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14. ABSTRACT The Traumatic Brain Injury Endpoints Development (TED) Initiative is a 5-year, Department of Defense (DoD) funded project that is working toward the ultimate goal of developing better designed clinical trials leading to effective treatments for traumatic brain injury (TBI). TED is comprised of leading academic clinician-scientists, along with innovative industry leaders in biotechnology and imaging technology, patient advocacy organizations, and philanthropies, working collaboratively with regulators, specifically the US Food and Drug Administration. The TED Initiative Contact Principal Investigator is Geoffrey T. Manley, MD PhD of the University of California, San Francisco.					
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Table of Contents

Introduction	4
Keywords	5
Accomplishments	6
Impact	12
Changes/Problems	13
Products	13
Participants	14
Other Collaborating Organizations	62
Appendices	63

INTRODUCTION

The Traumatic Brain Injury Endpoints Development (TED) Initiative is a 5-year, Department of Defense (DoD) funded project that is working toward the ultimate goal of developing better designed clinical trials leading to more precise diagnosis and effective treatments for traumatic brain injury (TBI). Our aims are to gain consensus as to TBI outcomes and biomarkers that presently signify the strongest evidence of regulatory readiness, and ultimately begin to validate their use by FDA and other regulatory agencies in drug and device development processes. TED is comprised of leading academic clinician-scientists, along with innovative industry leaders in biotechnology and imaging technology, patient advocacy organizations, and philanthropies, working collaboratively with regulators, specifically the US Food and Drug Administration. The TED Initiative Contact Principal Investigator is Geoffrey T. Manley, MD PhD of the University of California, San Francisco.

KEYWORDS

traumatic brain injury, concussion, blood-based biomarker, neuroimaging biomarker, clinical outcome assessment, Glial Fibrillary Acidic Protein (GFAP), pathoanatomic lesion, clinical trial, regulatory readiness, brain magnetic resonance imaging (MRI), brain computed tomography (CT)

ACCOMPLISHMENTS

What were the major goals of the project?

Technical Objective 1: Establish a collaborative, multidisciplinary team to advance the identification and validation of clinical outcome assessments (COAs) and biomarkers for use as potential FDA qualified drug development tools (DDTs), and initiate development of CDISC data standards for trials involving diagnosis and treatment of mTBI to modTBI.

Aims:

- Organize and host a multi-stakeholder consensus conference in Year 1 (CC1) to assess the current landscape of COAs and biomarkers for potential qualification as DDTs.
- Engage in information exchange and collaboration with FDA and regulatory experts to ensure that the consensus process, workstreams, and intended deliverables are consistent with established FDA guidelines.
- Curate and harmonize data on candidate clinical outcome assessments (COAs) and biomarkers from existing military, civilian, and sports mTBI and modTBI databases with well-characterized samples (**The TED Metadataset**).
- Establish Expert Working Groups (EWGs) to organize the analyses of individual studies and the TED Metadataset, and review existing TBI COA and biomarker literatures.
- Collaborate with the Clinical Data Interchange Standards Consortium (CDISC) to conform TBI Common Data Elements (TBI-CDEs v.2) to CDISC standards for FDA regulatory submission.
- Solicit, evaluate, and collaboratively develop “seed projects” to further the TED goals of identification and validation of endpoints for diagnostic and therapeutic trials.

What was accomplished under these goals?

TED Consensus Conference 1 (CC1)

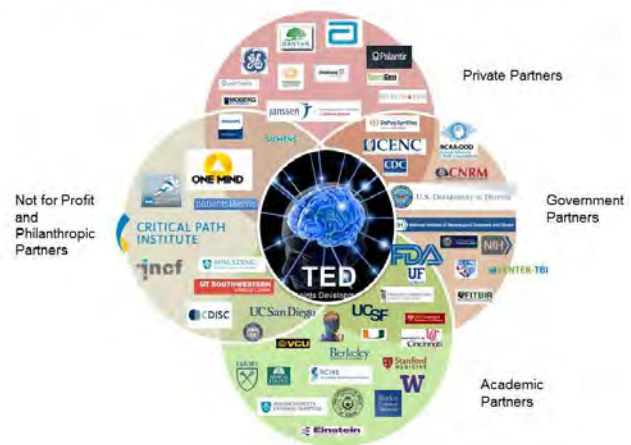
TED's first Consensus Conference (CC1) was held on February 2-3, 2015 at the Natcher Conference Center on the NIH Campus. The conference drew over 120 attendees from the research, regulatory (Food and Drug Administration [FDA]), drug and device development, and philanthropic communities to share expertise toward the common goal of developing more precise TBI diagnostic tools, clinical endpoints, and effective therapies. We designed and executed an interactive program that combined educational panel sessions on FDA's process for assessing regulatory readiness and qualification for drugs and devices under the Drug Development Tool (DDT) and Medical Device Development Tool (MDDT) programs with case study presentations and question and answer opportunities. Expert Working Groups (EWGs), which were formed prior to the conference, were formally established and convened during multiple breakout sessions at the conference. During these breakout sessions, the EWGs reviewed and refined landscape analyses of existing and pipelined TBI Clinical Outcome Assessments, as well as genomic, proteomic, and imaging biomarkers, and emerging technology devices. EWGs also developed work plans for moving TBI endpoint validation research forward. FDA representatives attended and participated in the EWG sessions. Rapporteurs for each EWG provided post-conference reports. The agenda for CC1 is attached as Appendix 1.

