TBI Clinical Trials: Past, Present, and Future

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US Army Medical Research and Materiel Command
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The views expressed in this presentation are those of the author and do not reflect official policy or position of the Department of the Army, Department of Defense or the U.S. Government. I have no relevant financial relationships to disclose.
Traumatic Brain Injury: 2015

Classification

GCS
(Glasgow Coma Scale)

Mild
Severe
Moderate

Outcome

GOS
(Glasgow Outcome Scale)

Death
Vegetative
Good Recovery

A Complex and Heterogeneous Disease
TBI Clinical Trials: Past

Almost All Phase 3 Clinical Trials for Traumatic Brain Injury Have Failed
<table>
<thead>
<tr>
<th>Publication (Funding)</th>
<th>Agent/Intervention (Mechanism)</th>
<th>Centers</th>
<th>Study Population</th>
<th>No.</th>
<th>Year of Study</th>
<th>Status</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braakman et al., 26 1983 (inv. initiated)</td>
<td>High dose dexamethasone (various processes)</td>
<td>2</td>
<td>Comatose patients after nonmissile TBI</td>
<td>161</td>
<td>1978–1981</td>
<td>Completed</td>
<td>No sign. Tx. effect</td>
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<tr>
<td>Dearden et al., 27 1986</td>
<td>Dexamethasone (various processes)</td>
<td>1</td>
<td>Severe head injury</td>
<td>130</td>
<td>1980–1983</td>
<td>Completed</td>
<td>No sign. Tx. effect</td>
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<tr>
<td>Grumme et al., 28 1995 (Inv. initiated)</td>
<td>Triamcinolone (various processes)</td>
<td>9</td>
<td>Severe head injury, not further defined</td>
<td>396</td>
<td>1985–1990</td>
<td>Completed</td>
<td>No sign. Tx. effect</td>
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<tr>
<td>Bailey et al., 18 1991 (Bayer - HIT I)</td>
<td>Nimodipine (Ca-mediated damage)</td>
<td>6</td>
<td>Not obeying commands</td>
<td>351</td>
<td>1987–1989</td>
<td>Completed</td>
<td>No sign. Tx. effect</td>
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<tr>
<td>Bailey et al., 19 1994 (Bayer - HIT II)</td>
<td>Nimodipine (Ca-mediated damage)</td>
<td>21</td>
<td>Not obeying commands</td>
<td>852</td>
<td>1989–1991</td>
<td>Completed</td>
<td>No significant effect in overall population</td>
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<tr>
<td>Rockswold et al., 29 1992 (Inv. initiated)</td>
<td>Hyperbaric oxygen (cerebral ischemia)</td>
<td>1</td>
<td>GCS ≤9</td>
<td>168</td>
<td>1983–1989</td>
<td>Completed</td>
<td>Reduced mortality</td>
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<td>Wolf et al., 29 1993 (NIH: 12587)</td>
<td>Tromethamine (THAM) (cerebral acidosis)</td>
<td>2</td>
<td>GCS ≤8</td>
