It Takes a Village

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Objectives

- Leading a complex clinical trial
- Overview of Neurological Emergencies Treatment Trials Network
- ProTECT III Progesterone for the Treatment of Traumatic Brain Injury
- IRB process
- Lessons learned

Financial Disclosures

- None

TEAMWORK

Coming together is a beginning.
Keeping together is progress. Working together is success.

Henry Ford

Neurological Emergencies Treatment Trials (NETT) Network

NETT
Neurological Emergencies Treatment Trials

ProTECT™ III:

Progesterone for Traumatic Brain Injury

ProTECT™

Why is This Important?

Traumatic Brain Injuries

Estimated 1.7 million TBIs

↓

1,365,000 Emergency Department Visits

↓

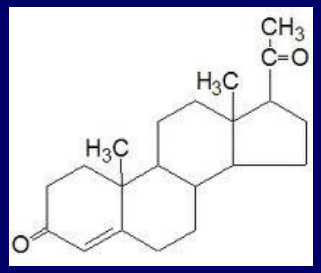
275,000 Hospitalizations

↓

52,000 Deaths

Faul, M et al. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, 2010

Progesterone and TBI



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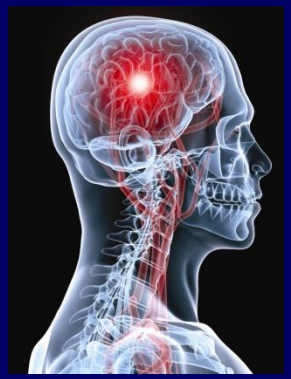


Proposed Mechanisms:

- **Protects blood brain barrier**
- **Reduces cerebral edema**
- **Down-regulates inflammatory cascade**

Purpose

To determine the efficacy of progesterone in pts with moderate to severe TBI

Inclusion Criteria

1. Blunt traumatic brain injury

2. GCS 4-12

3. Can start infusion within 4 hours of injury

4. Age ≥18 yrs

Consent Process

- How would this work in patients with moderate to severe traumatic brain injury?
- Exception from Informed Consent 21 CFR 50.24
  - Does not mean informed consent is not ultimately obtained

Exception from Informed Consent for Emergency Research: 21 CFR 50.24

- ✓ Life-threatening situation needing urgent intervention
- ✓ Available treatments unproven or unsatisfactory
- ✓ Participation holds prospect of direct benefit to the subjects

IRB Requirements

- Before IRB approval
- Community Consultation
- Public Disclosure
- IRB final determination

Identifying the Community

- Local colleges
- Brain Injury Association
- Health Care for Homeless
- Neighborhood Meetings
- Health Fairs
- Trades Associations
- Police Meetings

CC and PD Plans

- Focus Groups
- Presentations
- Surveys
- Opt Out
- Media
  - TV
  - Radio
  - Newspapers

The Boston Globe

Health & wellness

Hospitals want to test drug with no consent

By Chelsea Conaboy | GLOBE STAFF JUNE 08, 2013

A group of Boston doctors is proposing to join a study that would provide emergency treatment for brain-injured patients without obtaining the trauma victims' consent, arguing that they often arrive at the hospital unconscious or without family members who can speak on their behalf.

Federal law and the generally accepted ethics of medical research require that patients or their surrogates be told about any risks of participating in a study and have the chance to refuse enrollment. But the law allows for an exemption in certain cases involving emergency care.

This would be the first study using the exemption at a Boston hospital since the Food and Drug Administration created the rules allowing it in 1996, said Dr. James Feldman, an investigator and the chairman of a Boston University Medical Campus panel that reviews research.

