pulse Ox ≥ 90%	☐ ICP < 20 mmHg	☐ Physiologic Na+ 135-145*
☐ PaO2 ≥ 100 mmHg	☐ PbtO2 ≥ 15 mmHg	☐ INR ≤ 1.4
☐ PaCO2 35-45 mmHg	☐ **CPP ≥ 60 mmHg**	☐ PLTS ≥ 75 x 10^3 / mm^3
☐ SBP ≥ 100 mmHg	☐ Temp 36.0-38.1°C	☐ Hgb ≥ 8 gm/dl
☐ pH 7.35-7.45	☐ Glucose 80-180 mg/dL	

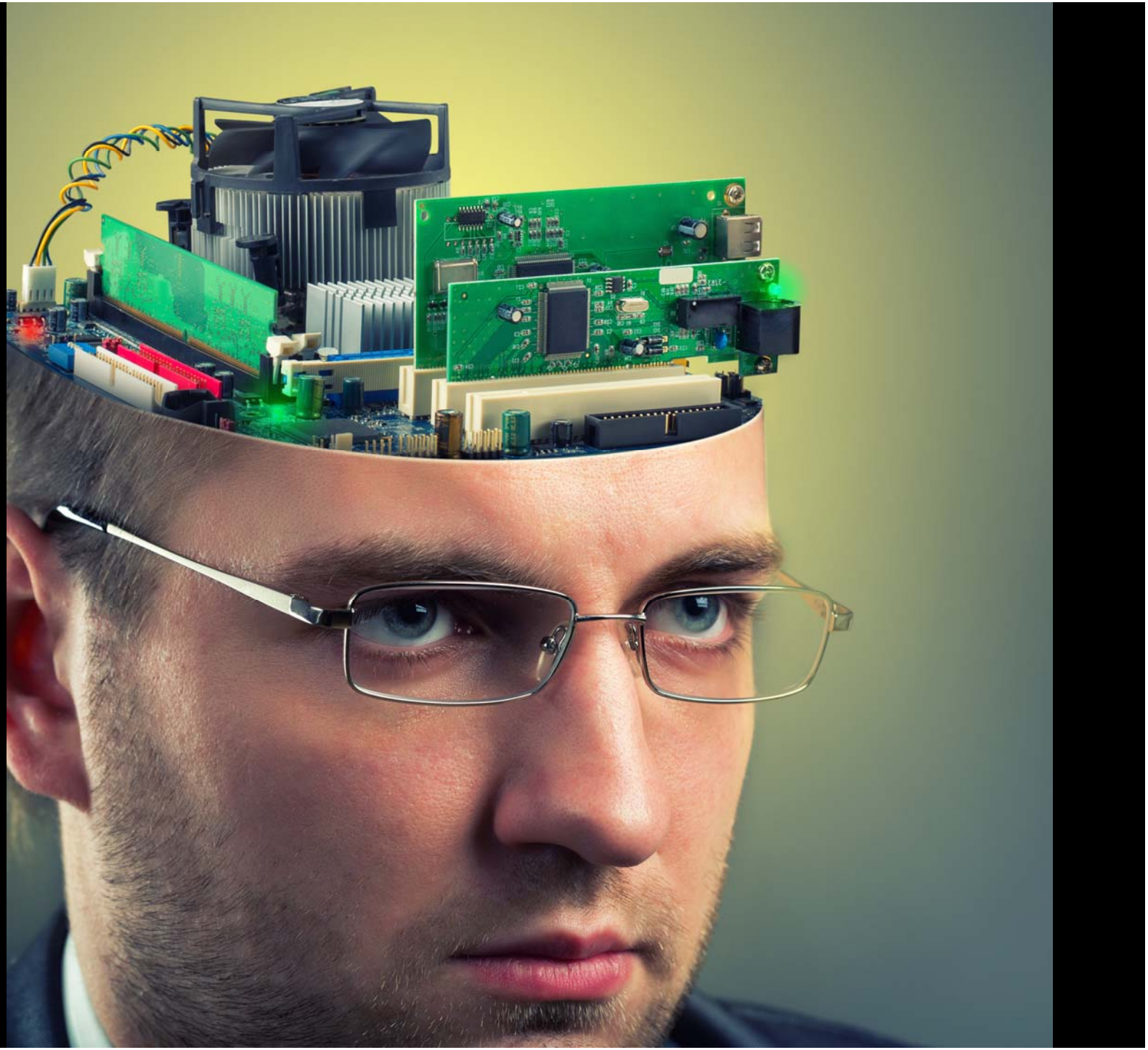
**Hypertonic saline therapy: Na+ range: 145 mmol/L (minimum) to 160 mmol/L (maximum)*

