

American Brain Injury

Technical Center

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November 25, 2006

Division of Dockets Management (HFA-305)
Food and Drug Administration
5360 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Clinical Trials in Traumatic Brain Injury

Dear Sir/Madam:

I am writing on behalf of the **American Brain Injury Consortium**, a network of approximately 120 neurosurgical centers in the US that are committed to improving the outcomes from traumatic brain injury (TBI). I am the Chairman of the Department of Neurosurgery at the University of Cincinnati and my career has been devoted to the study of TBI. I have served as consultant to the FDA, NIH and to several pharmaceutical companies that have attempted to develop new treatments for TBI. I have also been involved in trying to console thousands of families over the decades when their loved one has been killed or permanently disabled by a TBI suffered as a result of an accident or fall. I therefore have extensive experience in this field and have long hoped to see the day when we have an effective treatment to offer these patients.

Background: It should be noted that over the past two decades the mortality from severe TBI has been reduced from approximately 50% to 30%. However, these improvements have all been due to better organization of trauma care, more rapid surgical intervention, better neurosurgical critical care and more effective management of the brain swelling and ischemia. Furthermore, this remarkable reduction in mortality has come without an increase in the proportion of vegetative survivors (6%), but rather due to an increase in the good recovery or moderately disabled categories (over 50%). This suggests that further improvements can be made in the treatment of this devastating injury.

At the risk of being redundant, I would like to emphasize that TBI is a major cause of mortality and morbidity in the US as well as globally. It is also a major cause of death and disability in the military setting. However, despite its obvious public health importance and the huge burden it places on society, there has been limited research in TBI and it is studied much less than many other conditions that are far less common and have much less associated mortality and morbidity. As a result, there is not a single drug that has yet been proven effective for patients with TBI.

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The Problem: Numerous laboratory studies have shown that it is essential for most interventions in TBI to be given as early as possible, typically within the first 4 hours after injury - TIME IS BRAIN. Clearly, patients with TBI are generally unable to give consent themselves to participate in a study. The patient's family members are often not available when the patient first arrives in the hospital, and often there is a considerable delay before they can be contacted. Not being able to enter these patients into a study makes it difficult, if not impossible, to accrue sufficient patients into the study to evaluate the intervention in a timely manner. With this limitation, most trials, if they are undertaken at all, are grossly underpowered or take so long to complete that their conclusions become suspect because of changes in clinical practice that occur with the passage of time. This has also resulted in many pharmaceutical companies shying away from this area of research, thus making an understudied neurologic condition even more of a pariah.

The current rules that the FDA has in place, that require community consultation are cumbersome and time consuming and it is far from clear that they have the desired effect of obtaining community support. As best as we can tell, the main effect of this rule has been to keep many potential investigators away from this field. We therefore need to modify the system so that it is more efficient, protects the interests of the patients and is not so cumbersome that it discourages both the neurosurgeons and the pharmaceutical companies from doing research in this understudied field.

A Proposed Solution: We therefore propose that the FDA put into place a national IRB that would review all studies that require waived consent. This IRB would have representation from the scientific, clinical, business, legal, ethics and lay community. Once this committee has approved a particular study, it could be put before the local IRBs. Announcements could be made in the local newspaper, although the value of such notification is questionable.

Summary:

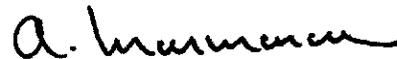
1. **TBI is a major cause of death and disability in the civilian and military setting**
2. **It is grossly understudied because of the complexities of emergency research**
3. **There is not a single proven therapeutic agent currently approved for TBI**
4. **Decades of laboratory research indicates that it is vital for therapeutic interventions to be made within the first 4-6 hours after the injury. A delay will probably result in a failed trial (Time is Brain)**
5. **Patients with TBI cannot give consent themselves**
6. **Family members are often not immediately available. Hence "waived consent" is vital in order to be able do studies in TBI**
7. **The currently recommended community notification mechanism is cumbersome and of questionable value.**
8. **There has been a chilling effect on TBI research due to poor patient accrual in trials and the reluctance of both investigators and pharmaceutical companies to deal with the hassles of the community notification policy**
9. **It is proposed that the FDA set up a National IRB with broad representation from the lay and the scientific community. Once a study with "waived consent" has been approved by this National IRB, it could be submitted to the local IRB for consideration.. The lengthy and inefficient process of multiple town hall meeting presentations would thus be eliminated without compromising the integrity of oversight.**

Thank you for your kind consideration and allowing us to comment on this important issue.

Respectfully submitted,

Handwritten signature of Raj K. Narayan.

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