Boston.com Comments

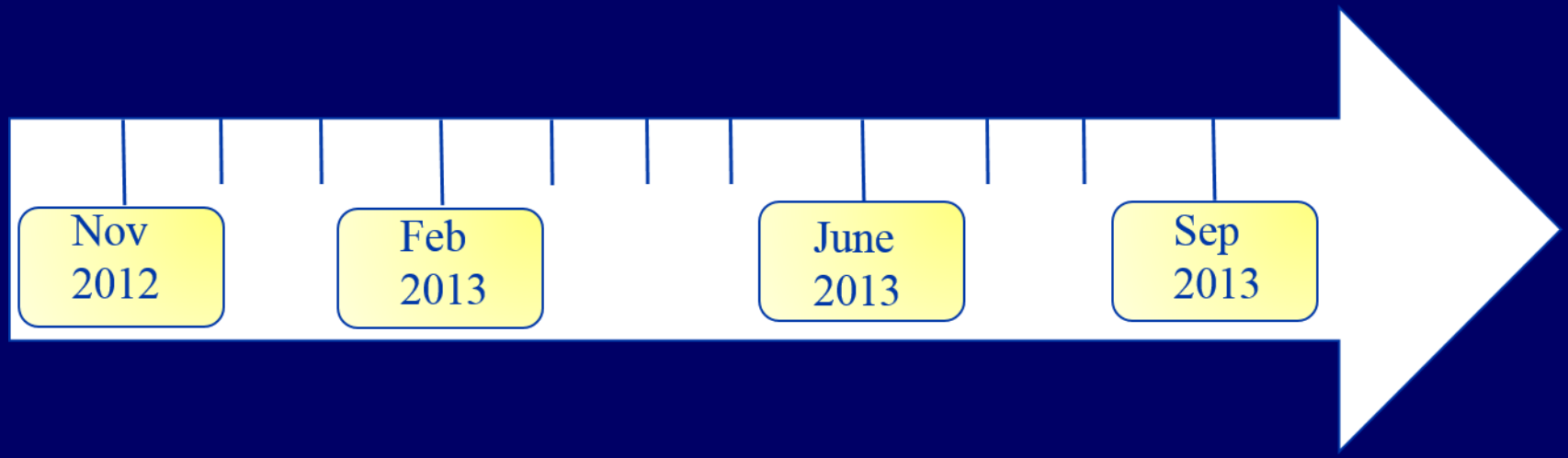
Is this because they want to help the patient or just want a guinea pig?

If doctors would like this from “us”…how about they allow us to run some experiments on “them” without their consent?

I don’t know what they are smoking over at these formerly prestigious institutions, but they might want to put it away for awhile and breath in some fresh air…They have lost all sense of reality

Experimenting on people who cannot say no. Can we get a list of these new age Nazi’s?

Timeline



Investigational Drug

- Treatment and placebo – indistinguishable
- Total infusion 96 hours
- Blood Draws:
  - Baseline, 24 and 48 hours

