Neuroimaging Biomarker Studies

Food and Drug Administration (FDA) Recognition of Traumatic Brain Injury Endpoints Development (TED) Initiative Advancement of Neuroimaging Biomarkers for Use in FDA-Regulated Trials

Treatment and diagnostics for traumatic brain injury (TBI) have been the subject of research, development, and clinical trials for over two decades. This topic receives significant media attention with respect to Service members, Veterans, and professional sports athletes. At the end of FY17 there are no FDA-approved diagnostics or therapies specific for TBI. Well-defined endpoints and changes to clinical trial design are needed to support successful regulatory-driven development of diagnostics and therapeutics for TBI. This includes advancing the identification, validation, implementation, and dissemination of Clinical Outcome Assessments (COAs) and biomarkers that are acceptable in regulatory review of FDA-qualified medical device and Drug Development Tools for mild to moderate TBI. The TED Initiative, made up of researchers from over 20 research institutions including, University of Pittsburgh Medical Center (Pittsburgh, Pennsylvania), University of Washington, University of Florida, Harvard University (Spaulding Rehabilitation Hospital and Massachusetts General Hospital, Boston, MA), University of Texas (Austin, Texas), and led by researchers at the UCSF (San Francisco, California).

The TED Initiative seeks to provide the foundational framework for improved clinical trials which can be used to support regulatory approvals for TBI diagnostics and therapeutics. The TED Initiative represents a network of public and private partnerships in a team science approach to collectively advance the field of regulatory science for TBI. In FY17, the TED Initiative's most notable accomplishments resulted from the team's efforts in advancing regulatory science in TBI (*Manley et al. 2017*).

Members of the TED team submitted a proposal stemming from one of the TED Initiative Seed Projects, focused on prognostic neuroimaging biomarkers to the FDA's Medical Device Development Tools (MDDT) Program. This was the first proposal to be accepted by the Center for Devices and Radiological Health (CDRH) into the Incubator Phase of the MDDT Pilot Program, and is now moving toward the validation phase. In addition, the FDA has recognized the role and efforts of the TED Initiative in advancing TBI regulatory science via two major communications: A Letter of Support from the Center for Drug Evaluation and Research in 2017 and a Recognition of Research Support Letter from the CDRH in 2016.

One of the Seed Projects, led by researchers at the Spaulding Rehabilitation Hospital (Boston, Massachusetts)/Harvard Medical School (Cambridge, Massachusetts) compared Glasgow Outcome Scale-Extended (GOSE) data against other outcome measures in the Transforming Research and Clinical Knowledge in Traumatic Brain Injury Pilot Study. The team found that a single Clinical Outcome Assessment (COA), such as the GOSE, was insufficient in addressing the heterogeneous nature of TBI (*Dikmen, Machamer, and Temkin 2017, Nelson et al. 2017*).

Another project led by researchers at Spaulding Rehabilitation Hospital/Harvard Medical School, addresses challenges related to well-defined, widely accepted, and validated cognition endpoints for TBI. Work published in the Journal of Neurotrauma, addressed the development of a composite cognitive endpoint COA, with regulatory considerations that would be well suited for use in TBI clinical trials (*Silverberg et al. 2017*).

Another project, led by researchers at University of Florida (Gainesville, Florida), is working to advance the regulatory readiness of biofluid biomarkers was published in the Journal of the American Medical Society Neurology (*Rubenstein et al. 2017*).

In conclusion, advances in regulatory science for TBI will facilitate FDA clearances, diagnostics, and approvals for therapeutics which, in turn, can be used in the care and management of TBI in Service members.

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