TBI Endpoints Development Initiative

A collaborative for advancing diagnosis and treatment of TBI

Request for Applications

Two (2) $275,000, 1-year Seed Project Awards | Two (2) $150,000, 1-year Exploratory Seed Project Awards

- Friday, July 31, 2015 | Letter of Intent (LOI) due
- Friday, September 4, 2015 | Notification of invitation to submit full application
- Friday, October 2, 2015 | Full application due
- Friday, January 5, 2016 | Notification of award

The Traumatic Brain Injury Endpoints Development (TED) Initiative is pleased to announce that the first phase of its application process for Seed Project Awards is now open. The TED Initiative will award two (2) 1-year **Seed Project Awards of $275,000 each**, and two (2) 1-year **Exploratory Seed Project Awards of $150,000 each**, with a start date in January 2016.

Program background and goals

As of 2015, no drug has been approved by the US Food and Drug Administration (FDA) to treat traumatic brain injury (TBI). Decades of well-designed clinical trials have failed. The TED Initiative, funded by the Department of Defense, with support from a robust private-public partnership, is a 5-year direct collaboration between leading academic clinician-scientists, the FDA, industry leaders in biotechnology and imaging technology, philanthropies, and patient advocacy groups. Our ultimate goal is to advance the design of clinical trials that will lead to the first successful treatments of acute TBI.

Through early and iterative collaboration with FDA, TED's overarching aims are to provide the field with a set of validated tools for TBI research; to precisely diagnose this multi-dimensional condition, to accurately stratify patients into trials based on characteristics of their injury, reliably measure the effects of injury over time, and to confirm that experimental drugs and devices are engaging their molecular target at the dose and schedule tested. Such tools will overcome the inherent limitations of the long-used symptom-based TBI classification approaches that divide patients into crude categories of mild, moderate, and severe, using the Glasgow Coma Scale (GCS); outcomes have traditionally been measured using the equally rudimentary Glasgow Outcome Scale-Extended (GOS-E). These measures do not permit mechanistic targeting for clinical trials or detection of differential effectiveness among TBI phenotypes. The GOS-E and GCS, along with head CT, are currently the only FDA-accepted tools for stratifying patients into TBI clinical trials and measuring outcomes.

TED's immediate goals, in collaboration with FDA, are to assess the regulatory readiness of a variety of clinical outcome assessments (COAs), blood-based biomarkers, and neuroimaging biomarkers that may be used as tools for TBI clinical trials. COAs, by the FDA's definition, "*…measure a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions.*" FDA defines a biomarker as a "*characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes, or biological responses to a therapeutic intervention."* Predictive biomarkers provide a forecast of the potential for a patient to respond to one or more specific treatments. Pharmacodynamic biomarkers are dynamic assessments that show a biological response has occurred in a patient following a therapeutic intervention. Diagnostic biomarkers distinguish between patients with a particular

disease and those who do not have the disease or disease subset. Prognostic biomarkers inform about the aggressiveness of the disease and/or the expectation of how a particular patient would fare in the absence of therapeutic intervention. Their measurement often precedes clinical outcome measures of drug effect and need not be indicative of clinically meaningful effects. FDA assessment of COA and biomarker regulatory readiness, validation as endpoints, and qualification as potential drug development tools is made according to FDA's definitions and pathways. Details of these programs may be found here:

FDA's Clinical Outcome Assessment Qualification Program

FDA's Biomarker Qualification Program

Critical to this assessment for both COAs and biomarkers is establishing their validity for a given Context of Use (COU), and additionally for COAs, to establish this within a specific Concept(s) of Interest (**COI**) **COU** as …*a comprehensive statement that fully and clearly describes the way the COA is to be used and the drug development-related purpose of the use. The context of use defines the boundaries within which the available data adequately justify use of the COA and describes important criteria regarding the circumstances under which the COA is qualified*. A biomarker's COU is defined similarly, as *a comprehensive and clear statement that describes the manner of use, interpretation, and purpose of use of a biomarker in drug development*.

Ultimately, validation studies will provide more accurate disease/condition diagnosis, identify patient subpopulations likely to benefit from therapy/intervention, and provide refined outcome assessments to confirm efficacy.