Targets for Goal Directed Therapy

Multidisciplinary

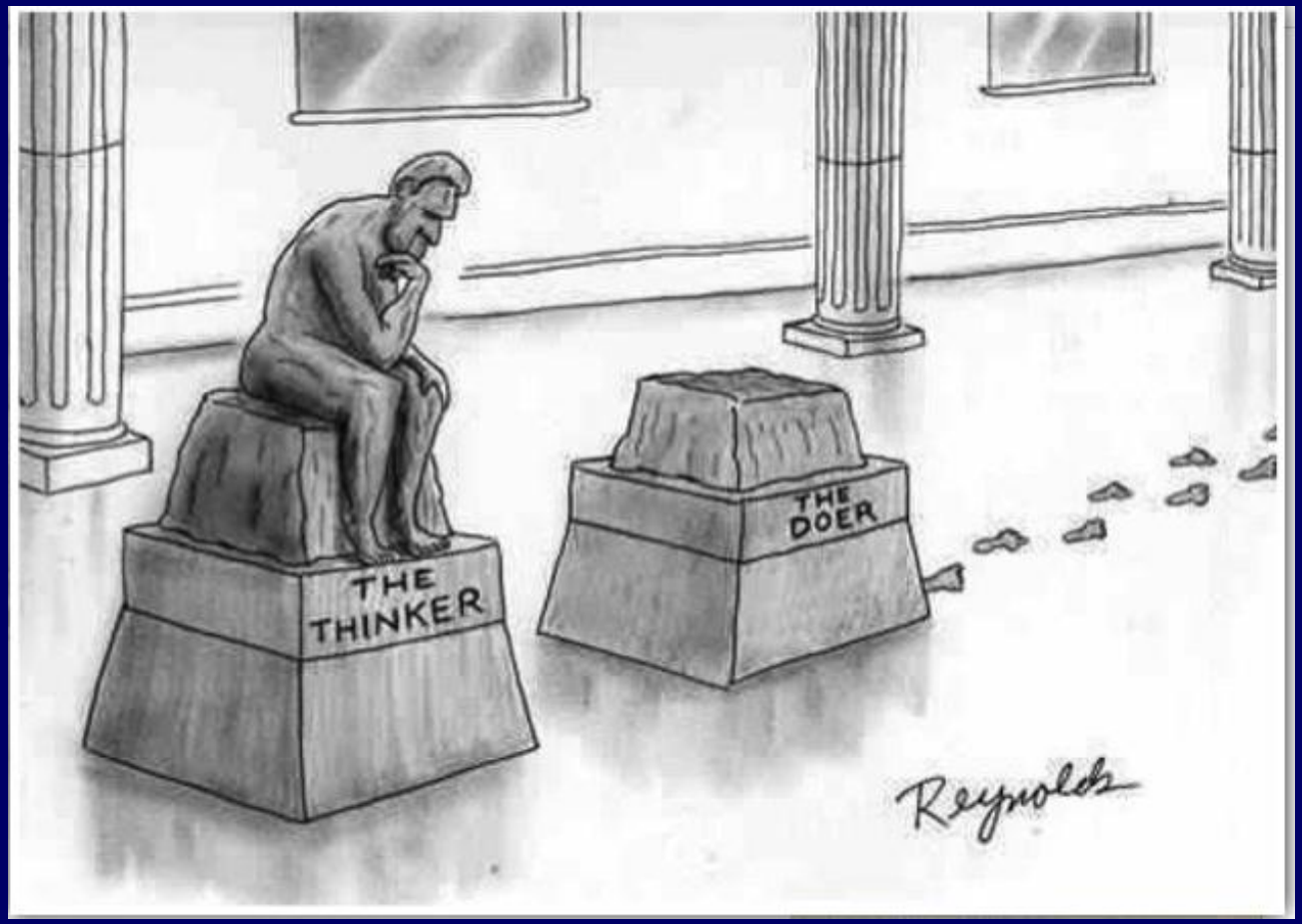
- EMS
- Emergency Medicine
- Trauma Surgery
- Neurosurgery
- Anesthesia

- Nursing: ED, SICU, OR, PACU, Radiology
- Pharmacy: IPS, ED, Critical Care, Main
- Laboratory Medicine
- Respiratory
- Radiology
- IT
- Neuropsych for follow up

Investigator Requirements

- Multiple trainings
- Certifications
- Recertifications

Where Do I Start?