Heterogeneity

- Mechanism
- Individual Resilience/genetics/age/comorbidities
- Severity/underlying pathology
- Acute Treatment
- Rehabilitation
- Social determinants (support structure)


Rehabilitation

Outcome measures



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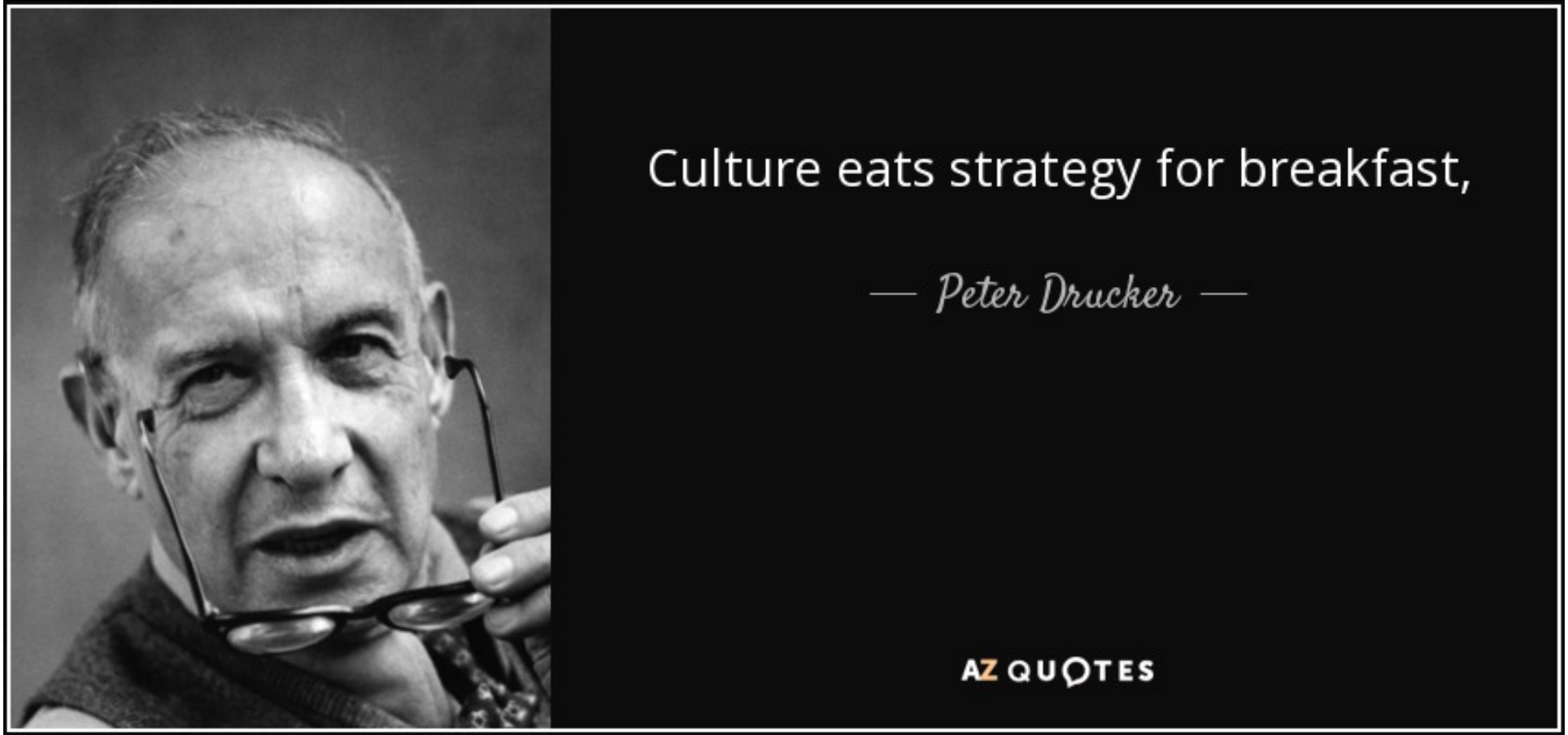
OPERATIONAL LESSONS



