



Clinical trials in mild traumatic brain injury



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ABSTRACT

Background: Traumatic brain injury is an increasingly prevalent injury seen in both civilian and military populations. Regardless of the mechanisms of injury, the most common sub-type of injury continues to be mild traumatic brain injury. Within the last decade, there has been tremendous growth in the literature regarding this disease entity.

Purpose: To describe the obstacles necessary to overcome in performing a rigorous and sound clinical research study investigating mild traumatic brain injury. This examination begins by a consideration of changing standards for good faith open and total reporting of any and all conflicts of interest or commitment. This issue is particularly critical in mTBI research. We next examine obstacles that include but are not limited to diagnostic criteria, inclusion/exclusion criteria, source of injury, previous history of injury, presence of comorbid conditions and proper informed consent of participants. Frequently, multi-center studies are necessary for adequate subject accrual with the added challenges of site coordination, data core management and site specific study conduct. We propose a total reversal to the traditional translational research approach where clinical studies drive new concepts for future basic science studies.

Conclusions: There have been few mild traumatic brain injury clinical trials in the literature with treatments/interventions that have been able to overcome many of these described obstacles. We look forward to the results of current and ongoing clinical mild traumatic brain injury studies providing the tools necessary for the next generation of basic science projects.

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1. Introduction

Traumatic brain injury is an increasingly common public health issue (Centers for Disease Control and Prevention, 2010; Coronado et al., 2012; Defense and Veterans Brain Injury Center, 2015; Harmon et al., 2013; Hendricks et al., 2013; Hoge et al., 2008; Lew et al., 2011; Okie, 2005; Schneiderman et al., 2008; Terrio et al., 2009; Warden, 2006). Every year over 3.8 million individuals in the United States are diagnosed with traumatic brain injury with common causes to include motor vehicle accidents, sports injury, and work related accidents. The situation is even more serious in the military where 20% of all individuals who have been deployed to Southwest Asia sustain at least one head injury. Head injury/trauma

and the resulting sequelae can be stratified into several different classes including mild, moderate, and severe traumatic brain injury. Moderate and severe traumatic brain injury are complex neurological disorders often resulting in invasive procedures and long term specialty care. As a result, these disorders have received significant attention in the literature over time. Mild traumatic brain injury (mTBI), however, is over ten times more common than mild or moderate brain injury yet has not been studied in nearly as much detail (Centers for Disease Control and Prevention, 2010). In this manuscript we will begin by focusing on the obstacles to studying mTBI and then describe the elements of an adequate trial highlighting one recent study with significant outcomes (Hoffer et al., 2010, 2013). We will begin the discussion however with a very important examination of conflict of interest with respect to translational research particularly in regards to mTBI research.

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2. Conflict of interest

The consideration of conflicts of interest for investigators, institutions and private sector sponsors has been a shifting terrain over the past fifteen years. From the perspective of participants, concerns include a financial interest of the researcher (personal income, stock ownership or patent ownership), but may also extend to University patent or investment interests that may be affected by the outcome of study (Kim et al., 2004). The discussion of conflicts of interest in the physician–industry relations area has been broader than strictly the implications of corporate sponsorship of research (Angell, 2008; Rothman and Chimonas, 2008). From the perspective of academic investigators, there is a strong belief that disclosure of potential conflicts is an acceptable and sufficient tool for management (Glaser and Bero, 2005; Mecca et al., 2015). The importance of these perceptions may be enhanced by public sensitivity to the concussion problem. Litigation has magnified these issues in relation to claims of potential bias in even peer-reviewed publications about concussion/mTBI. For example, cases regarding claims of concussion reduction systems in football helmets have included public airing of both complaints of over-interpretation and misuse of published results to explicit criticism of interpretation of a published study (Collins et al., 2008) with a participating author from the helmet manufacturer (Case 1:12-cv-20613-PCH <https://www.truthinadvertising.org/wp-content/uploads/2014/01/In-Re-Riddell-Concussion-Reduction-Litigation-amd-cmpt.pdf> Civil Action No. 13-7585 (JBS/JS) United States District Court, D. New Jersey. August 3, 2015. <http://www.leagle.com/decision/In%20FDCO%2020150805978/In%20re%20Riddell%20Concussion%20Reduction%20Litigation#>). The very existence of a research partnership and co-authorship on a peer-reviewed manuscript can complicate matters if differences of opinions or agendas emerge among the participants. As a result, due diligence in avoiding even the appearance of a conflict of interest seems to be a prudent course of action.