Development of a Unique Collaborative to Tackle TBI

Figure 1

As of 2015, no drug or device has been approved by the U.S. Food and Drug Administration (FDA) to treat acute TBI, and decades of well-designed clinical trials have failed. The TED Initiative was launched to address these shortcomings and develop a new model to take on this multi-faceted condition. This has required multisite, multi institutional research collaboration that also leverages the expertise and experience of philanthropies, patient advocacy organizations, and a committed cadre of pharmaceutical, imaging, and emerging technology industry members (Fig.1). TED is disrupting the traditional model of siloed TBI research with its creation of a collaborative model in the precompetitive space, which stretches across domains, institutions, and industry.

The Collaboratory: a Precompetitive Ecosystem



Expertise from across domains is evidenced by Co-Investigators representing over 20 academic institutions (and growing) in the fields of neurotrauma surgery, neuropsychology, neuroradiology, psychiatry, neurology, sports medicine, pediatrics, geriatrics, health economics, biostatistics, and informatics who all play key roles in advancing TED's goals. TED investigators have also engaged early and often with FDA representatives as described elsewhere in this report. Expert guidance in the regulatory arena has been provided by C-PATH, CDISC, and One Mind, also outlined elsewhere in this report. Industry partners are showing great interest in the TED model of an “end-to-end” research enterprise, and have provided both monetary and in-kind support to test and/or validate new proteomic, neuroimaging, and genomic biomarkers, as well as to develop advanced analytic methodologies and novel platforms for executing them. This type of cross-cutting collaboration is essential to overcome the myriad challenges of TBI research.

Establishment of Expert Working Groups

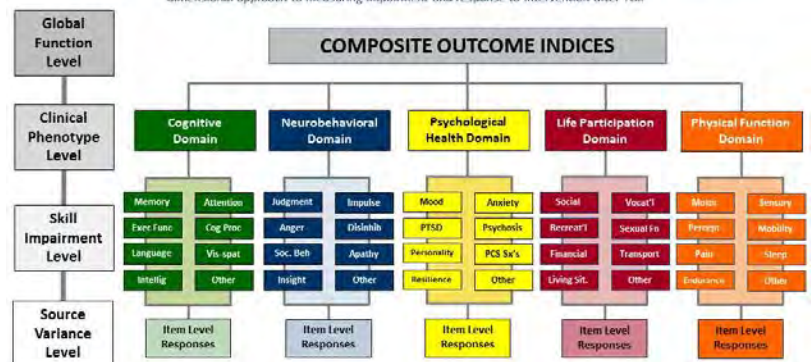
One of the main goals of the Consensus Conference was to establish Expert Working Groups and develop work streams for moving forward. This goal was achieved with the formation of four EWGs: Blood-Based Biomarkers, Clinical Outcome Assessments, Emerging Technologies, and Neuroimaging Biomarkers. Over the past year, these EWGs have been holding bi-weekly conference calls to build on work plans set forth during CC1.

Figure 2

The **Outcomes EWG** is charged with a multidimensional set of aims and deliverables relevant to the identification, study, and validation of outcome measures appropriate for use in applied clinical trials of therapeutic interventions for TBI. The ultimate goal of the Outcomes EWG is the development of a complex, multi-dimensional modeling of TBI outcome measurement that moves us in closer to a neurobiopsychosocial understanding of TBI effects and recovery. The Outcomes EWG has made great progress

Multi-Dimensional Assessment of TBI Outcome A Collaborative Effort of TRACK-TBI and TED

The proposed model intends to measure outcomes across functional domains commonly affected by TBI in a hierarchical framework that allows characterization of acquired impairment at the global, phenotypic, or specific skill level. Advanced statistical methods also enable the ability to weight the contribution of specific skills/impairments to global disability. Ultimately this model will provide a multi-dimensional approach to measuring impairment and response to intervention after TBI.



Proposed Work Flow: TRACK-TBI and TED COA Working Groups lead and commission SME groups to refine the multi-dimensional outcome model, and identify core measures in each domain for validation studies, leveraging NINDS CDE's and existing literature.