<td>149</td>
<td>1988–1989</td>
<td>Completed</td>
<td>No overall treatment effect</td>
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<td>Gaab et al., 30 1994 (inv. initiated)</td>
<td>Dexamethasone (various processes)</td>
<td>10</td>
<td>GCS ≤13</td>
<td>300</td>
<td>1986–1989</td>
<td>Completed</td>
<td>No sign. Tx. effect</td>
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<td>Young et al., 21 1996 (Sanofi-Winthrop)</td>
<td>PEGSOD (free radical damage)</td>
<td>29</td>
<td>GCS ≤8</td>
<td>1562</td>
<td>1993–1995</td>
<td>Completed</td>
<td>No sign. Tx. effect</td>
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<tr>
<td>Unpublished (SyntheLabo)</td>
<td>Etiliprol (glutamate excitotoxicity)</td>
<td>20+</td>
<td>GCS 4–8</td>
<td>452</td>
<td>1993–1995</td>
<td>Completed</td>
<td>No sign. Tx. effect</td>
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<tr>
<td>Harders et al., 9 1996 (Bayer - HIT III)</td>
<td>Nimodipine (Ca-mediated damage)</td>
<td>21</td>
<td>tSAH</td>
<td>123</td>
<td>1994</td>
<td>Completed</td>
<td>Significant reduction in unfavorable outcome</td>
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<tr>
<td>Robertson et al., 32 1999 (Inv. initiated, NIH NS27616)</td>
<td>CBF vs. ICP directed management (cerebral ischemia)</td>
<td>1</td>
<td>Motor score ≤5</td>
<td>189</td>
<td>1994–1997</td>
<td>Completed</td>
<td>No difference in neurologic outcome. Decrease in episodes of jugular desaturation</td>
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<tr>
<td>Morris et al., 33 1999 (Ciba-Geigy, Novartis)</td>
<td>Selfotel (glutamate excitotoxicity)</td>
<td>95</td>
<td>GCS 4–8</td>
<td>693</td>
<td>1994–1996</td>
<td>Terminated</td>
<td>No sign. Tx. effect</td>
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<tr>
<td>Clifton et al., 16 2001 (Inv. initiated, NIH NS 32786)</td>
<td>Hypothermia - NABIS (various processes)</td>
<td>11</td>
<td>GCS 3–8 Motor score 1–5</td>
<td>392</td>
<td>1994–1998</td>
<td>Halted</td>
<td>No effects on outcome. Reduced incidence of ICP &gt;30</td>
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<tr>
<td>Unpublished (Sandoz, Novartis)</td>
<td>D-CPP-ene - Saphir (glutamate excitotoxicity)</td>
<td>51</td>
<td>Not obeying commands, ≥ one reactive pupil</td>
<td>924</td>
<td>1995–1997</td>
<td>Completed</td>
<td>No sign. Tx. effect</td>
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<tr>
<td>Marmarou et al., 22 1999 (SmithKline Beecham/Cortech Inc.)</td>
<td>Bradyx/c/CP-0127 (bradykinine antagonist)</td>
<td>31</td>
<td>GCS 3–8</td>
<td>139</td>
<td>1996</td>
<td>Terminated</td>
<td>12% improvement in favorable outcome (p = 0.26)</td>
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</tbody>
</table>