EMS Training

- What
- When
- Where
- How
- Why

Nurses and MDs

ED, Anesthesia, OR, PACU, SICU, Neurosurgery, Radiology

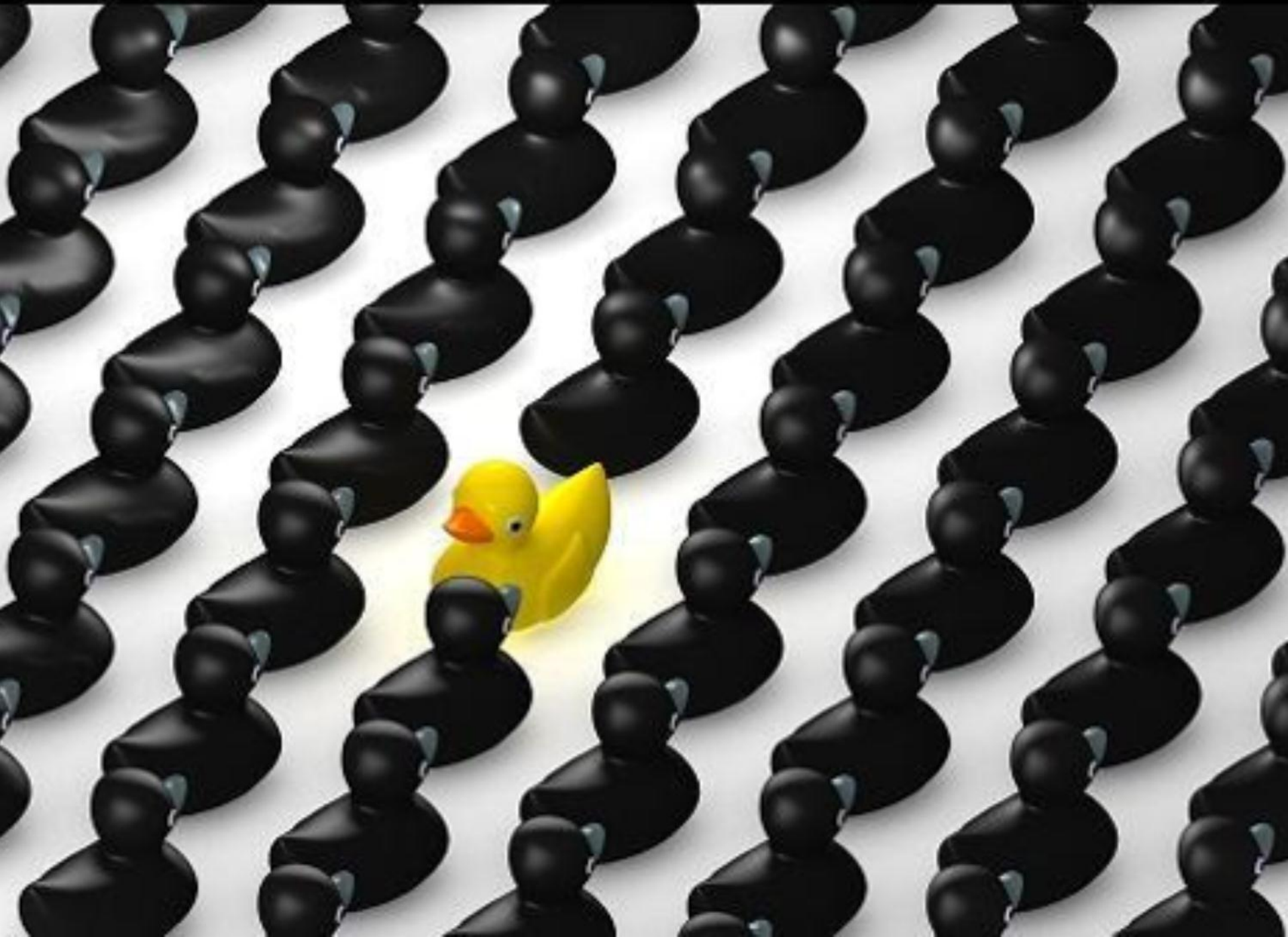
Lab

- Serum EtOH
- B-HCG
- Super STAT

Respiratory

Pharmacy

“I need this medication right away!”



Education and Training

- Step by step
- Develop systems and contacts in EVERY department

Time Saving Tips

- Mock screening and enrollment
- Create your own checklists
  - Pocket Cards
  - Info sheets
  - Posters

ProTECT III

ProTECT

Inclusion Criteria

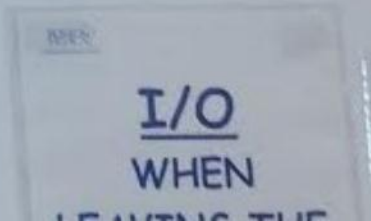
- Blunt TBI
- GCS 4-12
  - Motor 2-5 if intubated
- Age ≥ 18
- ED arrival ≤ 3 hour from Injury

