How should clinical trials in brain injury be designed

Alexis F. Turgeon MD MSc FRCPC
Associate Professor and Director of Research
Department of Anesthesiology and Critical Care Medicine
Division of Critical Care Medicine
Université Laval
Québec City, Québec, Canada

Scientific Director
Cochrane Canada Francophone

Deputy Director
Population Health and Optimal Health Practices Unit, CHU de Quebec – Université Laval Research Centre
Recent major clinical trials in TBI

Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: NABIS)  

Erythropoietin in traumatic brain injury (EPO-TBI): a double-blind randomised controlled trial

Alistair Nicholl, Craig French, Lorraine Little, Samir Haddad, Jeffrey Presneill, Yaseen Arabi, Michael Bailey, D James Cooper, Jacques Duranteau, Olivier Huet, Anne Mak, Colin McArthur, Ville Pettilä, Markus Skrifvars, Shirley Vallance, Dinesh Varma, Judy Wills, Rinaldo Bellomo, for the EPO-TBI Investigators and the ANZICS Clinical Trials Group*

Decompressive Craniectomy in Diffuse Traumatic Brain Injury

D. James Cooper, M.D., Jeffrey V. Rosenfeld, M.D., Lynnette Murray, B.App.Sci., Yaseen M. Arabi, M.D., Andrew R. Davies, M.B., B.S., Paul D’Urso, Ph.D., Thomas Kossmann, M.D., Jennie Ponsford, Ph.D., Ian Seppelt, M.B., B.S., Peter Reilly, M.D., and Rory Wolfe, Ph.D., for the DECRA Trial Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group*

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*
What to get from these recent major clinical trials?

• Interventions thought to be beneficial in the management of severe TBI have not been shown to improve outcomes

• Could limitations in trial design explain part of these results?
What could explain that most recent clinical trials did not observe improved clinically significant outcomes?

• Too optimistic effect size (sample size) ?
• Suboptimal outcome measures ?
• Suboptimal use of good outcome measures ?
• Unbalanced baseline prognostic risk ?
Are we looking at too optimistic effect size?

- NABISH II: 17% difference in the percentage of patients with poor outcome
- DECRA: 20% absolute increase in the percentage of favorable outcome
- EPO-TBI: 28% relative risk reduction (14% absolute)
- Rescue-ICP: 15% absolute increase in favorable outcome
- POLAR: 15% absolute risk increase in favorable outcome
Are we looking at too optimistic effect size?

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Clinical trials of interventions observed to be beneficial in critical care looked at smaller absolute difference.
What outcome measure should be used?

• We must think beyond mortality
  • Most of the trials conducted in the overall critically ill population are thus not designed for this specific sub-group of patients
  • Inferences are more difficult to make

• Two main types of outcome measures
  • Functional outcome measures
  • Quality of life scales
What outcome measure should be used?

- We must think beyond mortality
  - Most of the trials conducted in the overall critically ill population are thus not designed

Outcomes measures must be clinically significant but more importantly patient oriented for an optimal shared decision making process

- Quality of life scales
What outcome measure should be used?

• The ideal outcome measure must be:
  • Logistically simple to administer: short interview time, can be used in different formats
  • Reliable: be reproducible notwithstanding who administers it, be used by proxy
  • Valid: the score should reflect the burden of disability
  • Stable: reproducible over time and not varying without change in the severity of the injury
  • Free: copyright free

Nichols et al. Injury 2011
What outcome measure should be used?

- Functional measurement scales
  - GOS and GOSe
  - DRS
  - FIM

- Quality of life scales
  - Generic instruments
    - SF-36 / SF-12
    - EQ-5D
  - TBI-specific instruments
    - QOLIBRI, Neuro-QOL

Nichols et al. Injury 2011
What outcome measures are currently used?

Outcome measures used in clinical trials over the last 5 years

- Functional outcome measures not always used
- Very few measured beyond 6 months

What is the best timing of outcome assessment?

Prevalence of unfavourable outcome according to the timing of assessment:

Evaluation beyond 6 months does not seem to add information.

Asselin et al. Crit Care 2013
The GOSe is still the outcome measure to use in clinical trials in TBI

<table>
<thead>
<tr>
<th>GOSe (8 point scale)</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent vegetative state</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severely disabled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately disabled</td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>Good recovery</td>
<td>Lower</td>
<td>Upper</td>
</tr>
</tbody>
</table>
How should we use the GOSe for sample size calculation?