(Table continues)
<table>
<thead>
<tr>
<th>Publication (Funding)</th>
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<th>Study Population</th>
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<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unpublished (Parke Davis)</td>
<td>SNX-111 (Glutamate excitotoxicity)</td>
<td>? (multi-center)</td>
<td>GCS 4–8</td>
<td>237</td>
<td>1997–1998</td>
<td>Terminated</td>
<td>Higher mortality</td>
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<td>Unpublished (Bayer HIT IV)</td>
<td>Nimodipine (Ca-mediated damage)</td>
<td>36</td>
<td>GCS &lt;15 + tSAH</td>
<td>592</td>
<td>1997–1999</td>
<td>Completed</td>
<td>No significant effect</td>
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<td>Yurkewicz et al., 2005 (Pfizer)</td>
<td>Traxoprodil (CP-101606) (Ca-channel blocker)</td>
<td>? (multi-center)</td>
<td>GCS 4–8</td>
<td>404</td>
<td>1998–2001</td>
<td>Completed</td>
<td>Higher mortality, nonsignificant effect</td>
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<td>Cooper et al., 2004 (inv. initiated, MRC-Aus: 124330)</td>
<td>Hypertonic saline (hypovolemia)</td>
<td>12</td>
<td>GCS ≤8</td>
<td>229</td>
<td>1998–2002</td>
<td>Completed</td>
<td>No sign. Tx. effect</td>
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<td>Temkin et al., 2007 (inv. initiated, NIH: NS 19643)</td>
<td>Magnesium sulfate (multiple mechanisms)</td>
<td>1</td>
<td>GCS ≤12</td>
<td>499</td>
<td>1998–2004</td>
<td>Completed</td>
<td>Poorer outcome in treated group</td>
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<td>Maas et al., 2006 (Pharmos Corp.)</td>
<td>Dexamabolin (multiple processes)</td>
<td>86</td>
<td>Motor score 2–5 + CT abnormalities</td>
<td>861</td>
<td>2000–2004</td>
<td>Completed</td>
<td>No sign. Tx. effect</td>
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<td>Edwards et al., 2005 (MRC UK)</td>
<td>Methylprednisolone (multiple mechanisms)</td>
<td>239</td>
<td>GCS ≤ 14</td>
<td>10008</td>
<td>1999–2004</td>
<td>Terminated</td>
<td>Higher mortality in Tx. group (p &lt; 0.001)</td>
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<tr>
<td>Cruz et al., 2001 (Investigator initiated)</td>
<td>High-dose mannitol (raised ICP)</td>
<td>1</td>
<td>ASDH</td>
<td>178</td>
<td>1997–2000</td>
<td>Completed</td>
<td>Significant better outcome (p &lt; 0.01)</td>
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<tr>
<td>Cruz et al., 2002 (Investigator initiated)</td>
<td>High-dose mannitol (raised ICP)</td>
<td>1</td>
<td>Temporal lobe hemorrhage with abnormal pupils</td>
<td>141</td>
<td>1997–2001</td>
<td>Completed</td>
<td>Significant treatment effect</td>
</tr>
<tr>
<td>Zhi et al., 2003 (Investigator initiated)</td>
<td>Mild hypothermia (various processes)</td>
<td>1</td>
<td>GCS ≤ 8</td>
<td>396</td>
<td>1997–2001</td>
<td>Completed</td>
<td>Reduction of mortality and improved outcome</td>
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<tr>
<td>Lu et al., 2003 (Investigator initiated)</td>
<td>Decompr. craniectomy (raised ICP)</td>
<td>1</td>
<td>GCS ≤ 8</td>
<td>230</td>
<td>1998–2001</td>
<td>Completed</td>
<td>Significant reduction of mortality</td>
</tr>
<tr>
<td>Jiang et al., 2005 (Investigator initiated)</td>
<td>Standard trauma craniectomy vs. limited craniectomy (raised ICP)</td>
<td>5</td>
<td>GCS ≤ 8 + refractory intracranial hypertension</td>
<td>468</td>
<td>1998–2001</td>
<td>Completed</td>
<td>Better outcome with large craniectomy</td>
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<tr>
<td>Jiang et al., 2006 (Investigator initiated)</td>
<td>Long-term mild hypothermia (multiple mechanisms)</td>
<td>3</td>
<td>GCS ≤ 8</td>
<td>215</td>
<td>2000–2003</td>
<td>Completed</td>
<td>5-day mild hypothermia is more efficacious than 2-day short term</td>
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<tr>
<td>Xiao et al., 2008 (Investigator initiated)</td>
<td>Progestosterone (multiple mechanisms)</td>
<td>1</td>
<td>GCS ≤ 8</td>
<td>159</td>
<td>2004–2007</td>
<td>Completed</td>
<td>More favorable outcome in Tx. group (p = 0.048)</td>
</tr>
</tbody>
</table>

