It Takes a Village

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Department of Emergency Medicine
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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
ProTECT™ III:
Progesterone for Traumatic Brain Injury
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

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
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 Medical Campus panel that reviews research.
Experimenting on people who cannot say no. Can we get a list of these new age Nazi’s?

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.

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

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)
MANAGEMENT OF INCREASED ICP

GENERAL RECS
- Vent – O2; Sat >90, PaO2 >80, PCO2 <35-45
- Monitor SBP & MAP – avoid hypotension, SBP >100 mmHg
- Normotherm goal <38.5°C, tx fever w/ acetamin.
- Cooling Blankets: 2ºc &/or cooling blankets
- Adjust C-collar placement if applicable
- Consider repeat brain CT, if ICP >5 mmHg
- Consider repeat brain CT, if mass or unexpected intracranial lesion
- Crani for surgical lesions: see outline in section IV

TIER 1
- Head of bed ≥ 30 degrees
- Sedation & Analgesia regimens (propofol, lorazepam, ketamine)
- Pain relief & sedation are maintained in intub PLR, Pain relief & sedation are maintained in intub PLR, Pain relief & sedation are maintained in intub PLR
- Approp Initial perfusion goal 80 mmHg for ICP monitor & drainage
- Ventric l & extraventric l drain to 10 mmHg for ICP ≥ 20 mmHg
- 20 mmHg sustained for ≥ 5 min, Prehospital for 10 min
- Ventric l & extraventric l drain to 10 mmHg for ICP > 20 mmHg
- Monitor ICP for ≥ 30 min, return to intub, return to intub, return to intub
- Mannitol – 2 g/kg, ICP ≥ 20 mmHg

TIER 2
- Hyperosmol Therapy:
  - Mannitol int. boluses (0.25 – 1 gm/kg body weight) Maintain euolemia when mannitol used
  - Assess serum Na & OSM q 6 hr
  - Hold add doses if serum OSM > 320 mosm/L, Mannitol serum OSM <320 mosm/L or at – Osmolar gap <20. Hold Mannitol if evidence of hypoosmol.

GCS

<table>
<thead>
<tr>
<th>Eye Opening</th>
<th>Spontaneously</th>
<th>To Command</th>
<th>To Pain</th>
<th>None</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Best Verbal Response

<table>
<thead>
<tr>
<th>Best Motor Response</th>
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</thead>
<tbody>
<tr>
<td>Obeys Commands</td>
</tr>
<tr>
<td>Localizes Pain</td>
</tr>
<tr>
<td>Withdraws to Pain</td>
</tr>
<tr>
<td>Flexes to Pain</td>
</tr>
<tr>
<td>Extends to Pain</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Item</td>
</tr>
<tr>
<td>------</td>
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</tbody>
</table>
| Screen: inclusion / exclusion (except labs) | 1. Check Opt out registry: [http://em.emory.edu/protect/optoutformadminlogin.cfm](http://em.emory.edu/protect/optoutformadminlogin.cfm)  
2. EMS Trip Sheet info: [https://epcr.bostonem.org/spenterprise-php/](https://epcr.bostonem.org/spenterprise-php/)  
Username: pmitchellbmc / Password: Research |
| Estimated weight ______ lb ______kg | Either Jim Feldman, Lauren Nentwich or Peter Burke |
| Best GCS: E _____ V _____ M _____ Total _____ | 
| Contact investigators on call | ED Pharm x-45609; Menino 5 x-47687 |
| Preliminary notification to Pharmacy | Form 04 Informed Consent Log p. 13 – 15 |
| Seek LAR | 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](https://webdcu.musc.edu/login.asp)  
2. Form 14 Randomization p. 5 & Form 6 Baseline p. 6 |
| Study doctor orders drug | ED Pharm Fax 4-5608; if closed goes directly to Menino 5 Pharm  
*Medication stored in compartment #22  
*Remind about pink labels |
| Fax/ Bring to Pharmacy: paper order, randomization form, specific dosing instructions (make copies for our files), Pharmacy Manual, & Patty’s Pharmacy Guide for enrollment | 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. E mail both: Julie.silva@bmc.org and Daniel.Gavin@bmc.org  
2. page Respiratory; Beeper # 1548 |
| Inform Respiratory that pt has been enrolled in ProTECT Study | 
| Complete & enter these nine remaining Forms: 00, 14, 01, 02, 42, 04, 25, 05, 43 | 00 Eligibility p. 1-4  
04 Informed Consent Log p. 13-15  
14 Randomization p. 5  
01 Baseline p. 6  
05 Study Drug p. 18 Lines 1-2  
03 Demographics p. 7  
25 Labs p. 16-17  
02 Baseline p. 8  
43 Blood Sample Collection p. 20-21 |
Prepare for the Worst

- Anticipate
- Resistance
- Obstruction
- Challenges
Resistance to Change
Managing Resistance

Hello
My Name Is
Stubborn
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
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

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)