Seed Projects

An RFA [1] inviting letters of intent for competitive submissions for a total of four awards was released in July 2015, outlining the objectives of the Seed Project program and review criteria. Forty one letters of intent were reviewed by the TED Executive Committee. Of these, eleven teams were invited to submit full applications, of which ten were eventually submitted. These applications were evaluated by two reviewers with content expertise external to the TED Initiative and scored on their scientific merit. Applications were also evaluated by a reviewer with expertise in FDA regulatory readiness, as well as by a biostatistician. The TED Government Steering Committee was presented with the complete applications and review packets. Following its review, the Government Steering Committee selected four awardees, who received funding for 1-year projects commencing in 2016.

Joseph Giacino, PhD, Primary Investigator | Spaulding Rehabilitation Hospital

An Evidence-Based Clinical Outcome Assessment Platform (EB-COP) to Advance the Identification and Validation of Clinical Outcome Assessments for use as FDA-qualified Drug Development Tools

The primary aim of the Evidence-Based Clinical Outcome Assessment Platform (EB-COP) was to design, build, and pilot-test a semi-automated assessment platform to enable the efficient, transparent, systematic and context of use (COU)-specific grading of COAs to inform selection of suitable candidate measures for submission to the FDA. The Platform will also be disseminated to Investigators as a tool to help foster validation of existing COAs.

The EB-COP evaluates the strength of COAs using a six-step process that begins with the guided specification of the COU. The COA is ultimately graded using a four-tiered recommendation scheme based on the number of mandatory quality indicators appraised as adequate.

The team has pilot tested the EB-COP on the Glasgow Outcome Scale-Extended for the detection of treatment effects in patients with moderate/severe TBI of subacute duration. Results from this pilot test were presented to the Government Steering Committee on March 17, 2017 and at the Second TED Consensus Conference held on the NIH campus on April 4-5 th, 2017. In collaboration with the American Academy of Neurology, the investigators are finalizing a Qualtrics software platform designed to semi-automate the COA review and grading process.

Grant Iverson, PhD, Primary Investigator | Harvard Medical School

Noah Silverberg, PhD, Co-Investigator | University of British Columbia

Development and Validation of a Cognition Endpoint for Traumatic Brain Injury Clinical Trials

Dr. Iverson proposed to develop and initiate validation of a new performance-based clinical outcome assessment (COA) for cognition after TBI. The COA is a neuropsychological

composite score that can be applied across studies and datasets, even those with non-overlapping neuropsychological test batteries. It will overcome obstacles by (i) aggregating test data from multiple cognitive domains without ?averaging out? unique patterns of impairment for each subject, (ii) adjusting the composite score for demographic variables and estimated premorbid intelligence to remove error variance associated with pre-injury functioning and better isolate the effect of TBI, and (iii) being applicable to any battery of neuropsychological tests that meets the context of use requirements.

There is no well-defined, widely accepted, and validated cognition endpoint for TBI clinical trials. The long-term goal initiated by this Seed Project is to fill this need. A cognition endpoint that has excellent measurement precision across a wide functional range and is sensitive to the detection of small improvements (and declines) in cognitive functioning would enhance the power and precision of TBI clinical trials, accelerating drug development research.

Kevin KW Wang, PhD, Primary Investigator | University of Florida

Enhancing the ?Regulatory Readiness? of Top 4 TBI Biomarkers Towards FDA Drug Development "Biomarker Qualification Program" Submission

Using an evidence-based multi-criteria-approach, Dr. Wang and his team have identified the top four biofluid-based TBI protein biomarkers with the highest potentials of serving as predictive and/or pharmacodynamic biomarkers for therapeutic development. They are astroglial markers GFAP, S100b, neuronal markers UCH-L1, Tau. In accordance with goals of the TED Initiative, they have also identified a number of currently unaddressed knowledge gaps in terms of FDA ?Regulatory Readiness? for these four biomarkers. In this project, Dr. Wang sought to identify and secure access to 2-3 most used assay formats for each of the four key TBI biomarkers (UCH-L1, S100?, GFAP, Tau). He produced quantified high-purity antigen protein gold standard solution for each biomarker for assay cross-referencing purposes. Additionally, the team quantified these gold-standard human TBI biomarker analyte test solutions in all available assay formats. Lastly, the team generated five pooled human TBI CSF (pooled from 5 subjects each) and three pooled control CSF samples (pooled from 5 subjects each) to establish assay performance, assay cross-referencing capability, ability to detect natively released biomarker antigen, and differentiation between TBI samples from normal controls. The overall objective of this project was to systematically and rapidly fill in the knowledge gaps for the four key TBI biomarkers and improve their overall ?regulatory-readiness? towards the FDA?s Biomarker Qualification Program.

Esther Yuh, MD PhD, Primary Investigator | UCSF

Harvey Levin, PhD, Co-Investigator | Baylor College of Medicine

CT and MRI Prognostic Biomarkers for Mild to Moderate TBI

The high failure rate of clinical trials for TBI therapies has been attributed to heterogeneous pathology, particularly in mild/moderate TBI, that is not accounted for by the crude tools currently used for patient recruitment (GCS, ?positive? vs. ?negative? head CT, etc). Recent research has identified promising MRI and CT biomarkers for better stratification of TBI patients according to likely outcome. However, the interrater reliability and prognostic validity of these potential biomarkers both remain unconfirmed to date. The Seed Project of Drs. Yuh and Levin set out to establish *interrater reliability* through comparison of 3 sets of independent expert readings of CT and MRI exams from the TED metadataset. The team then set out to

determine the *prognostic validity of the biomarkers* through regression techniques, using 3-, 6- and 12-month assessments of global function, memory, cognition, and psychological health as our long-term outcome measures.

In order to obtain FDA approval for their statistical analysis plan to assess the prognostic validity of CT and MRI CDEs, Dr. Yuh and team attended several advisory sessions and meetings with FDA CDRH. This led to a submission of written application for admission into the FDA Medical Device Development Tools (MDDT) Pilot Program. The proposal was accepted and has progressed to the Qualification Stage of the MDDT program.

Contact Us
UCSF Main Site

Links
[1] https://tbiendpoints.ucsf.edu/seed-projects