ASDH = acute subdural hematoma; CBF = cerebral blood flow; CT = computed tomography; GCS = Glasgow coma score; HIT = Head Injury Trial; ICP = intracranial pressure; NABIS = National Acute Brain Injury Study; PEGSOD = polyethylene glycol-conjugated bovine superoxide dismutase; Tx. = treatment.

*The studies reported by Cruz et al., 24, 25, 26 have been subjected to severe criticism, and the reliability and validity of the results have been questioned.
Very Early Administration of Progesterone for Acute Traumatic Brain Injury


A Clinical Trial of Progesterone for Severe Traumatic Brain Injury

Brett E. Skolnick, Ph.D., Andrew I. Maas, M.D., Ph.D., Raj K. Narayan, M.D., Roland Gerritsen van der Hoop, M.D., Ph.D., Thomas MacAllister, Ph.D., John D. Ward, M.D., Neta R. Nelson, M.P.H., and Nino Stocchetti, M.D. for the SYNAPSE Trial Investigators

ProTECT
“This clinical trial did not show a benefit of progesterone over placebo in the improvement of outcomes in patients with acute TBI.”

SYNAPSE
“Primary and secondary efficacy analyses showed no clinical benefit of progesterone in patients with severe TBI.”

Should we be surprised at the results of the ProTECT and SYNAPSE trials?
Preclinical Data for Progesterone

Over 200 studies – no primate studies
Study Subjects

Rodent

25-30 gm littermates
3 mm anterior to bregma
5 mm tip, 2.25 m/s
Depth 2.5 mm

Human

17 – 94 years old
GCS 4 - 12

Contusion/Hematoma
Outcome Assessment

Rodent

Morris Water Maze

A test of memory and learning
Outcome Assessment

Rodent

Latency to Target (sec) in Morris Water Maze (Trials 1 and 2 averaged)

<table>
<thead>
<tr>
<th>DAYS POSTSURGERY</th>
<th>SHAM</th>
<th>VEH</th>
<th>PROG</th>
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<tr>
<td>11</td>
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<tr>
<td>20</td>
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</tbody>
</table>

Human

GOS-E at 6 months

1 = Dead
2 = Vegetative State
3 = Low Severe Disability
4 = Upper Severe Disability
5 = Low Moderate Disability
6 = Upper Moderate Disability
7 = Low Good Recovery
8 = Upper Good Recovery

Condition of unawareness with only reflex responses but with periods of spontaneous eye opening.

Patient who is dependent for daily support for mental or physical disability, usually a combination of both. If the patient can be left alone for more than 8h at home it is upper level of SD, if not then it is low level of SD.

Patients have some disability such as aphasia, hemiparesis or epilepsy and/or deficits of memory or personality but are able to look after themselves. They are independent at home but dependent outside. If they are able to return to work even with special arrangement it is upper level of MD, if not then it is low level of MD.

Resumption of normal life with the capacity to work even if pre-injury status has not been achieved. Some patients have minor neurological or psychological deficits. If these deficits are not disabling then it is upper level of GR, if disabling then it is lower level of GR.
Outcomes Assessment: GOS-E

Independence outside home:

3a. Are they able to shop without assistance?

☐ Yes  ☐ No (upper SD)

Note: this includes being able to plan what to buy, take care of money themselves and behave appropriately in public. They need not normally shop, but must be able to do so.

Disability Score – not brain specific
Brainscope Quantitative EEG System (AHEAD-100)

• 2010: Brainscope filed an IDE to perform a pivotal trial of the AHEAD-100 system as an aid to diagnosis of TBI

• 2011: After about 17 months of negotiation with the FDA, Brainscope finally acceded to an Indication for Use (IFU) of a positive test as an correlate of the New Orleans Criteria for a CT scan

• 2014: Received FDA clearance for this IFU in November 2014. Have chosen not to market the AHEAD-100 system for this IFU, focusing instead on the AHEAD-200 Android-based device, which is now FDA cleared.
Biomarker Assessment for Neurotrauma Diagnosis and Improved Triage System (BANDITS)

• 2011: Nearly a decade of research and clinical study sponsored by the Army showing high sensitivity and specificity of 2 protein markers as indicators for brain injury.

• Banyan filed a IDE to evaluate the utility of the Banyan Glial Fibrillary Acidic Protein (GFAP)/ Ubiquitin C-terminal Hydrolase-L1 (UCH-L1) Biomarkers Test as an aid in the diagnosis of Traumatic Brain Injury (TBI).

• 2012: After about 1½ years of intense negotiation with the FDA, Banyan settled on the following indication for use: An aid in the evaluation of patients over the age of 18 presenting with suspected mild traumatic brain injury (Glasgow Coma Scale score 13-15) within 12 hours of injury to determine the need for a CT scan of the head.

• 2,000 subject multi-site pivotal study has been completed, specimens now being tested.

• Results of clinical trials: almost 100% sensitivity, but 23% specificity (CT indication).
Extensive Review Literature

• Review Articles:
  – Narayan et al. (2002) provided a review and analysis of TBI therapy trials that took place prior to 2002.
  – Maas, Roozenbeek, and Manley (2010) provided a review and analysis of TBI therapy clinical trials that took place between 1980 and 2009.