Information needed from EMS

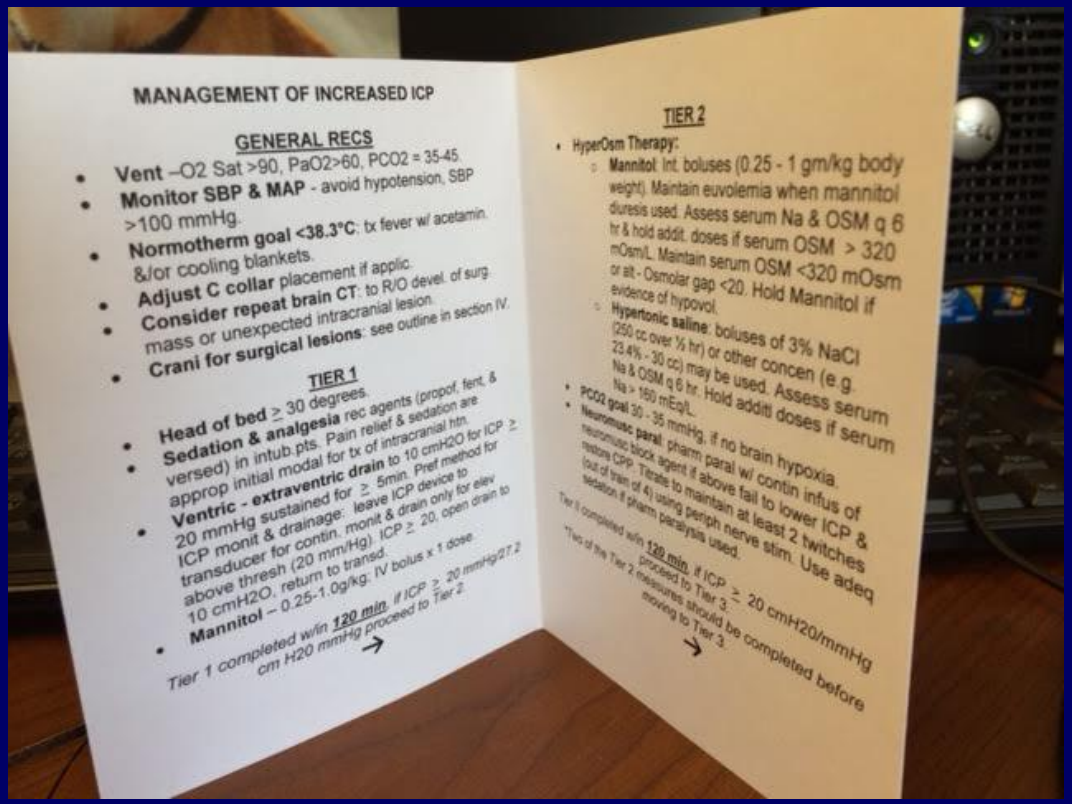
- Time of Injury
- Best GCS (E, V, M)
- Any SBP <90 mmHg for 5+ min
- O2 Sat <90% for 5+ min

Questions? Page ProTECT 7764 (PROG)


ProTECT III
Exclusion Criteria
Questions? Page ProTECT 7764


I/O
WHEN


ProTECT
I/O
WHEN
LEAVING THE
TRAUMA
ROOM



MANAGEMENT OF INCREASED ICP

GENERAL RECS

- **Vent** –O2 Sat >90, PaO2>60, PCO2 = 35-45.
- **Monitor SBP & MAP** - avoid hypotension, SBP >100 mmHg.
- **Normotherm goal <38.3°C**: tx fever w/ acetamin. &/or cooling blankets.
- **Adjust C collar** placement if applic.
- **Consider repeat brain CT**: to R/O devel. of surg. mass or unexpected intracranial lesion.
- **Crani for surgical lesions**: see outline in section IV.

TIER 1

- **Head of bed** ≥ 30 degrees.
- **Sedation & analgesia** rec agents (propof, fent, & versed) in intub pts. Pain relief & sedation are approp initial modal for tx of intracranial htn.
- **Ventric - extraventric drain** to 10 cmH2O for ICP ≥ 20 mmHg sustained for ≥ 5min. Pref method for ICP monit & drainage: leave ICP device to transducer for contin. monit & drain only for elev above thresh (20 mm/Hg). ICP ≥ 20, open drain to 10 cmH2O, return to transd.
- **Mannitol** – 0.25-1.0g/kg: IV bolus x 1 dose

*Tier 1 completed w/in **120 min**. If ICP ≥ 20 mmHg/27.2 cm H20 mmHg proceed to Tier 2*