Intended Work Product: empirically-based consensus recommendations on specific measures for TBI trials, and on concept of use (CDU) (what measures to use based on acuity, population, setting, and form of intervention under study).

McCrea, Giacino, Dikmen, Marley 2015

towards this goal with the development of a new multi-dimensional assessment tool for TBI. (Fig. 2) This proposed model intends to measure outcomes across functional domains commonly affected by TBI in a hierarchical framework that allows characterization of acquired impairment at the global, phenotypic, or specific skill level.

The **Neuroimaging EWG** has set an overarching goal to identify the requirements and expectations necessary for validation of an imaging method for utilization as a diagnostic, prognostic or predictive modality for TBI. A secondary objective is to review current imaging methods as they pertain to TBI and make recommendations regarding what, if any, further validation is required and/or if new imaging modalities are needed. A major deliverable of the Neuroimaging EWG was their response to the FDA Request for Information on identifying potential biomarkers. This response addressed the critical need for more definitive diagnostic markers of mTBI for better stratification into therapeutic and rehabilitative interventions. The group posits that pathoanatomic lesions on brain magnetic resonance imaging (MRI) will provide greater diagnostic sensitivity for better stratification of mTBI patients for therapeutic intervention. The full text of the RFI response is attached as Appendix 2.

The **Blood-Based Biomarker EWG** was created to achieve the following goals: 1) coordinate biosample collection and data collection among TED-linked major clinical TBI studies such as TRACK-TBI, CENTER-TBI, and MISSION CONNECT; 2) standardize the sample request form for biomarker studies; and 3) collaborate with FDA toward use of biomarkers as tools for therapeutic development and clinical trials, including moving one or more blood-based biomarkers towards the FDA biomarker qualification program. This EWG has made great strides in achieving these goals as evidenced by its response to the FDA Request for Information on identifying potential biomarkers. This response proposed using Glial Fibrillary Acidic Protein (GFAP) as a paradigm TBI biomarker because it fulfills a majority of key attributes of a predictive, pharmacodynamic and/or efficacy-surrogate biomarker for TBI drug development. The response also included an extensive list of candidate CSF and/or blood-based TBI protein biomarkers that could be used as biomarkers to assist drug development, while focusing on the example of GFAP and its breakdown products. The full text of the RFI response is attached as Appendix 3.

This EWG's team leaders and members also formally joined the International Initiative for TBI Research (InTBIR) Biomarkers Working Group that include members from NINDS, CENTER-TBI, and the Brain Canada Project. There were several biweekly conference calls that led up to the InTBIR meeting in Brussels, Belgium on Oct. 13-14, 2015. Key items discussed were categorizing biosamples available for each major TBI study, building consensus of the top biomarkers for initial assessment, identification of a test set of plasma and serum samples that include TBI of different severities, and the inclusion of non-TBI trauma controls and normal controls for standardization and to establish biomarker assay performance.

The **Emerging Technology EWG** has an overarching goal to validate tools that will provide greater objectivity and complement existing neurocognitive measures for the diagnosis and/or prognostication of mild TBI or concussion. As TED moves into year two, this EWG will form multi-disciplinary subgroups according to the concept of interest and context of use that a technology applies to.

Engagement with FDA and Regulatory Experts

Early and consistent communication and collaboration with the FDA has been an integral goal of the TED Initiative. This tone of collaboration was set at CC1 as Dr. Douglas Throckmorton, Deputy Center Director for Regulatory Programs at Center for Drug Evaluation and Research (CDER), led the speakers in the first of the moderated tri-panel sessions at the conference. His presentation describing 'FDA Regulatory Pathways' was followed by a panel discussion consisting of five FDA representatives, including Dr. Billy Dunn, Director, Division of Neurology Products, CDER. Consultation to discuss strategies for moving forward towards a path to FDA regulation and validation has continued throughout the year.

In February 2015, the FDA released Federal Register notice docket FDA-2014-N-2187 requesting comments on 'Identifying of Potential Biomarkers for Qualification and Describing Contexts of Use to Address Areas Important to

Drug Development.’ TED investigators drafted two responses to this Request for Information. A response was submitted that proposed a new imaging biomarker for mTBI, specifically, pathoanatomic lesions on brain magnetic resonance imaging (MRI) (Appendix 2). TED investigators also submitted a response proposing that TBI protein biomarkers could be useful in assisting drug development for use as predictive, pharmacodynamic, or surrogate biomarkers. This response focused on Glial Fibrillary Acidic protein (GFAP) as it fulfills a majority of the attributes of a biomarker for TBI drug development. (Appendix 3).