• Peer-Reviewed Articles:
  – Bullock et al., 2002; Dickinson et al., 2000; Farin and Marshall (2004); Kabadi and Faden (2014); Li, Menon, & Janowitz (2014); Loane and Faden (2010); and Tolias and Bullock (2004).
Reasons That May Have Contributed To The Failure Of Previous Clinical Trials

• **Maas et al. (1999)**
  - Pathophysiologic mechanisms and bioavailability
  - Heterogeneity in the study population
  - Selection of GOS score as primary endpoint

• **Maas, Roozenbeek, and Manley (2010)**
  - Lack of relevant mechanistic endpoints
  - Problems in translating results from experimental studies to clinical practice (e.g., a treatment time window determined in the preclinical model is not relevant in real-life clinical practice)
  - Lack of understanding of what pathophysiologic mechanisms or targeted pathways are active and at what point they are active after injury
  - Prevalence of underpowered TBI clinical trials.
Recommendations

• **Maas et al. (1999)**
  – Clarify the pharmacokinetics
  – A more modest effect size than 10%
  – More advanced prognostic modeling and adaptive design techniques

• **Narayan et al. (2002)**
  – Identify and target the specific mechanisms of cellular injury
  – Obtain adequate preclinical data
  – Focus a trial on an appropriate subgroup of participants
  – Confirm adequate delivery to the brain
  – Improve clinical management
  – Choose the “right” outcome measures
  – Improve mechanism for obtaining informed consent or waiver of consent
Findings from the IMPACT studies

Funded by NINDS starting in 2003.
• Analyzed individual participant data from eight randomized controlled trials (RCTs) and three observational studies

Resulting Efforts and Recommendations:
• Common Data Elements (CDEs)
• Novel Research Methods to Address Heterogeneity and Increase Statistical Power
  – Covariate adjustment and prognostic modeling.
  – Sliding dichotomy and proportional odds analysis.
• Comparative Effectiveness Research
  – FITBIR
• Increasing Effective Translation of Experimental Findings to Clinical Therapies
  – Improve animal model studies
  – Target clinical therapy to multiple mechanisms of brain injury
  – Direct therapy to the appropriate study population
  – Determine whether the trial medication can penetrate the brain in humans.
• Careful Statistical Evaluation Before and During a Trial to Avoid Pitfalls in Recruitment and Analysis
  – Use stratification to balance heterogeneous clinical trial study populations
  – Consider gender-specific differences
  – Standardization of treatment and methods to reduce inter-center variability
  – Use large clinical trials to increase statistical power
  – Using the GOS and GOSE to assess clinical outcome
  – Using surrogate measures to assess clinical outcome
  – Sequential analysis of clinical trials to analyze outcome data continuously
Analyses of TBI Clinical Trials

Traumatic Brain Injury Pharmacotherapy Clinical Trials: Challenges and Opportunities
May 28, 2014
Fort Detrick, MD

Diagnostic Assays for Traumatic Brain Injury: Challenges and Opportunities
December 19, 2014
Fort Detrick, MD

Medical Product and Regulatory Development Lifecycle Supporting Traumatic Brain Injury Clinical Trials
May 22, 2014
Fort Detrick, MD

Submitted to Defense Technical Information Center (DTIC) for General Public Availability
Recommendations

• Improve the translation of experimental results to the bedside
• Ensure that an appropriate study population has been selected to minimize heterogeneity
• Identify appropriate primary and secondary endpoints
• Conduct careful statistical analysis
TBI Clinical Trials

• Present
Traumatic Brain Injury: 2015

Classification

GCS
(Glasgow Coma Scale)

Severe
Moderate
Mild

Outcome

GOS
(Glasgow Outcome Scale)

