TBI Clinical Trials: Past, Present, and Future

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I have no relevant financial relationships to disclose.
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.
Traumatic Brain Injury: 2015

Classification
GCS
(Glasgow Coma Scale)

Outcome
GOS
(Glasgow Outcome Scale)

A Complex and Heterogeneous Disease

Mild
Severe
Concussion

Vegetative
Death
Good Recovery
Disease Classification: Cancer

Modern disease classification is a mixture of anatomic, cellular, physiologic, metabolic, immunologic, and genetically defined diseases.
TBI Clinical Trials

• Past
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
Analysis of TBI Clinical Trials

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  (courtesy of Dr Geoff Manley)
Preclinical Data for Progesterone

Over 200 studies – *no primate studies*
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?
Study Subjects

Rodent

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

Human

- GCS 4 - 12
- 17 – 94 years old
- Contusion/Hematoma
- 3 mm anterior to bregma
- 5 mm tip, 2.25 m/s
- Depth 2.5 mm
Outcome 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
TBI Clinical Trials

• Current Foundational Efforts
Data Standards, TBI-CDEs, and CDISC

COMMENTARY

Common Data Elements for Research on Traumatic Brain Injury and Psychological Health: Current Status and Future Development

John Whyte, MD, PhD, Jennifer Vasterling, PhD, Geoffrey T. Manley, MD, PhD

SPECIAL COMMUNICATION

Common Data Elements in Radiologic Imaging of Traumatic Brain Injury

Ann-Christine Duhaime, MD, Alisa D. Gean, MD, E. Mark Haacke, PhD, Ramona Hicks, PhD, Max Wintermark, MD, Pratik Mukherjee, MD, PhD, David Brody, MD, Lawrence Latour, PhD, Gerard Riedy, MD, Common Data Elements Neuroimaging Working Group Members, Pediatric Working Group Members

SPECIAL COMMUNICATION

Common Data Elements for Traumatic Brain Injury: Recommendations From the Biospecimens and Biomarkers Working Group

Geoffrey T. Manley, PhD, Rannon Diaz-Arrastia, MD, PhD, Mary Brophy, MD, MPH, Doortjie Engel, MD, PhD, Clay Goodman, MD, Katrina Gwinn, MD, Timothy D. Veenstra, PhD, Geoffrey Ling, MD, PhD, Andrew K. Ottens, PhD, Frank Tortella, PhD, Ronald L. Hayes, PhD

Position Statement: Definition of Traumatic Brain Injury

David K. Menon, MD, PhD, Karen Schwab, PhD, David W. Wright, MD, Andrew I. Maas, MD, PhD, on behalf of The Demographics and Clinical Assessment Working Group of the International and Intergency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health
FITBIR Data Repository: (Federal Interagency TBI Research)

A collaboration between NIH and DoD to develop a biomedical informatics system to accelerate scientific discovery and treatment in Traumatic Brain Injury

Database with multiple contributors and multiple accessors
FITBIR is part of the New Research Model: Collaboration
FITBIR Modules

**DATA DICTIONARY**
- Defines and Validates Data
  - Creates, manages, and searches data elements and form structures
  - Validates research data against the defined validation rules

**DATA REPOSITORY**
- Study Management and Data Submission
  - Defines and manages study information and access
  - Contributes, uploads, and stores the research data
  - Defines federated data stores

**GUID**
- Global Unique Identifier System
  - Allows researchers to share data specific to study participants
  - Correlates participants across studies without exposing personally identifiable information (PII)

**PROFORMS**
- Clinical Trial / Research
  - Defines electronic case report forms
  - Schedules and collects clinical data
  - Exports, analyzes and reports on collected data

**QUERY**
- Query, Report and Export Data
  - Includes locally collected research data
  - Includes research data from defined, federated sites

**MIPAV IMAGE PROCESSING**
- MIPAV Imaging Data Submission
  - Image submission tool
  - Image analysis tool
  - 3D Image visualization
FITRIR Submission Dataflow

- Capture
  - Neuroimaging
  - Genomics
  - Assessment Data

- Validate & Submit

- Researcher Use

- Collaboration

- Qualified Access
A Fragmented Approach to TBI Research

INJURY $$\times$$ OUTCOME
Solution: Integration Across Disciplines and Research Studies

Injury Characteristics

Patient Characteristics

Time
Big Picture Solutions:
Collaborative, Integrated, Multidimensional Research Networks

Patient Characteristics

Injury Characteristics

Time

All data shared in FITBIR

NCAA-DOD

TED

CENC

CENTER-TBI

C-LEARN

TRACK-TBI

CRC

NCAA-15yr

GE-NFL

FITBIR

CRC-GE

NCAA-DOD

TED

NCAA-15yr

FITBIR

CENC

CENTER-TBI

C-LEARN

TRACK-TBI
Study Landscape

- TRACK-TBI
- CENTER-TBI
- Mission Connect
- Canadian Pediatric Mild TBI Study
- Project Head to Head
- Army STARRS
- NCAA-DoD Grand Challenge
- CENC
- INTRuST
- ADNI-DOD
- NCAA Long term Follow-up (15 yr)

TBI:
- 6 MONTHS
- 12 YEARS

TED (Endpoints)
BTEC (Dynamic Model)
Brain Trauma Evidence Center

PI: Jamshid Ghajar  Org: Brain Trauma Foundation, Centers for Disease Control

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 retrospective 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
**TBI Endpoints Development (TED)**

**PI:** Geoffrey T. Manley  
**Org:** University of California, San Francisco

### Study/Product Aims

- **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 5 “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 Conf.

### 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.

### Goals/Milestones

**CY14 Goals** – Consensus Conference 1; Integrate multiple TBI datasets; ID methodologies; Initiate contact with FDA  
- Commence Expert Working Group and Core Analyses  
- Publish Consensus Conference proceedings

**CY15 Goal** – Consensus Conference 2; TBE-CDEs in CDISC Standard  
- Select Seed Demonstration/Feasibility Projects  
- Prioritize and select measures for Stage 2 validation  
- Launch FDA Qualification Process (Stages 1 and 2)  
- Produce manuscripts for peer-reviewed journals

**CYS16-17 Goals** – Conduct Validation studies  
- Produce manuscripts for peer-reviewed journals

**CY18 Goals** – Complete validation studies/Implementation Conference  
- Roadmap for completion of FDA Qualification Process (Stage 3); Dissemination of TED lessons learned

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**Activities** | **CY** 14 | 15 | 16 | 17 | 18
---|---|---|---|---|---
Integrate/Analyze TBI datasets |  |  |  |  | **Complete**
Consensus Conferences 1 and 2 |  |  |  |  | **Complete**
Conduct Validation studies |  |  | **Complete** |  |  
Implementation Conference |  |  |  | **Complete** |  

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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.
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
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