Working with regulatory experts from C-PATH, TED investigators have drafted and plan to submit a Critical Path Information Meeting (CPIM) request to FDA CEDR by or before November 9, 2015. These meetings address issues in drug and device development and are a method by which CDER and investigators from academia and the private sector can communicate at early stages of investigation to improve the efficiency and ultimate success of drug or device development. The purpose of this initial CPIM is to utilize paradigm examples of: 1) a neuroimaging biomarker (e.g., structural MRI), and 2) a blood-based biomarker (e.g., Glial Fibrillary Acid Protein [GFAP]) to explore with FDA the potential pathways to regulatory readiness for these candidate biomarkers.

In mid-2015, FDA announced that it would appoint a TED research fellow, tasked with coordinating FDA’s collaborations with the TED enterprise, and with the agency’s efforts to engage the research and industry communities in the field of TBI more generally.

As noted above, in addition to working with representatives from the FDA, TED has developed a strong working relationship with Critical Path Institute (C-PATH). C-PATH is an independent, non-profit organization dedicated to bringing scientists from the FDA, industry, and academia together to collaborate and improve the drug development and regulatory processes for medical products.

Creation and Curation of the TED Metadataset

By leveraging legacy datasets from studies led by TED Co-Investigators, the wider international TBI community, and the ongoing TRACK-TBI study, the TED Metadataset has been created. The Metadataset contains granular data on nearly 6,000 mild-moderate and severe TBI study participants. The constituent studies include TRACK-TBI Pilot, TRACK-TBI, COBRIT, TBICare, Concussion Research Consortium, ProTECT III, the University of Washington mTBI cohort of behavioral outcome studies, the Valproate and Mag-Sulfate studies and a neuroimaging study led by Dr. Pratik Mukherjee. These datasets combine to form a wealth of mild-modTBI and severe clinical trials, and include a wide range of clinical outcome assessments, neuroimaging data, and biospecimens.

Figure 3

TED Metadataset Table of Contents (10/23/2015)										
Study	Timepoints	Sample Size	Sample Size Mild Moderate Severe	Population	Type of Study	Length of Follow up	Range of Injury Severity for Entry	Biospecimens collected (Type)	Imaging Data Collected (Abstracted)	Imaging Data Collected (Files)
TRACK-TBI Pilot	ED, Hospital, Rehab, 3 Month, 6 Month, 12 month	586	Mild: 480 Mod: 28 Severe: 42 Unk: 5	Adults/Children with TBI	Observational	12 months	GCS 3-15	Yes (plasma, whole blood)	Yes	Yes
TRACK-TBI	ED, 2 week, 3 Month, 6 month, 12 month	1193 as of 10/22/15	TBD	Adults/Children with TBI	Observational	12 months	GCS 3-15	Yes (serum, plasma, DNA, RNA)	Yes	Yes
COBRIT	daily timepoints after injury (day 1-7), 3 follow up timepoints at 30 day, 90 day, 180 day	1207	Mild: 651 Moderate: 116 Severe: 440	Adults with TBI	Randomized	180 days	GCS from 3-12, motor < 6 or qualifying abnormality	Safety Labs collected + plasma and serum of self-selected participant donors	No	Yes

A major challenge in creating the TED Metadataset has been to devise a methodology to harmonize the data collected from the myriad outcome assessments used in the different studies. Extensive and ongoing work by TED teams at UCSF and University of Pittsburgh has resulted in the creation of a Metadataset Table of Contents (Fig 3. partial excerpt of Metadataset Table of Contents) and individual tables that map the baseline characteristics and clinical variables that have been collected across Metadataset studies. (Appendix 4).

This essential step will now permit TED investigators and potential collaborators to have both a high-level overview of the Metadataset, as well as harmonized demographic and clinical data when planning potential research projects. This table of contents of accessible via the TED website. The baseline and clinical variables table is a crucial step in harmonizing data fields that will allow accurate interrogation across studies.

Data Use and Human Materials Transfer Agreements, a Publication and Authorship Policy Guideline, and a Research Collaboration Policy for the TED Initiative have also been drafted and posted to the TED website to serve as the backbone intellectual property agreements for the creation of the TED Metadataset. (Appendix 5)

TED has also formed a partnership with Palantir, a leading Silicon Valley data analysis company. Palantir's Gotham platform and associated analytic capabilities is now being tested for interrogation of the Metadataset. Subsets of three studies have been loaded onto the Gotham platform. Palantir has held several in-person and online training webinars for TED investigators to become conversant with this novel object-oriented platform. Palantir has partnered with TED by providing in-kind analytic and technical support. A Palantir representative will be showcasing the analytic potential at the November 9-10, 2015 Investigators Meeting.