→

TIER 2

- HyperOsm Therapy:
  - **Mannitol**: Int. boluses (0.25 - 1 gm/kg body weight). Maintain euvolemia when mannitol diuresis used. Assess serum Na & OSM q 6 hr & hold addit. doses if serum OSM > 320 mOsm/L. Maintain serum OSM <320 mOsm or alt - Osmolar gap <20. Hold Mannitol if evidence of hypovol.
  - **Hypertonic saline**: boluses of 3% NaCl (250 cc over ½ hr) or other concen (e.g 23.4% - 30 cc) may be used. Assess serum Na & OSM q 6 hr. Hold additi doses if serum Na > 160 mEq/L.
- **PCO2 goal** 30 - 35 mmHg, if no brain hypoxia
- **Neuromusc paral**: pharm paral w/ contin infus of neuromusc block agent if above fail to lower ICP & restore CPP. Titrate to maintain at least 2 twitches (out of train of 4) using periph nerve stim. Use adeq sedation if pharm paralysis used.

*Tier II completed w/in **120 min**, if ICP ≥ 20 cmH20/mmHg proceed to Tier 3.*

Two of the Tier 2 measures should be completed before moving to Tier 3.

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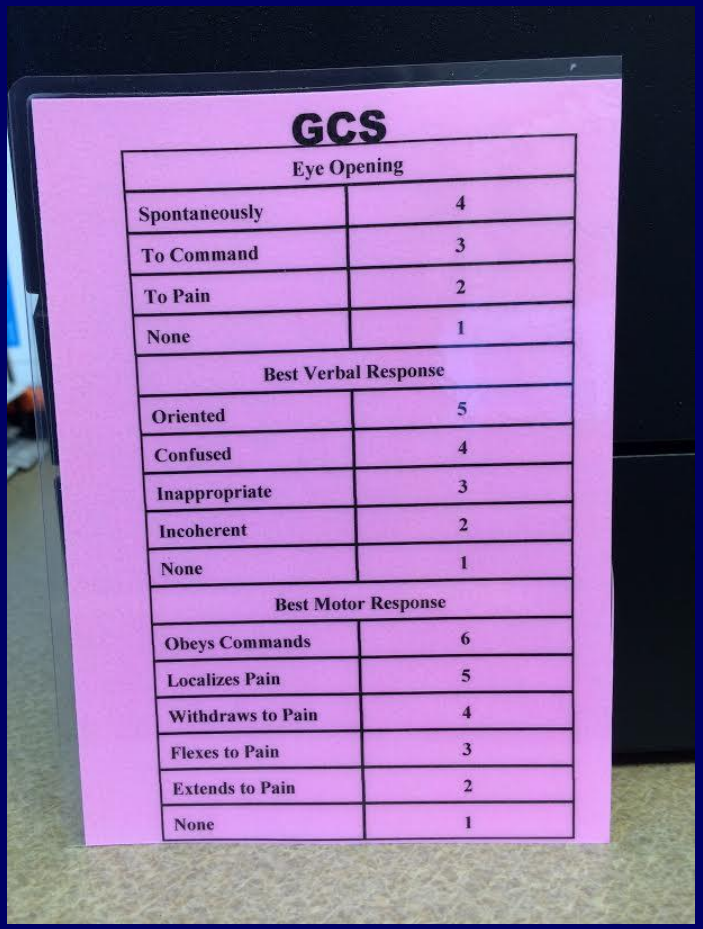

GCS

Eye Opening	
Spontaneously	4
To Command	3
To Pain	2
None	1
Best Verbal Response	
Oriented	5
Confused	4
Inappropriate	3
Incoherent	2
None	1
Best Motor Response	
Obeys Commands	6
Localizes Pain	5
Withdraws to Pain	4
Flexes to Pain	3
Extends to Pain	2
None	1