Toward this end we have created the TED Metadataset, an interrogatable, integrated set of 8 individual ongoing and legacy studies, comprising well-characterized civilian, sport, and military cohorts. The Metadataset contains longitudinal and detailed clinical data on over 3500 subjects across the injury and demographic spectrum, along with CT/MRI imaging, available blood (serum, plasma) biospecimens, and detailed outcomes. Clinical data is housed on a state-of-the art database platform, and neuroimaging studies and biosamples are maintained in accessible repositories. Together, these data form a resource for international investigation of TBI. NOTE: Before obtaining access to the TED Metadataset all researchers/users are required to acknowledge receipt of and execute the TED Data Use Agreement, the TED Publication and Authorship Guideline, and the TED Research Collaboration Policy (available on the TED website).

The Metadataset may be interrogated as a whole, or limited to any one or more of its component studies. A table of contents for the TED Metadataset, including descriptions of the cohorts, domains of data collected, and data dictionaries is attached as **Exhibit 1.** The complete Exhibit 1 table can be downloaded here.

What are the objectives of the awards?

The $275,000 Seed Projects are designed to encourage investigators to identify and work toward validation of TBI COAs, blood-based biomarkers, and neuroimaging biomarkers using novel and traditional methodologies that will be presented to the FDA as validated endpoints and outcomes. These endpoints should support enrichment of patient selection/stratification for TBI clinical trials, and/or may serve as treatment endpoints. Seed projects must address the goals and bridge research gaps identified by the TED Steering Committee and its Government Steering Committee (GSC) (see **Categories of Eligible Research for Awards**, following). Seed Projects, in most cases, will focus on integrated and systematic analysis of the TED Metadataset for either: (i) existing clinical or imaging data, and/or (ii) collection of new data from existing biosamples. *Applicants are encouraged to collaborate with private industry partners to leverage resources.* Two Seed Projects will be funded for a duration of one year, at $275,000 each, including indirect costs. The maximum allowable indirect cost rate is 26%.

The $150,000 Exploratory Seed Projects are designed to support exploratory analysis of COAs, blood-based biomarkers, and neuroimaging biomarkers through interrogation of the TED Metadataset; and/or provide additional metadata to expand the TED Metadataset, e.g., feature extraction from existing TED imaging studies. Projects must address the goals and bridge research gaps identified by the TED Steering Committee and its GSC (see **Categories of Eligible Research for Awards,** following). Two Exploratory Seed Projects will be funded for a duration of one year, at $150,000 each, including indirect costs. The maximum allowable indirect cost rate is 26%.

Who is eligible to apply?

TED Seed Projects and Exploratory Seed Projects are open to the global scientific community. **However, applicants are required to identify at least one TED investigator to serve as a resource and "sponsor" for their application** (TED Investigators are listed on the TED website)**.** Applicants may come from academia, federal and military laboratories, the philanthropic sector, and/or private industry. Collaborative efforts bridging sectors are encouraged.

Projects should address one or more of the following goals:

A. Research to support TBI clinical outcome assessment tools that are suitable for use in clinical trials. Currently, almost all severe TBI therapeutic trials use incidents of adverse events (e.g., mortality) as a short-term outcome measure; the GOS, GOS-E, and Disability Rating Scale (DRS) are employed as long-term (3-6 month) primary endpoints for assessing drug efficacy. Most of these tools were developed for more severe forms of TBI, thus they may not be sufficiently sensitive to detect the diverse neurobehavioral deficits that can result from **mild/moderate TBI**. Validation of additional COAs could help enhance and improve these aspects of TBI clinical trials.

B. Research to support the use of TBI diagnostic biomarkers (blood-based and imaging) for patient stratification that are acceptable for use in therapeutic trials submitted to the FDA; to enrich for TBI populations that might be most responsive to treatment, to ultimately enhance and improve TBI therapeutic trials.

C. Research to support the use of TBI predictive biomarkers for patient stratification that are acceptable for use in therapeutic trials submitted to the FDA; to enrich for TBI patients that are likely to develop persistent post-concussive symptoms, to ultimately enhance and improve TBI therapeutic trials.

D. Research to support the use of pharmacodynamic biomarkers that are acceptable for use in therapeutic trials submitted to the FDA; to track whether therapeutic agents are effectively reaching their targets and exerting beneficial effects. The use of a TBI pharmacodynamic biomarker in conjunction with primary outcome data could provide more detailed insights as to why clinical efficacy is not demonstrated in subsets of subjects and help shed light on future improvements of drug trials of the same or related compounds.

Categories of eligible research for awards

Priority will be given to projects that utilize the TED Metadataset for the following categories of research:

A. CLINICAL OUTCOME ASSESSMENTS

1. Identify and provide evidence in support of validation of clinical outcome measures appropriate for use in applied clinical trials of therapeutic interventions for TBI. FDA's Context of Use and Concept of Interest should be specified for the validation. Depending on the context, a measure may be validated for use at a single point in time, or for evaluating a change over time. Priority outcome measurement approaches include those that allow assessment of treatment- or recovery-related change along multiple distinct functional dimensions, across a wide range of functional levels within a specific COU, and those that fill measurement gaps, particularly at the lower and higher ends of the recovery continuum.