Collaboration with the Clinical Data Interchange Standards Consortium (CDISC)

TED investigators have worked closely with the CDISC, C-PATH, and One Mind to conform the NINDS TBI Common Data Elements (TBI-CDEs) to CDISC standards. The FDA Data Standards Strategy calls for comprehensive data standards to facilitate the efficient and effective review of regulatory submissions, and will soon require CDISC standards.

The now conformed TBI data standards represent another essential go-forward mechanism to enable efficient analyses and integration of future prospective TBI studies that integrate novel blood-based and neuroimaging biomarkers into observational and randomized controlled clinical trials.

CDISC, a global non-profit Standards Developing Organization, offers a suite of open standards, spanning protocol representation and study design through analysis and reporting, that are being implemented widely around the world.

Seed Projects

The application process is near completion for the four, one-year Seed Project awards that will be selected by the Government Steering Committee (GSC) for launch in early 2016. Under the guidance of the GSC, we anticipate that two Seed Project awards will be granted for \$275,000 each, and two Exploratory Seed Projects will be granted for \$150,000 each. 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. 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.

Seed Project eligibility was open to the global scientific community. Through a collaborative effort between the TED Executive Committee and GSC, an RFA and review criteria were drafted and disseminated on July 1, 2015. (Appendix 7) Dissemination of the RFA included circulation via the TED mailing list, posting to the recently created TED website and the TRACK-TBI website, and distribution via mailing lists and listservs of the International Initiative for Traumatic Brain Injury Research (IntBIR), CENTER-TBI, National Institute of Neurological Disorders and Stroke (NINDS), FDA, and One Mind.

Following publication of the RFA, 41 Letters of Intent (LOI) were received. These LOIs were reviewed internally by the TED Executive Committee. Of these 41 LOIs, eleven were invited to submit full applications; ten full applications were received.

Internationally known experts across all relevant domains of TBI investigation, including clinical outcomes assessment, proteomic biomarkers, neuroimaging, and biostatistics were empaneled as reviewers. In addition, each full application will be reviewed by C-PATH to assess state of FDA regulatory readiness. Scores and reviews are due

on November 6, 2015, and will be delivered to the GSC for final selection.

What opportunities for training and professional development has the project provided?

Nothing to report.

How were the results disseminated to communities of interest?

Figure 4

TED launched a website (Fig 4) in July 2015 that provides an overview of the goals and objectives of program, highlights the leadership and key investigators, announces key news items and events, publicizes recent publications, and provides resources for TBI patients and researchers. As of writing, the website has garnered over 11,000 page views.



Lead PI Geoff Manley presented at the 2015 Military Health System Research Symposium (MHSRS). His presentation titled, “Private-Public Regulatory Research Collaboration Toward Validation of TBI Endpoint Development (TED): Phase 1 Progress and Forward Planning” introduced TED to a diverse group of Department of Defense and academic scientists, as well as military medical military medical care providers. Other TED Co-Is and Co-PIs who presented at the MHSRS included Harvey Levin, PhD, Christine MacDonald, PhD, Nancy Temkin, and Ramon Diaz-Arrastia, MD.

Dr. Manley also presented the keynote address, “Healing the Injured Brain: A Team Science Approach” at the September 19, 2015 [BrainHealth Summit](#) in Napa, California, which reached several hundred members of a lay audience interested in brain health. He also presented the progress to date for the TED initiative at the October 12, 2015 International TBI Research initiative meeting in Brussels, Belgium, attended by investigators and staff from the DoD, NIH, European Commission, and the Canadian Institute of Health Research.

What do you plan to do during the next reporting period to accomplish the goals?

- Fund 4 Seed Projects that will encourage investigators to identify and work towards validation of TBI COAs, blood-based biomarkers, and neuroimaging biomarkers using novel and traditional methodologies for validation as endpoints and outcomes for FDA regulatory advancement
- Publish conference proceedings manuscript of CC1 to *Journal of Neurotrauma*
- Complete harmonization of studies in TED metadataset; load harmonized data into Palantir to allow for interrogation by TED investigators
- Secure CPIM meeting and act on guidance received as to which FDA regulatory pathway is most appropriate for advancing the proposed types of biomarkers for use in TBI clinical trials
- Secure meeting with FDA Division of Neurology Products for development of TBI outcome measures
- Identify and select blood-based and neuroimaging biomarkers that are closest to regulatory readiness
- Other validation efforts internal to TED investigators to be determined and explored