en ete]	Item	Comments/Documents/Contacts
	Screen: inclusion / exclusion (except labs) Estimated weight _____ lb _____kg Best GCS: E___ V____M____Total_____	1.Check Opt out registry: http://em.emory.edu/protect/optoutformadminlogin.cfm 2. EMS Trip Sheet info: https://epcr.bostonems.net/spenterprise-php/ Username:pmitchellbumc / Password:Research
	Contact investigators on call	Either Jim Feldman, Lauren Nentwich or Peter Burke
	Preliminary notification to Pharmacy	ED Pharm x-45609; Menino 5 x-47687
	Seek LAR	Form 04 Informed Consent Log **p. 13 – 15**
	Check for lab exclusions	serum EtOH <250 mg%; If female, urine or serum pregnancy test (-) #4-513
	LAR Consent or EFIC	
	Complete Inclusion/Exclusion	Form 00 Eligibility **p. 1-4**
	Randomization in Web DCU (Time of randomization is time team notifies Pharmacy what kit to use)	1.https://webdcu.musc.edu/login.asp 2.Form 14 Randomization **p. 5** & Form 6 Baseline **p. 6**
	Study doctor orders drug	
	Fax/ Bring to Pharmacy: paper order, randomization form, specific dosing instructions (make copies for our files), Pharmacy Manual, & Patty's Pharmacy Guide for enrollment	ED Pharm Fax 4-5608; if closed goes directly to Menino 5 Pharm *Medication stored in compartment #22 *Remind about pink labels
	Pharmacy prepares drug	
	Start 1. Designated line and 2. [BIOPROTECT] (Time of blood draw __:__)	1.[BIOPROTECT]: Draw 3 Tiger tops (using kit), process and freeze 2.Form 43 Blood Sample Collection **p. 20-21**
	Start Study drug: loading dose of 14.3 cc/hr x 1 hr (Time __:__) Stay with pt until rate decreased	Form 05 Study Drug Infusion Log **p. 18 lines 1-2**
	Change Study drug infusion rate: after 1 hr change to 10cc/hr x 23 hrs (Time __:__)	Form 05 Study Drug Infusion Log **p. 18 lines 3-4**
	Inform Receiving team of study and provide nurse caring for pt with " Pt Bedside Info Binder"	1) Nursing info sheet 2) Infusion info sheet 3) Anesthesia info sheet 4) CST Guidelines 5) Copy of Protocol
	Inform Respiratory that pt has been enrolled in ProTECT Study	1.E mail both: Julie.silva@bmc.org and Daniel.Gavin@bmc.org 2. page Respiratory; Beeper # 1548
	Complete & enter these *nine* remaining Forms: 00, 14, 01, 02, 42, 04, 25, 05, 43	00 Eligibility **p. 1-4** 14 Randomization **p. 5** 01 Baseline **p. 6** 02 Demographics **p. 7** 04 Informed Consent Log **p. 13-15** 25 Labs **p. 16-17** 05 Study Drug **p.18 Lines 1-2** 43 Blood Sample Collection **p. 20-21**

Prepare for the Worst

- Anticipate
  - Resistance
  - Obstruction
  - Challenges

Resistance to Change

Managing Resistance

All Systems Go

- Multiple practice runs
- Entire team was fully prepared
- Active screening started 9/24/13

DSMB Report

- October 1, 2013
  - 844/1140 subjects enrolled
  - Continue enrollment and follow-up per protocol

DSMB Report

- **What we DIDN'T know**

ProTECT

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DEPARTMENT OF EMERGENCY MEDICINE
49 Jesse Hill Jr. Dr. FOB Suite 126 Atlanta, GA 30303

EMERGENCY NEUROSCIENCES
DEPARTMENT OF EMERGENCY MEDICINE

Phone: (404) 778-1709
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November 4th, 2013

Dear ProTECT III Team,

It is with a profoundly heavy heart that I inform you that the ProTECT III clinical trial has been permanently closed to enrollment by the NINDS/DSMB due to futility. As you can imagine I am stunned by this revelation. Obviously I am as interested as everyone to know more details, but we remain blinded to the data. We must complete all outcomes as scheduled (the last enrolled subject's f/u date is due in April 2014), finish monitoring all subjects, and complete database cleaning before the database can be locked and we can break blinding.

The one silver lining is that the NINDS and DSMB repeatedly commented on the stellar way the ProTECT III trial was conducted. I also recognize the efforts of this amazing team and am grateful to have had the opportunity to work with each of you.

DESPAIR

It's Always Darkest just Before it goes Pitch Black.

"Don't Cry
Because It's Over,
Smile Because It
Happened." DR. SEUSS

What Happened at BMC?

