Traumatic brain injury trials
What’s next?

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Objectives

- Epidemiology: TBI remains important
- Registered ongoing recruiting trials in adults and paediatrics
- Interventional and observational trials
- Comparative effectiveness research
- International TBI Research Initiative
  - Who – when – why and what it means for patients and clinicians?
Epidemiology – Injury Deaths

Generated from CDC 2007 WISQARS – Top 10 Causes of Death in United States
## Average Estimated Costs Nonfatal Hospitalized TBI
### Ages 0 to 17, USA 2005

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Avg Medical Cost</th>
<th>Avg Work Loss Cost</th>
<th>Avg Combined Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>$51,147.71</td>
<td>$124,571.95</td>
<td>$175,719.7</td>
</tr>
<tr>
<td>5-9</td>
<td>$50,382.69</td>
<td>$123,661.41</td>
<td>$174,044.1</td>
</tr>
<tr>
<td>10-14</td>
<td>$56,262.05</td>
<td>$129,555.59</td>
<td>$185,817.6</td>
</tr>
<tr>
<td>15-19</td>
<td>$60,948.37</td>
<td>$129,760.28</td>
<td>$190,708.6</td>
</tr>
</tbody>
</table>

*Source: CDC WISQARS April 2012*
### Total Life Time Estimated Medical & Work Lost Nonfatal Hospitalized TBI

**Ages 0 to 17, USA 2005**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Combined Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>$2,226,646,616.00</td>
</tr>
<tr>
<td>5-9</td>
<td>$1,321,161,176.00</td>
</tr>
<tr>
<td>10-14</td>
<td>$1,827,535,883.00</td>
</tr>
<tr>
<td>15-19</td>
<td>$2,397,475,290.00</td>
</tr>
</tbody>
</table>

*CDC WISQARS April 2012*
TBI Incidence maintained

• Outcomes are not uniformly poor
• Clinical research should address the broad age group, both the very young and very old
• Spectrum of disease
• From concussion, mild, moderate, and severe
• Huge burden of disease in countries with emerging economies
Attractive preclinical studies

- Cyclosporine  *Mazzeo 2009*
- Erythropoietine  *Yatsiv 2005, Zhang 2009*
- Progesterone  *Xiao 2008*
- Statins  *Tapia-Perez 2008*
- Vit D and/or Nutritional intervention  *Prins 2009*
- Neuro-restoration  *Penn 2009*
- Stem cells  *Harting 2008*
- Combination therapy with hypothermia therapy
Interventional Studies
Traumatic brain injury | Recruiting | Interventional Studies | 33 Child, 157 Adult, 82 Senior | 162 studies

ClinicalTrials.gov October 2012
Interventional Study Example

- Effects of Erythropoietin on Cerebral Vascular Dysfunction and Anemia in Traumatic Brain Injury
  C. Robertson, Baylor, NINDS
  - N= 200 expected completion Jan 2013
  - RCT 2X2 Factorial 2 doses rhEPO X 2 Hb levels
  - GOS 6 months
    - Cerebral blood flow
    - Cerebrovascular function
    - hemoglobin concentration
    - number of transfusions required
    - infection rate
Observational Studies

Traumatic brain injury | Recruiting | Observational Studies | 12 Child, 74 Adult, 37 Senior | 76 studies

ClinicalTrials.gov October 2012
Observational Study Example

- Biomarkers in TBI in children
- J. Hutchison, ONF & VNI, CCCTG
- ~ 50% Recruitment planned 250
- Expected completion 2014
- Are there biomarkers associated with quality of life in paediatrics after TBI?