- Plan and execute Consensus Conference 2, tentatively scheduled for July 2015

IMPACT

The importance of the TED collaborative as a paradigm for “a new way of doing business” is already taking hold. We set out to create a pre-competitive research ecosystem in which academic collaboration would be advanced by synergistic contribution by historically siloed private industry competitors, and guided by the key scientific and community stakeholders. Our essential goal is to effectively and efficiently design TBI clinical trials that will lead to diagnostics and treatments that will receive approval by FDA. In the year since our launch, we have brought together over 20 academic institutions, more than 15 private industry partners, and the key departments within FDA. FDA continues to elevate TBI to a higher priority status for therapeutic standards development; in addition to improved regulatory review, standards will reduce variability of data mapping, and enable reviewers to combine data from multiple sources in a consistent format for analysis. Collecting prospective clinical trial data with CDISC standards will streamline clinical research data flow across the life of a study. We have created an informatics platform that will soon contain data on thousands of subjects from multiple studies of mild, moderate, and severe TBI. The ability to study the natural history of the disease over time, and conduct analyses that are powered to test hypotheses regarding the trajectories of recovery or decline are essential to the discovery and validation of biomarkers and outcome assessments that will advance the field of TBI toward effective diagnostics and treatments.

What was the impact on the development of the principal discipline(s) of the project?

The building of the Metadataset will have a lasting impact on the field of TBI research. We are beginning to test its promise as a widely interrogatable dataset to which forthcoming studies can add their data and provide the investigation platform not only for the current TED investigators, but the wider scientific community. The Metadataset will soon be accessible via the One Mind portal, which is an open science, interactive data exchange portal designed to enable clinician and industry collaboration, data sharing and data mining on an unprecedented scale, all governed by purpose-built intellectual property agreements that recognize the individual stakes and priorities of the collaborators.

What was the impact on other disciplines?

The pre-competitive collaborative model that TED has built is directly applicable to other neurocognitive and neurodegenerative diseases that similarly rely on the combination of outcome assessments to measure recovery or decline over time, and the validation of biomarkers to assess disease progression and to test drug targets and regimens. The model is extensible to psychiatric conditions that share these same attributes of multi-dimensional assessment via outcome measures and biomarkers.

What was the impact on technology transfer?

The collaborative model of data and analytics sharing is the foundation of precision medicine and personalized medicine. We are creating the necessary components of both the research and analytic pipelines that allow us to confidently step onto and across the bridge, even as we are building it, because we are attending most carefully to the quality of the data curation and harmonization as the Metadatset is expanded, and utilizing both traditional and novel approaches, in sync, to test our methods.

Our efforts appear to have been embraced by FDA, with the contribution of senior FDA officers at our conferences, within our Expert Working Groups, and with the on-boarding of a research fellow dedicated to TED and to FDA's TBI efforts overall. We are at an inflection point in regulatory collaboration, as FDA has signaled its intentions to utilize all of its available regulatory pathways, Qualification of Drug and Device Development Tools, Guidance Documents, and

Letters of Support to propel our efforts.

TED collaborators from industry have already contributed in-kind and monetary resources to assist our efforts to build analytic tools and the platform. Pharmacologic/biologic companies that abjured the field of TBI for years are approaching us for access to existing data and in ongoing studies to add sub-studies to test potential drug targets. We have forged these relationships in an atmosphere of transparency, and with signed agreements to abide by our ethos of collaborative scientific discovery.

What was the impact on society beyond science and technology?

TBI remains a major public health issue that impacts patients and their families. The lifetime incidence of TBI is 40% and nearly every family has been touched by this injury. With the annual cost to Americans estimated to be over \$70 billion a year, TBI has an economic impact on everyone. TED is providing new tools for clinical trials such as the new CDISC TBI data standards that will improve the efficiency and costs of all future clinical trial in TBI. It is anticipated that as we identify and validate better tools for patient stratification and enrichment along with improved clinical outcome assessment tools, we usher in a new era in clinical trials that will lead to improved diagnostic tools and new therapeutics for TBI.

CHANGES/PROBLEMS:

Nothing to report

PRODUCTS

Publications

Yue JK, Pronger AM, Ferguson AR, **Temkin NR**, Sharma S, Rosand J, Sorani MD, **McAllister TW**, Barber J, Winkler EA, Burchard EG, Hu D, Lingsma HF, Cooper SR, Puccio AM, Okonkwo DO, **Diaz-Arrastia R**, **Manley GT**; COBRIT Investigators; TRACK-TBI Investigators. Association of a common genetic variant within ANKK1 with six-month cognitive performance after traumatic brain injury. Neurogenetics 2015 Jul;16(3):169-80. PMID: 25633559.

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Lingsma HF, Yue JK, Maas AI, Steyerberg EW, **Manley GT**; TRACK-TBI Investigators, Cooper SR, Dams-O'Connor K, Gordon WA, Menon DK, **Mukherjee P**, Okonkwo DO, Puccio AM, Schnyer DM, Valadka AB, Vassar MJ, Yuh EL. Outcome prediction after mild and complicated mild traumatic brain injury: external validation of existing models and identification of new predictors using the TRACK-TBI pilot study. J Neurotrauma 2015 Jan 15;32(2):83-94. PubMed PMID: 25025611

Private-Public-Regulatory Research Collaboration Toward Validation of TBI Endpoint Development (TED): Phase 1 Progress and Forward Planning. Geoffrey T Manley. Presentation. 2015 Military Health System Research Symposium (MHSRS).