Vegetative
Death
Good Recovery

A Complex and Heterogeneous Disease
TBI Research Landscape

Pre-Clinical Studies
Genetics, Pre-injury Factors
Injury Biomechanics, Kinematics
Acute Clinical Effects
Imaging Biomarkers
Blood/Proteomic Biomarkers
Treatment Studies, RCT’s
Longterm Health Outcome
Neuropathology Studies

Premorbid
Acute Injury & Recovery
“Latency” Period
Disease Expression

Acute Injury Studies
DoD Project Head to Head
TRACK-TBI
Concussion Research Consortium (CRC)
GE-NFL HHC
Army STARRS
NCAA Initiative
CENTER-TBI, Mission Connect

Longterm Outcome Studies
TBI Endpoints Development (TED)
NCAA 15 Year Study
C-LEARN
INTRuST
DVBIC 15 Year Study

Post-mortem, CTE Studies
CENC
NIH-NFL Health Program Studies
Others
TBI Endpoints Development (TED)
Log Number: PT130798 W81XWH-13-PHTBI-TED
PI: Geoffrey T. Manley  Org: University of California, San Francisco  Award Amount: $17m

Study/Product Aim(s)
- OVERALL: Validate endpoints to improve clinical trial design to inform/accelerate FDA approval of TBI diagnostic tools and therapeutic agents
- Stage I: Identify candidate endpoints/surrogate markers for mTBI and modTBI across: TBI severity, spectrum of time, domains of function; Select 4 “seed projects” to demonstrate feasibility and reproducibility of promising prognostic and predictive properties; Convene 2 Consensus Conferences
- Stage II: Validate clinically relevant endpoints and surrogate markers identified during Phase I; Convene Implementation Conference

Approach
ID clinically relevant endpoints/surrogate markers using data-driven analytic approach; reach consensus via Delphi process to select most promising endpoints to validate in Stage II, based on their practical utility to support FDA approval. Collaborate with stakeholders to ensure implementation and dissemination.

Timeline and Cost

<table>
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<tr>
<th>Activities</th>
<th>CY14</th>
<th>CY15</th>
<th>CY16</th>
<th>CY17</th>
<th>CY18</th>
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<tr>
<td>Integrate/analyze TBI datasets</td>
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<td>Consensus Conferences 1 &amp; 2</td>
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<tr>
<td>Fund 4 Seed Projects</td>
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<tr>
<td>Conduct Validation Studies</td>
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<td>Implementation Conference</td>
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<td>Estimated Budget ($17M)</td>
<td>$3M</td>
<td>$2M</td>
<td>$4M</td>
<td>$4M</td>
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Reportable Outcomes
- TED Consensus Conference 1 (CC1) held on 02/02-03/2015 with over 120 attendees
- Landscape frameworks created of existing and pipelined COAs and biomarkers
- Expert Working Groups established and are meeting regularly via teleconference to build on work plans developed during CC1
- Attended GSC meeting
- Representatives from the FDA’s CDER, CHRR, and SEALD participated in CC1. Collaboration has continued with follow-up conference calls.
- Datasets have been readied and loaded into the Palantir platform for initial testing with webinar trainings
- Abstract covering TED’s launch and progress has been submitted to the 2015 Military Health Systems Research Symposium
- Responses to the FDA’s Request for Comment Identifying Potential Biomarkers for are being drafted and will be submitted by the April 14, 2015 deadline

Our coalition of investigators and public/private partners represent the nation’s leading TBI innovators. Leadership and recruited Core expertise will produce deliverables predicted to improve care and outcomes for all populations affected by TBI.
Public-Private Partnership
Government Partners

- FDA (Food and Drug Administration)
- U.S. Department of Defense
- CENC (Chronic Effects of Neurotrauma Consortium)
- CNRM (Center for Neuroscience and Regenerative Medicine)
- NIH (National Institute of Neurological Disorders and Stroke)
- U.S. Department of Veterans Affairs
- CDC (Centers for Disease Control and Prevention)
- FITBIR (Federal Interagency Traumatic Brain Injury Research Informatics System)
Academic/Research Partners