2. Examine functional domains affected by TBI that validate measures to examine response to therapeutic interventions in several targeted areas, including:

- Behavioral control
- Global outcome
- Performance-based assessment of cognitive functioning
- Psychological/emotional health
- Perceived quality of life
- Physical function
- Participation in activities of everyday life
- Composite outcome measures based on combinations of the above measures

3. Apply advanced statistical modeling toward the validation of global composite outcome indices for TBI, particularly those that incorporate a multi-dimensional, hierarchical model built on measurement at the domain and skill impairment level.

4. Design and evaluate platforms that enable systematic review and grading of outcome measures. This proposal category will center on development of the *processes* used to vet the strength of outcome measures, as opposed to the measures themselves.

5. Develop complex, multi-dimensional modeling of TBI outcome measures that moves the field closer to a neurobiopsychosocial understanding of TBI effects and recovery.

B. IMAGING BIOMARKER CATEGORIES

1. Imaging-based biomarkers that would help guide early diagnosis, in particular with mild or concussive brain injury in which there is an unremarkable CT.

2. Early imaging markers that show prognostic efficacy for more definitive risk stratification for therapeutic intervention, or predictive value for assisting drug development.

3. Analytical optimization of advanced MR methods. These include approaches to quantitative volumetric, diffusion, and functional-based imaging in addition to automated approaches to more accurate, precise, and quantitative pathoanatomic lesion identification and characterization on conventional image acquisitions. Use of the TED Metadataset is encouraged.

4. Intra-rater and inter-rater reliability for extraction of the NINDS-TBI imaging common data elements (CDEs). Reproducible interpretations of structural neuroimaging studies for abnormal pathoanatomic findings are likely to remain a key feature of most diagnostic and prognostic models in TBI. Inclusion of expert reviewers at more than one institution and use of computational tools that provide estimates of quantitative descriptors of pathoanatomic lesions, as described within the TBI CDEs, is also encouraged. Use of the TED Metadataset is encouraged.

C. BLOOD-BASED BIOMARKER CATEGORIES

1. Blood-based TBI biomarkers of high priority are those useful in assisting drug development for predictive, pharmacodynamic, or efficacy purposes.

2. Blood-based diagnostic and prognostic TBI biomarkers. Diagnostic biomarkers distinguish between patients with TBI vs. non-TBI and can be utilized to ensure that patients selected for a clinical study have the disease or the disease subset

of interest. Prognostic biomarkers provide information on the likely course of disease in an untreated individual, and can help identify patients who are at higher risk of developing poorer outcomes.

Which categories of research are *not* eligible for Awards?

- Development of *new* biofluid-based biomarkers
- Development of *new* imaging data acquisition methods (protocols/pulse sequences/scanning parameters)
- Animal studies/models

What is the application process?

Applicants must submit a **Letter of Intent** (LOI) using the submission form attached here as **Exhibit 2**, by **5:00 PM PST** on **July 31, 2015**. The LOI should briefly describe the background/rationale for the research question, the statistical plan, include mock tables, and must be accompanied by the PI's biosketch. **A TED Investigator sponsor is required whether or not the application will use the TED Metadataset for the project.**

The LOI Form + 2-page description of proposed project + PI biosketch (**combined into a single pdf**) should be emailed to Brian Fabian, TED Program Analyst.

Applicants selected to submit a **full application** will be notified and receive further content and submission instructions by **September 4, 2015**.

Full applications will be evaluated according to the criteria below, and are due by **5:00 PM PST** on **October 2, 2015**.

Following peer review, the Government Steering Committee will select the four successful proposals. **Awardees will be notified on/or before January 5, 2016** and funding is expected to begin in **early-to-mid January 2016**, pending Department of Defense release of funds.

What are the review criteria?

Proposals will be reviewed based on their relevance to the TED Initiative's overall goal of developing clinically meaningful COAs and biomarkers. The scope of work must be realistic to complete in a one-year time frame. Proposals will be reviewed using the NIH scoring system (1-9) on the criteria below:

1. What is the problem; why is it hard to solve?
2. What is the new idea; what do we need to achieve success now?
3. What is the impact if successful?
4. How will immediate results be generated? How will you measure success in the 1-year timeframe?
5. Qualifications of investigators
6. Research environment

Where may I find further instructions?