Website | <https://tbiendpoints.ucsf.edu>

OTHER PRODUCTS

Nothing to report

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

<i>Name</i>	<i>Project Role</i>	<i>Research Identifier (e.g. ORCID ID)</i>	<i>Nearest person month worked</i>	<i>Contribution to Project</i>	<i>Funding support</i>
UCSF					
Geoffrey Manley	Co-PI		1	Responsible for the coordination, direction, and execution of the proposed project. He serves as Chair of the Executive Committee and the Government Steering Committee's (GSC) and DoD's primary point of contact.	5% cost sharing support from professional fees.
Kimberly Cantero	Program Administrator		2	Led the planning and execution of the first Consensus Conference held in Bethesda, MD in February 2015.	
J. Brian Fabian	Program Administrator		8	Supports the multicenter project planning efforts and operations for the Administrative Core. He supports the efforts among the six Core Leaders to implement and manage the tasks and deliverables and aim to assure that milestones are achieved in accordance with the study timelines.	
Pratik Mukherjee	Co-PI		1	Leads the Neuroimaging Core and serves on the Steering and Executive Committees. Dr. Mukherjee is involved in all stages of the project in support of the work for the Consensus and Implementation Conferences and Validation studies.	
Mary Vassar	Emerging Tech Core Administrator		1	Leads the Emerging tech core.	
BCM					
Harvey Levin	Co-I		1	Dr. Levin is involved in all	

				phases of the project in support of the Outcomes Core for the Consensus and Implementation Conferences and Validation studies.	
<u>UP</u>					
Stephen Wisniewski	Co-PI		1	Member of Executive Committee, curate data from existing studies, design and conduct data analysis	
David Okonkwo	Co-Investigator		1	Evaluation of measures, and the selection of biomarkers	
Michael Bell	Co-Investigator		1	Provide expertise of the evaluation of measures and biomarkers	
<u>MCW</u>					
Michael McCrea	Co-PI		1	Dr. McCrea is on the Executive Committee and participates in bi-weekly conference calls related to the TED project. Co-leads Outcome EWG; Dr. McCrea has evaluated the array of clinical outcome measures and has assisted with overall study execution and oversight. Dr. McCrea has co-led a joint effort of the TED COA EWG and TRACK-TBI outcomes team to maximize efficiencies of the two groups, avoid duplication of effort, and accelerate achievement of key aims for both studies. Dr. McCrea has pushed a clinical research data set from sports concussion research to TED for testing on the Palantir platform.	
<u>NCIRE</u>	--				
<u>RTI</u>	--				
<u>HMJE</u>					
Ramon Diaz-Arrastia	Co-PI		2	Dr. Diaz-Arrastia is on the Executive Committee has participated in bi-weekly conference calls related to the TED project and co-leads the Blood-based Biomarker EWG. He also attended a 2-day in-person meeting in Bethesda, where he presented information	

				about the TED Biomarkers effort and took part in panel discussions. He also participated in the TED Request for Proposals, acting as a sponsor for several projects as well as referee of which projects should go forward. We have not yet hired the post-doctoral fellow to work on this project, as the TED Metadataset is not yet available for analysis	
<u>UCSD</u>					
Murray Stein	Co-PI		1	Dr. Stein is on the Executive Committee and has conducted literature reviews in support of validation of candidate COAs and biomarkers. His expertise in PTSD has assisted with data analysis.	
<u>UCB Sub#1</u>					
Robert Knight	Co-I		1 summer month	Dr. Knight has conducted a literature review of the TBI-EEG literature. In addition he is in contact and advising an Israeli company, ELMINDA, that has just completed a large TBI-EEG study. He recently worked with them to develop and application from them for a Seed Project Award for the TBI Endpoints Development Initiative. Dr. Knight will be presenting this work at the DOD TEN event Nov 9-10	
<u>UCB Sub #2</u>					
William Jagust	Co-I		1 summer month	Examination of pharmacokinetic and binding properties of tau tracers	
<u>UF</u>					
Kevin K. Wang	Co-I	0000-0002-9343-6473	1	Co-leads the Blood-based Biomarker EWG Biomarker strategy, FDA interface, interface with InTBIR team	
<u>Stanford</u>					
Jamshid Ghajar	Co-I		1	Lead investigator in the Emerging Technology group.	
<u>USC</u>					
Toga, Arthur W.	Co-I		1	Dr. Toga is involved in the project in support of the	