Albert Einstein Healthcare Network (MRH)
Baylor College of Medicine
Emory University
Massachusetts General Hospital
Medical College of Wisconsin
Northern California Institute for Research and Education
Research Triangle Institute
Spaulding Rehabilitation Hospital
Stanford University
University of California, Berkeley
University of California, San Diego
University of California, San Francisco
University of Cincinnati
University of Florida
University of Maryland Baltimore
University of Miami
University of Pittsburgh
University of Southern California
University of Texas at Austin
UT Southwestern Medical Center
University of Washington
Uniformed Services University of the Health Sciences
Virginia Commonwealth University
Power of Collaboration

• It’s the most efficient game in town
  – Multiple stakeholders with multiple needs
  • No single company, university, or governmental agency will have sufficient resources, expertise, or information bas to undertake the work.
  – Builds consensus, expanding use
  – Many examples of success of collaboration
    • PCAST report calls for it,
    • IOM is applying it, work on clinical trials certification
    • FDA is applying it in a variety of situations

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Brain Trauma Evidence Consortium

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NRAP Focus Area

• Epidemiology: develop a clinically useful definition and staging criteria of TBI

NRAP Required Action

• Complete the current DoD-CDC-Brain Trauma Foundation concussion classification project. Identify a process for developing a clinically-relevant system to replace mild/moderate/severe nomenclature (IMMEDIATE ACTION)

Phase I

  • Evidence-based foundation from which to develop protocols and tools for screening, diagnosis, and prognosis
  • Clearly defines future research needs (26 of 5617 papers)
  • By-product: Heat Map of current evidence
• Raw Data Review – RaDaR - Ongoing
  • Re-analysis of existing data targeting key questions.

Phase II

• Develop & validate dynamic model with restrospective and prospective studies
  • First meeting held Sep 2013, Second meeting held Jan 16-17, 2014, Third meeting held Jan 27-29, 2015.

Concussion Guidelines Step 1: Systematic Review of Prevalent Indicators

1. Observed and documented disorientation or confusion immediately after the potential concussive event
2. Impaired balance within 1 day after injury
3. Slower reaction time within 2 days after injury
4. Impaired verbal learning and memory within 2 days after injury.

Neurosurgery. 2014 Sep; 75 Suppl 1:S3-15

Scientific or Clinical Impact

• An architecture for understanding TBI that will cause a paradigm shift from a linear, 3-category system to a clinically useful dynamic model that accounts for the complexity of the disease.
• Will allow for better comparisons across research studies and comparative effectiveness research
• Will enable researchers to identify subpopulations in a heterogeneous condition
• Federally-funded studies will be required to adopt revised classification guidelines
Summary

- TBI is a continuum of extremely heterogeneous insults to the sub cellular and cellular structure and function of the brain; its effects can be life-long
- Co-morbidities (PTS, Pain, Depression) are more the rule than the exception, which complicates study
- Currently, physical and mental rest is the only validated “treatment” and there are no FDA approved therapies
- Regulatory science is inadequate—a reflection of the state of the science in general. Need for validated “endpoints” for both diagnosis and treatment.
- Because of our limited understanding of the pathobiology, along with a paucity of biomarkers, correlating the human condition with animal models involves a degree of subjective interpretation that is scientifically tenuous and leads to an inability to even compare one model to another
- The relationships between TBI, neurodegeneration and Chronic Traumatic Encephalopathy are yet to be clearly defined
- Does recovered mean recovered or does it mean compensated?
- Because of the inherent complexity of the CNS, we must be prepared for instances where we must dismiss reductionism and use evidence-based “what works” (i.e. some things may simply not be knowable with current technologies)
- Despite all of the above, we DO find ourselves at a “tipping point” where leveraging the resources of executive leadership, inter-agency collaboration, and public-private partnerships can yield paradigm shifts in our understanding and management of this complex injury
TBI Clinical Trials: Future

• Enriched study enrollment (“Stratified clusters” with common trajectories)

• Multiple, meaningful, primary, co-primary, and secondary endpoints to assess efficacy

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• Diagnostics or therapeutics selected based on pathophysiologic efficacy in preclinical studies

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• Approved Products and Techniques that Improve Outcome
Questions?