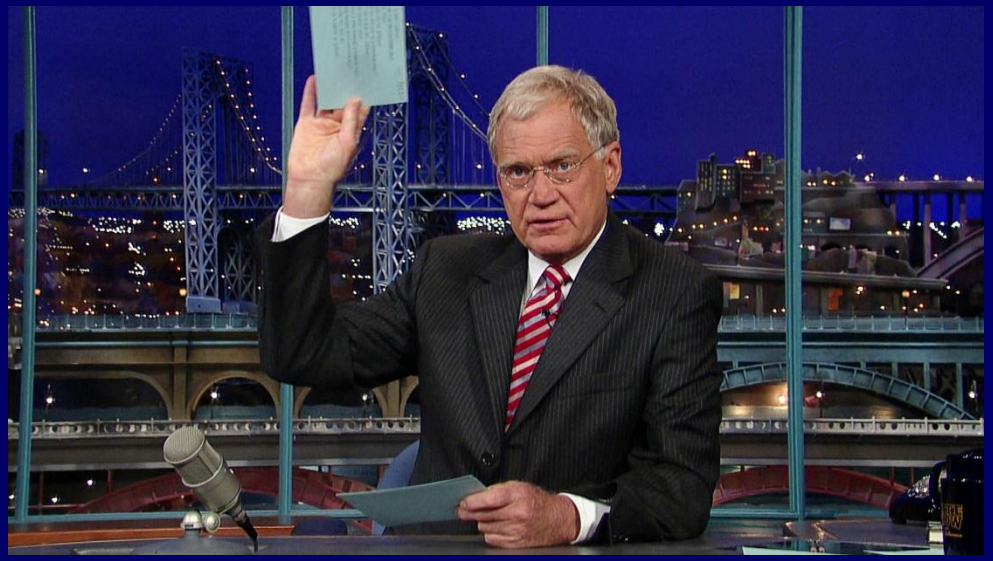
ZERO

ZERO

Priceless

Top 10 Clinical Research PEARLS of Wisdom

10. Excellent communication
9. Be organized and motivate others
8. Be enthusiastic
7. Clarity in everyone's roles
6. Adapt as necessary
5. Personal contact



PEARLS

4. Coordinator responsibility to know everyone's role
3. Minimize interference in clinical practice
2. Ask not what your clinician can do for you. Ask what you can do for your clinician.
1. BE A LEADER

It Really Takes a Village

Questions?

Exclusion Criteria

1. Non-Survivable Injury
2. Bilateral dilated unresponsive pupils
3. Cardiopulmonary Arrest
4. Hypotension: BP < 90 systolic for 2 consecutive readings 5+ minutes apart
5. Hypoxia: O2 saturation <90 for at least 5 consecutive minutes
6. Status Epilepticus on arrival
7. EtOH > 250 mg %
8. Inability to perform ADLs without assistance prior to injury
9. Spinal Cord Injury with Neuro Deficits
10. Known active breast or reproductive organ cancers
11. Known allergy to progesterone or Intralipid components
12. Known clotting disorder / Active thromboembolic event
13. Pregnant
14. Concern for inability to follow up at 6 months
15. Opt Out

Consent for Emergency Research: 21 CFR 50.24

Qualifications:

- ✓ **Life-threatening situation needing urgent intervention**
- ✓ **Available treatments unproven or unsatisfactory**
- ✓ **Need to collect data to determine safety & efficacy of the intervention**
- ✓ **Obtaining informed consent not feasible**
- ✓ **Intervention must be administered before consent can be obtained from subject's legally authorized representative**
- ✓ **No reasonable way to identify prospectively eligible individuals**
- ✓ **Participation holds prospect of direct benefit to the subjects**
- ✓ **The clinical investigation could not practicably be carried out without the waiver**

Potential Side Effects

- **Venous thromboembolic events(DVT or PE, phlebitis,)**
- **Arterial thromboembolic events (MI/Stroke)**
- **Allergic reactions (to intralipid component)**
- **Increase in LFTs(AST or ALT) > 5,000 U/L or a bilirubin >10 mg/dL**
- **Serious infections (pneumonia, sepsis, meningitis)**