• Pitfall in using an ordinal scale in a dichotomous way
  • Depends on the baseline prognostic risk
  • Patients with a good prognosis to start will achieve a favourable outcome based on a dichotomous scale no matter what is done.
  • Same for patients with a poor baseline prognosis who can’t achieve a good prognosis.

• However, an improvement in their original score may show the effect of an intervention.

Altman et al. BMJ 2006
How should we use the GOSe for sample size calculation?

- Pitfall in using an ordinal scale in a dichotomous way
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  - Same for patients with a poor baseline prognosis who
    't achieve a good prognosis.
  - However, an improvement in their original score
    may show the effect of an intervention.

Altman et al. BMJ 2006
How should we use the GOSe for sample size calculation?

- Consider the entire spectrum of the ordinal scale
- Two suggested methods
  - **Proportional odds**
    - Summary odds ratio over the different splits for collapsing the GOSe into a binary variable
    - Overall estimate of the shift in outcome
  - **Sliding dichotomy**
    - The point of dichotomy depends on the baseline prognostic risk of each patient
    - Major pitfalls: requires robust and reliable prognostic model at baseline (risk adjustment)

Maas et al. Neurotherapeutics 2010
How should we use the GOSe for sample size calculation?

• Allows considering the entire spectrum of the score.

• The extremes of the score, not considered in a dichotomous analysis, can now contribute to the analysis.
Comparison of the methods using the CRASH study database (n= 9,954)

CRASH trial Collaborators. The Lancet 2005
Dichotomous, proportional odds and sliding dichotomy methods

Table 3 Analysis of the treatment effect according to different dichotomizations and proportional odds logistic regression

<table>
<thead>
<tr>
<th>Dichotomous odds ratios</th>
<th>Adjusted odds ratio(^\wedge) (95% CI)</th>
<th>Wald statistic</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than good vs. good recovery</td>
<td>1.12 (1.01 to 1.23)</td>
<td>2.26</td>
<td>0.024</td>
</tr>
<tr>
<td>Unfavourable vs. favourable outcome</td>
<td>1.09 (0.98 to 1.21)</td>
<td>1.66</td>
<td>0.096</td>
</tr>
<tr>
<td>Death vs. survival</td>
<td>1.27 (1.13 to 1.43)</td>
<td>4.16</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Common odds ratio (proportional odds model)</td>
<td>1.15 (1.06 to 1.25)</td>
<td>3.41</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

Table 4 Analysis of the Glasgow Outcome Scale with the sliding dichotomy approach

<table>
<thead>
<tr>
<th>Dead</th>
<th>SD</th>
<th>MD</th>
<th>GR</th>
<th>Worse than expected</th>
<th>Better than expected</th>
<th>Odds ratio (95% CI)</th>
<th>Wald statistic</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled odds ratio, unadjusted</td>
<td></td>
<td></td>
<td>1.17 (1.07 to 1.27)</td>
<td>3.67</td>
<td>0.0003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled odds ratio, adjusted(^\wedge)</td>
<td></td>
<td></td>
<td>1.19 (1.08 to 1.30)</td>
<td>3.69</td>
<td>0.0002</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Roozenbeek et al. Crit Care 2011
Proportional odds or sliding dichotomy?

- Both have pros and cons
- Both approaches are appropriate

- Proportional odds method
  - Greater gain in efficiency of an intervention
  - Less clinically appealing

- Sliding dichotomy method
  - Lower potential increase in efficiency but more clinically appealing
Will these methods help reducing the sample size?

- Based on simulations:
  - Decreased sample size calculation by 25-30%
  - Increased power with the same sample size

Maas et al. Neurotherapeutics 2010
How should we consider the heterogeneous population of TBI?

- Use broad inclusion criteria
  - Simulations have been conducted to test for targeting more selective populations (average prognosis as opposed to extreme prognosis (remove the extremes))
  - Targeting according to selected prognostic features impedes not only on feasibility, but on the generalizability of the results
  - Benefit on sample size calculation and lower risk of B error

Roozenbeek et al. Crit Care Med 2009
How to deal with prognostic heterogeneity?

- Variable mortality across centers
  - Associated with variation in the incidence of withdrawal of life-sustaining therapies
- Variable rate of unfavourable outcomes across centers

Turgeon et al. CMAJ 2011

- Adjustment for a potential center-effect
  - Consider block randomisation per center
- Adjustment for covariates known to be associated with prognosis
  - Risk adjustment of analyses
What covariates should we adjust for?

