

Multiple Medical Therapies for Pediatric TBI; Comparative Effectiveness Approach (ADAPT)

Michael Bell and Stephen Wisniewski

Traumatic brain injury (TBI) is the leading killer of children with over 7000 deaths reported in the US in 2005. In addition to this loss of life, the yearly costs of TBI on the health and welfare of children in the US is over \$2 billion for acute care along and more than a million life-years are potentially at risk. Advances in care for children with severe TBI have been disappointingly slow. Randomized controlled trials (RCTs) of novel therapeutic agents and approaches have universally failed when applied in multiple centers. Evidenced-based guidelines are not sufficiently robust to generate meaningful recommendations because the literature has failed to demonstrate best practices for most aspects of TBI care. Variations in practices such as intracranial hypertension control, mitigation of secondary insults and metabolic support are substantial in contemporary clinical practice, leading to wide variations in patient outcomes and may ultimately overwhelm treatment effects that might be observed in a well-designed RCT.

We propose an observational cohort study of 1000 children with severe TBI to compare the effectiveness of pediatric TBI therapies within an international consortium from the US, UK and EU. We will test 3 specific aims that encompass a total of 6 TBI therapies - (i) intracranial hypertension strategies - cerebrospinal fluid diversion and hyperosmolar therapies; (ii) secondary insult detection - prophylactic hyperventilation and brain tissue oxygen monitoring (PbO₂); (iii) metabolic support - nutritional support and glucose management. Several statistical approaches, often used in comparative effectiveness research (CER) to control for confounders, will be employed including propensity score adjustments, regression analyses and novel statistical modeling. Successful completion of this proposal would provide compelling evidence to change clinical practices, provide evidence for several new recommendations for future guidelines and lead to improved research protocols that would be limit variability in TBI treatments - helping children immediately through better clinical practices and ultimately through more effective investigation.