The principle of disclosure of conflict of interest has focused most acutely on the area of significant financial interest. The U.S. Department of Health and Human Services updated its guidelines for financial interest reporting in 2011 (<http://grants.nih.gov/grants/policy/coi>). This update made conflict of interest reporting more timely but maintained the focus on financial gain as a criterion for conflict of interest. Other organizations, however, have moved toward a broader definition. A National Academy of Sciences (NAS) report proposed that: “A conflict of interest in research exists when the individual has interests in the outcome of the research that may lead to a personal advantage and that might therefore, in actuality or appearance compromise the integrity of the research.” This broader definition was motivated by a discussion that was initiated by the NAS own internal study that found that one in five NAS appointed committee members had real financial conflict of interest and an even higher number had conflict of interest by this broader definition (<https://www.cspinet.org/new/pdf/nasreport.pdf>).

From the perspective of this broader definition, the limited conflict of interest reporting required by NIH, by publishers and by venues hosting speakers is inadequate. Rather, it places an onus on the individual to explain any potential conflict of interest generated by intellectual property rights even if the University holds these rights and especially if the value of the intellectual property can be augmented by the study or communication. The issue becomes essentially the provision of sufficient contextual information regarding additional factors (e.g., financial gain, ideological biases or social relationships) that could influence either the conduct of the study or data interpretation. Karenman and colleagues, in *Teaching the Responsible Conduct of Research in Humans (RCRH)* an update to the 1999 American Academy of Medical Colleges

(AAMC), stated that: “A conflict of interest exists when two or more contradictory interests relate to an activity by an individual or an institution. The conflict lies in the situation, not in any behavior or lack of behavior of the individual. That means that a conflict of interest is not intrinsically a bad thing.” (<http://ori.hhs.gov/education/products/ucla/intro/intro.htm>) Hence, comprehensive disclosure has remained a preferred management strategy.

Academic components of research related to mTBI may be supported by pharmaceutical or medical device companies, consortiums of organizations (e.g. sports leagues or federation) and federal entities, including but not limited to the military and the NIH. It is obvious that the corporate sector has a vested interest in the outcome of product-related studies. Conflicts and means of management may be both less obvious and more complex when large organizations fund research in collaboration with corporate and/or government sector sponsors. For example, even the appearance of government favoritism or academic institutional favoritism for a particular corporate entity or product could have significant undesirable consequences.

In order for mTBI research to go forward we will now examine obstacles and research design concerns. All of these items can be overcome; it remains unclear whether this science and science in general can embrace a new way of reporting conflicts so that the audience truly understands the “situation.”

3. Obstacles

There are a variety of impediments that have plagued both basic science and clinical trial work in mTBI. An objective, consensus definition of mTBI has been an initial challenge for a diagnosis that relies on subjective reports of symptoms. Mild traumatic brain injury has been defined, by default, as traumatic brain injury that is mild, which includes an absence of structural evidence of frank brain injury. However, this definition suffers from boundary issues on both sides. How “severe” does the injury need to be before it crosses from mild to moderate? How “mild” does the injury need to be before it is not an injury at all? And, how is the term “concussion” related to mTBI? Is concussion a synonym, lay terminology, or does it represent a sub category of mTBI? Many investigators have discussed the fact that dividing the disorder into mild, moderate, or severe is a very naïve approach to the injury. These authors point out that there are very few disorders in medicine classified as grossly. While a more appropriate nosology would indeed help make this obstacle less challenging, it still remains to be seen if such a change would not face its own diagnostic challenges. This is in part because there is no accepted gold standard for mTBI diagnosis or injury recovery. As a result, clinical studies are forced to rely on a set of arbitrary inclusion/exclusion criteria and even more vague “recovery” metrics. The investigator must remember that even if they can establish diagnostic criteria for mTBI, the issue of precise inclusion and exclusion criteria will still have to be addressed in the absence of a nosology with a strong objective basis. These two factors (definition and inclusion/exclusion criteria) make meta-analysis particularly difficult.

Beyond the difficulty with a definition of mTBI and lack of a “gold standard” for diagnosis of the disorder, mTBI clinical research is complicated by individual differences in response to injury. In general, clinical trials are often affected by individual variations in disease course and manifestations but the variations in mTBI seem to be far greater. This is related to two factors: (1) source and site(s) of the injury and; (2) previous history and physical makeup of the affected individual. Mild traumatic brain injury can be caused by a range of different forces (e.g., blunt trauma, blast waves, and acceleration–deceleration profiles). Moreover, the incident forces not only vary in type but also have a variety of effects depending

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