- Those associated with baseline prognostic risk
- The three main ones
  - Age
  - Pupillary reactivity
  - GCS
- Others to consider
  - hypotension, hypoxemia, CT findings

Perel et al. BMJ 2008
Steyerberg et al. Plos 2008
How to minimize lost to follow-up and missing data?

- Lost to follow-up has always been a concern in brain injury trials
  - Change in residence following hospital discharge
  - Change in behaviour
  - Common practice: adjust the sample size by 5%
  - However, no lost to follow-up at 6 months in the Decra trial

- Ensure complete data collection
  - Prospective data collection
What else to consider when measuring the GOSe?

- Misclassification of the GOSe
  - More likely to affect the intervention arm
    Choi et al. J Neurotrauma 2002
  - Could decrease the potential to observe a treatment effect of an intervention by more than 3%
    Lu et al. J Neurotrauma 2008

- Training of outcome assessors
- Blinding of outcome assessment
What are the next steps to conduct relevant research and change practice?

- Avoid the weaknesses of previous research and study designs
  - Optimal outcome measures
  - Optimal study designs
  - Optimal effect size and sample size

- Methods and large collaborative networks
What are the next steps to conduct relevant research and change practice?

- Canadian TBI Research Consortium (CTRC)
  - CIHR-funded collaborative research network

- Based on the model of the CCCTG
  - Annual meeting
  - Investigator-led programs of research
  - Teaching and mentorship component
  - First meeting Halifax June 2016
Working together to improve outcomes and lessen the global burden of traumatic brain injury by 2020
Research priorities in TBI

• Comparative effectiveness research to determine the benefits of current and new treatments
• Prediction of outcome and how this is affected by patient, injury, and the quality of general and specific management across the continuum of care
• Development and validation of surrogate markers of injury and recovery
• A pathoanatomical and mechanistic patient classification system to enable targeted therapies
Projects Summary

Canadian Institutes of Health Research

A Longitudinal Prospective Study of mTBI in Youth Ice Hockey Players - Carol Emery, Willem Meeuwisse

Improving the Diagnosis and Treatment of mTBI in Children and Youth: The Power of Common Data - Isabelle Gagnon

“NeuroCare”: A Clinical Decision-Making Tool in Youth mTBI - Michelle Keightley

Post-Concussive Syndrome in Youth: GABAergic Effects of Melatonin - Karen Barlow

Predicting and Preventing Post-Concussive Problems in Pediatrics (5P) Study: A Prospective Multicentre Clinical Prediction Rule Derivation and Validation Study in Children with Concussion - Roger Zemek

TBI-Prognosis Multicenter Prospective Study - Alexis Turgeon

European Commission

Collaborative REsearch on ACute Traumatic Brain Injury in IntensiVe Care Medicine in Europe - Guido Bertolini

Collaborative European NeuroTrauma Effectiveness Research in TBI - Andrew Maas, David Menon

National Institutes of Health

Managing Severe TBI without ICP Monitoring - Guidelines Development and Testing - Randall Chesnut, Silvia Lujan, Carlos Rondina, Nancy Temkin

Multiple Medical Therapies for Pediatric TBI; Comparative Effectiveness Approach - Mike Bell, Steve Wisniewski

Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK -TBI) - Geoff T Manley, David O. Okonkwo, Pratik Mukherjee, Ramon Diaz-Arrastia, Joseph Thomas Giancino, Claudia S Roberts, Nancy R Temkin

www.ulaval.ca
Common Data Elements

NINDS Common Data Elements
Harmonizing Information. Streamlining Research.

CDEs > Traumatic Brain Injury

Traumatic Brain Injury

The National Institute of Neurological Disorders and Stroke (NINDS) and several Co-sponsoring Federal agencies have the common mission of developing data standards for clinical research. Through the efforts of subject-specific working groups, topic-driven data elements have been created. The first set of CDEs were developed in 2010 and were well-suited for hospital-based studies of acute TBI in adults. To broaden the utility of the TBI CDEs, experts were asked to update the recommendations to make them relevant to all ages, injury severity, and phases of recovery. The second version of the TBI CDEs (v.2) were developed in 2012 to be organized around four major study types:

1. Epidemiological research
2. Studies on acute, hospitalized patients
3. Studies of the rehabilitation for moderate/severe TBI
4. Mild TBI/Concussion research
Common Data Elements