BUILD A Committed TEAM

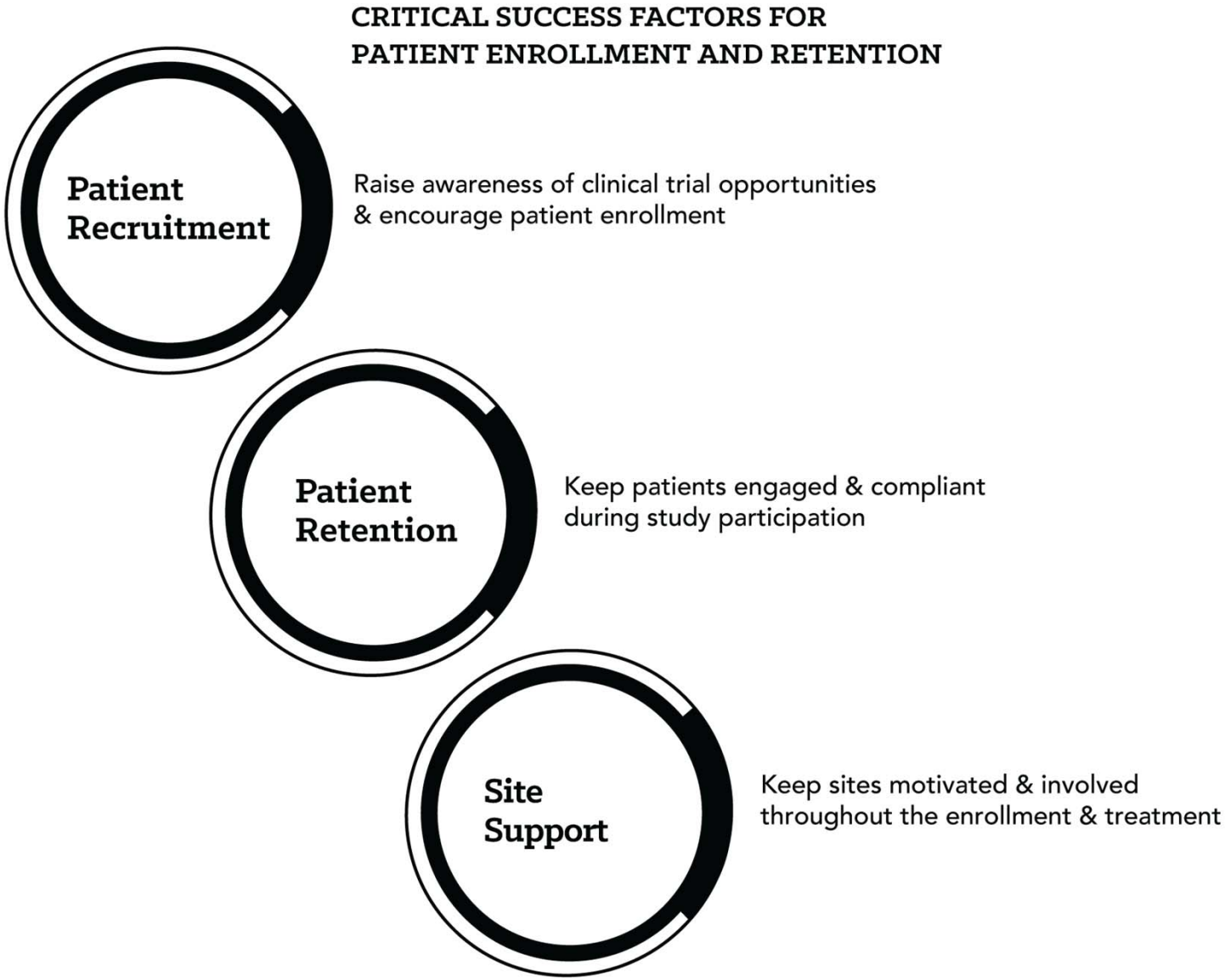
- Know your protocol backwards and forwards
- Know your team
- Do NOT make exceptions to the inclusion/exclusion criteria
- BE AVAILABLE!

Lessons Learned

- In person site visit
- Getting in-person verbal agreement btw key personnel (including primary services)
- Have sites show you their plan for competing studies.
- Close monitoring (keep up), monitor the monitors
- Acknowledge and reward good sites
- Adequate budget
- Centralize primary outcome
- Ensure good training (SV post 1-2 patient)
- Ask the team about lessons
- Be an enrolling site (confidence and ground truth)
- Deal with problems quickly

Be firm, but fair.

ENROLLMENT IS KING!




The difference between
mediocrity and excellence
is attention to detail.
SEBASTIAN J. BARBARITO