*(not registered in clinicaltrials.gov)*
Observational studies registered recruiting children

...under-reporting ~ ‘dashboard’

- Vasospasm in Pediatric TBI
- The EPIC Project Impact of Implementing the EMS TBI Treatment Guidelines
- The Differences Between Out-of-hospital Severe TBI (TBI) Treatment in a Physician-staffed Versus Paramedic-staffed Emergency Medical Service (EMS) Unit and Its Effect on Patient Prognosis
- Evaluating Use of Thromboelastography to Diagnose Coagulopathy After TBI
- Proteomics of Brain Trauma-associated Elevated Intracranial Pressure (ICP)
- Mild TBI Registry
- Evaluating a Novel Method of EEG Evoked Response Potential Analysis in Sport Concussion Assessment - Test Stability and Effect of Concussion
- Comparison of Brain Network Activation (BNA™) Analysis, Clinical Symptoms and Neuro-cognitive Performance in Concussed Children and Young Adults
- A Prospective Study of Brain Network Activation (BNA) Changes in High School Athletes Following Concussion

ClinicalTrials.gov October 2012
TBI - what has made a difference or not in clinical research?

• Huge gap remains between successful preclinical neuroprotective agents and RCT results

• Guidelines for severe TBI based on ICP monitored guided care
  – None for mild or moderate where no ICP measured
  – Adherence to guidelines remains imperfect and we have not yet learned to efficiently modify measured variation in care practices
Comparative Effectiveness Research

• Why this is important for your practice and your patients
• Not a new concept – but has not been broadly applied in TBI
• Definition
• Expected costs & impact

2010 National Neurotrauma Workshop & Maas 2012
Comparative effectiveness research – Definition

• Conduct and synthesis of systematic research comparing different interventions and strategies to prevent, diagnose, treat and monitor health conditions = TBI

• Purpose of this research is to inform patients, providers, and decision-makers, responding to their expressed needs, about which interventions are most effective for which patients type of severity = stakeholders > researchers

*Based on the American Department Health & Human Services Definition for CER
Methods applied in comparative effectiveness research

• 1. Systematic reviews of existing research, e.g., meta-analysis
• 2. Decision modeling, with or without cost information
• 3. Retrospective analysis of existing clinical or administrative data, including ‘natural experiments’
• 4. Prospective observational studies, including registries, which observe patterns of care and outcomes, without assigning patients to specific study groups
• 5. Experimental studies, including randomized clinical trials (RCTs), in which patients or groups of patients are assigned to alternative treatments, practices, or policies

Tunis 2010 Stats In Medicine
International TBI Research Initiative

Global effort and funding

• European Commission (30M EUROS)
• Canadian Institutes of Health Research (9M CAD)
• National Institutes of Health
  – National Institute of Neurological Disorders and Stroke
  – Center for Information Technology
• DOD : US Department of Defence
InTBIR Objectives by 2020

• To coordinate &
• To harmonise clinical research activities across the full spectrum of TBI
• With the long-term goal of improving outcomes and lessening the global burden of TBI
InTBIR Objectives

• Establishing and promoting the use of harmonised, international standards for TBI clinical data collection


• Common Data Elements
Note: CIHR’s Institutes in Neurosciences and Mental Health are supportive of their use in research
InTBIR Objectives

• Creating a TBI patient registry by building common databases and linking them through an accessible, user-friendly interface for both entry and data search
InTBIR Objectives

• **Developing** and **applying** sophisticated analytical tools to enable Comparative Effectiveness Research (CER) for TBI
• Identify best practices in early diagnosis and treatment
InTBIR Expected Impact

• Expected results or return in a reasonable timeframe
• Expected effort vs. costs
• Expected patient impact timeline
• Knowledge translation
• What will it imply on a day to day basis for the patient and clinician...
• Participation – participation - participation
Summary: TBI trials are going global

- More than multicenter trials or pragmatic trials
- Remain systematic application of research
- Common vocabulary
- Interdisciplinary
- Require strong and newer methodological paradigms for analyses
- Intend to serve the patients more immediately
- Clinicians must become engaged stakeholders
Why clinicians must be engaged stakeholders?

• Must remain expert advocates for their patients
• By becoming a stakeholder- you can the expectation of receiving regular results and interim reports/feedback
  – uncertainty remains about the impact of this changing wave on daily workload across domains of care
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