Table 1. Comparison of Versions 1 and 2 of the TBI Common Data Elements

<table>
<thead>
<tr>
<th>Tiers</th>
<th>Definition</th>
<th>v.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core</td>
<td>A very small set of items relevant to all TBI clinical studies</td>
<td>16</td>
</tr>
<tr>
<td>Basic</td>
<td>A small set of data elements, beyond the core, recommended for inclusion in specific types of studies</td>
<td>224</td>
</tr>
<tr>
<td>Supplemental</td>
<td>A large number of optional items for which inclusion depends upon the scope and focus of the research question</td>
<td>655</td>
</tr>
<tr>
<td>Emerging</td>
<td>Dropped from version 2.0 because the criteria for classifying a CDE as emerging or supplemental were overlapping</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>895</td>
</tr>
</tbody>
</table>

Hicks et al. J Neurotrauma 2013
Our Vision

The Federal Interagency Traumatic Brain Injury Research (FITBIR) informatics system was developed to share data across the entire TBI research field and to facilitate collaboration between laboratories, as well as interconnectivity with other informatics platforms. Sharing data, methodologies, and associated tools, rather than summaries or interpretations of this information, can accelerate research progress by allowing re-analysis of data, as well as re-aggregation, integration, and rigorous comparison with other data, tools, and methods. This community-wide sharing requires common data definitions and standards, as well as comprehensive and coherent informatics approaches.

Working with FITBIR
Current initiatives: InTBIR/CDE/FITBIR

• Important research efforts put on:
  • Creating large registries and databases
  • Use of common data elements
  • Data merging
  • ‘Comparative effectiveness research’
Current initiatives – pros and cons

• Important research efforts put on:

  • Creating large registries and databases
    • Absolutely needed – none oriented for TBI
    • Huge potential, but current initiatives are not perennial

  • Use of common data elements
    • Standardizing outcome measures, but also data collection
    • Current CDEs better for mild TBI and rehab
Current initiatives – pros and cons

• Important research efforts put on:
  • Data merging
    • Great potential
    • Complex to achieve (ethical and legal reasons)
    • Is the time for mandatory repositories?
  • ‘Comparative effectiveness research’
    • Rebranding of research with cohort studies for evaluating interventions
    • Cannot replace randomized clinical trials
    • Association and not causality – hypotheses generating
Future research - in summary

• Future research should focus on:
  • Improve prognostic evaluation and decision-making processes
  • Appraising our current management
  • Appraising new monitoring technologies at the bedside before early adoption without sufficient evidence

• Future research should involve
  • Large scale pragmatic clinical trials
  • Explore stratification with multimodal monitoring
Future research - in summary

• Use the GOSe as the primary outcome measure (for now)
• Use proportional odds or sliding dichotomy for sample size calculation and analyses with the GOSe
• Consider more appropriate sample size
• Consider using a quality of life scale as a secondary outcome measure
• Use a pragmatic approach for inclusion
• Adjust the analyses with covariates associated with baseline prognostic risk and for center effect
• Implement measures to prevent missing data and lost to follow-up
What are the key research topics in TBI clinical applied research?

- Prognosis
  - Prognostic models / risk stratification
  - Decision aids

- Monitoring
  - Multimodal monitoring

- Management
  - Appraisal of current management and standard of care
  - Novel interventions
What are the key research topics in TBI clinical applied research?

• Prognosis
  • Prognostic models / risk stratification
  • Decision aids

• Population different than the overall critically ill population
  • Sudden event
  • Young and healthy population
What are the key research topics in TBI clinical applied research?

- Monitoring
  - Multimodal monitoring
  - $Pb\text{O}_2$
  - Cerebral saturation
  - Concept of estimating autoregulation
  - Transcranial doppler
  - (micro-dialysis...)

- We must avoid repeating the same error as with the ICP monitoring
What are the key research topics in TBI clinical applied research?

• Management
  • Appraisal of current management and standard of care
    • Improve oxygen delivery/prevent secondary cerebral injury?
      • Optimal transfusion strategies
      • Optimal flow vs. optimal intracranial pressure
      • Temperature management – normothermia?
      • Level of sedation and type of hypnotics
  • Novel interventions/innovative therapies
    • Mesenchymal stroma cells?
    • Back to neuroprotective strategies?
Ongoing CCCTG programs/studies in TBI

• Prognosis
  • TBI-Prognosis (prognostic evaluation)
  • TBI-QualE (level of care decisions)

• Management
  • PIT-TBI study (pituitary disorders)
  • TsiTBI Program (RBC transfusion)