More details about the Seed Projects and application forms can be found on the TED website.

Exhibit 1. TED Metadataset Table of Contents
As of 06/23/2015

Study Name	CRFs Included	Protocol Included	Data Dictionary Included (Type)	Timepoints	Sample Size	Population	Type of Study	Length of Follow-up	Range of Injury Severity for Entry	Normal Controls Included	Biospecimens collected (Type?)	Imaging Data Collected (Abstracted)?	Imaging Data Collected (Files)?
TRACK-TBI Pilot	Some	Yes (PDF)	Yes (Excel)	ED, Hospital, Rehab, 3 Month, 6 Month	411	Adults/Children with TBI	Observational	6 months	GCS 3-15	No	Yes (plasma, whole blood)	Yes	Yes
TRACK-TBI	Yes	Yes (PDF)	Yes (Excel)	ED, 2 week, 3 Month, 6 month, 12 month	953 as of 6/2/15	Adults/Children with TBI	Observational	12 months	GCS 3-15	No	Yes (serum, plasma, DNA, RNA)	Yes	Yes
TBIcare	No	No	No	TBD	214	Adult male and female subjects between age of 18-91	Observational	TBD	Very mild = 3 pts; mild = 100pts; mild = 35pts; moderate = 38pts; severe = 38pts	Yes	Yes (blood)	Yes	Yes
Concussion Research Consortium (CRC)	No	See CRC Data Elements file in CRF folder	Yes (Excel)	Within 24 hours of injury ,days 2-5, days 6-8, day 15, day 45, day 90	~200	Concussed high school and college athletes & matched athlete controls (football, lacrosse, hockey, soccer)	Observational	6 months	Concussion like symptoms, loss of consciousness, postraumatic amnesia, retrograde amnesia	Yes	No	TBD	Yes - in select sub-studies
ProTECT III	Yes	No	Yes (Excel)	Within 24 hours , 6 months	882	Adults with moderate to severe TBI	Interventional	6 months	GCS from 4 to 12 or motor score from 2-5 if intubated	No	No	Yes	Yes
Macrostructural and Microstructural Imaging Biomarkers of Traumatic Brain Injury (Mukherjee R01)	No	No	No	1 month, 6 months, and 12 months post injury	~115 (234 enrolled with 1/2 healthy controls)	Adults aged 16-55	Observational	1 year	GCS 13-15	Yes	Yes (DNA)	Yes	Yes
COBRIT	Yes	No	No	daily timepoints after injury (day 1-7), 3 follow up timepoints at 30 day, 90 day, 180 day	1292	Adults with TBI	Randomized	180 days	GCS from 3-12, motor < 6 or qualifying abnormality	No	Safety Labs collected + plasma and serum of self-selected participant donors	?	Yes
MISSION CONNECT - Observational (PENDING)	Yes	No	Yes (PDF)	Baseline visit, day 3-4, 1 week, day 19-20, 1 month, 3 month, 6 month	200	Adults 18-50 yrs, mild head injury	Observational	6 months after injury	GCS 13-15	Yes	Yes (plasma, saliva)	?	Yes
MISSION CONNECT - Interventional (PENDING)	Yes	No	Yes (PDF)	Baseline visit, day 3-4, 1 week, day 19-20, 1 month, 3 month	130 mTBI (65 treated/65 untreated	Adults 18-50 yrs, mild head injury	Interventional (Atorvastatin Trial)	3 months after injury	GCS 13-15	Yes	Yes (plasma, saliva)	?	Yes

Exhibit 2. TED Seed Project and Exploratory Seed Project Letter Of Intent Submission Form

$275,000 Seed Project (Y/N)?

$150,000 Exploratory Seed Project (Y/N)?

Date:

Investigator's Name:

Clinical Center:

Telephone: E-mail:

TED Sponsor:

Other investigators who will be working on this project:

Study Title:

TED Metadataset studies to be used:

External Datasets to be used:

Please attach a 2-page narrative description of your proposed project. Include the following:

1) Short background/rationale justifying the research question

2) Primary variables to be used in the analysis (include mock tables on a separate page – tables do not count toward 2-page limit)

3) Brief description of methods and statistical analysis plan

4) What is the impact if successful?

5) Project Milestone Graphic (include graphic on a separate page - does not count toward 2-page limit)

E-mail the following 3 items as a single .pdf attachment by 5:00PM PST on July 31, 2015, to:
Brian Fabian (brian.fabian@ucsf.edu)

1. Completed LOI form

2. 2-page narrative description of project plan (with tables and Milestone Graphic)

3. PI Biosketch