				Consensus and Implementation Conferences and Validation studies.	
<u>AEHN</u>					
John Whyte, MD, PhD	Co-I		1	Dr. Whyte attends all scheduled teleconferences and reviews and advises on all outcomes measurement strategies.	10% effort provided of which 6.38% effort supported by this project and 3.62% funding provided as cost sharing by Einstein internal funds.
<u>SRH</u>					
Joseph T Giacino, PhD	Outcomes Expert Working Group Co-Lead	0000-0002-7916-9698	1	Dr. Giacino is on the Executive Committee and has participated in bi-weekly conference calls. Co-leads Outcomes EWG; Development of approach to outcome measure validation studies; Preparation and participation in consensus conference I	
<u>UW</u>					
Christine Mac Donald, PhD	Co-I		2	<i>Dr. Mac Donald is a member of the TED executive committee and Co-Lead on the Neuroimaging Expert Working Group.</i>	
<u>VCU</u>	--				

ACTIVE OTHER SUPPORT

UCSF

MANLEY, GEOFFREY T.

RO1 NS067092 (PI: Ferguson)

National Institutes of Health

Agency Point of Contact: Lyn Jakeman

Bioinformatics for Translational Spinal Cord Injury (SCI)

The major goal of this project is to pool data from several laboratories and make cross-species comparisons to identify common metrics of SCI that can be used for evaluating mechanisms of SCI that translate across species.

AIMS: 1) Build a pooled database of existing experimental rodent and primate SCI research data to provide a platform for knowledge discovery and multivariate quantification of translational features across diverse outcomes and experimental models. We will start with data from 5 major SCI research centers to provide a framework for later contributions from other research groups. 2) Identify syndrome measures in rodent SCI models, using the same multivariate techniques often used by clinical researchers to define and measure complex

05/01/10 – 04/30/16 (NCE)

\$206,872

Email: lyn.jakeman@nih.gov

0.12 calendar

(Effort reduced)

disease states.3) Identify which multivariate outcome patterns in rodent models are most sensitive to the effects of graded injury and which are most sensitive to change over time, with the goal of improving sensitivity and streamlining testing of therapeutic interventions. 4) Identify which multivariate outcome patterns in non-human primates are most sensitive to the effects of SCI and recovery over time, providing important information about the most sensitive outcomes for therapeutic testing in this valuable preclinical model. 5) Make translational multivariate comparisons of rodent and primate SCI data to identify which outcome patterns best translate across experimental models and which are species- and model-specific, setting the stage for future multivariate comparisons to human data.

Role: Co-Investigator

U10NS058931 (PI: C.J. Hemphill)	09/01/12-07/31/17	0.12 calendar
NIH/NINDS	\$192,840	(Effort reduced)
Agency Point of Contact: Janis Scott	Email: janiss@ninds.nih.gov	
<u>SF-NETT: San Francisco Neurological Emergencies Trials Network</u>		

Project Goals: National Institute of Neurological Disorders cooperative grant to create a hub-spoke hospital network from which to conduct streamlined phase III clinical trials testing new treatments for neurological emergencies such as status epilepticus, traumatic brain or spinal injury, and stroke.

AIMS: 1) To continue high-volume enrollment of research subjects in multiple acute phase III neurological emergency clinical trials using a scalable hub-spoke hospital system and a multidisciplinary group of acute care investigators; 2) To utilize SF-NETT as a platform for junior emergency medicine physicians to participate in neurological emergency clinical trials as part of an academic career development pathway; 3) To enhance the participation of underserved minorities in clinical trials of new treatments for neurological emergencies

Role: Co-Investigator

W81XWH-13-1-0441 (PI: Manley)	09/26/13-09/25/16 (NCE)	0.84 calendar
US Department of Defense	\$466,707	
Agency Point of Contact: Kimberly Carter	Email: kimberly.m.carter47.civ@mail.mil	
<u>Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TBI)</u>		

The major goals of this project are to determine an imaging phenotype for TBI; validate and develop prognostic and diagnostic models using the TBI Common Data Elements; and identify proteomic and genomic associations with TBI phenotypes from the patients enrolled into the TRACK TBI study at UCSF, University of Pittsburgh, Mt. Sinai and University of Texas, Austin.

AIMS: 1) To develop improved prognostic, diagnostic and outcome models for TBI; 2) To identify neuroimaging biomarkers for diagnosis and prognosis in TBI; 3. To identify proteomic and genomic associations with TBI phenotypes

Role: Principal Investigator

W81XWH-13-1-0297 (PI: Beattie)	09/30/13-09/29/16	0.12 calendar
DOD US Army Med. Res. Acq. Activity	\$250,000	
Agency Point of Contact: Jennifer Shankle	Email: jennifer.shankle@us.army.mil	
<u>Effects of Early Acute Care on Autonomic Outcomes in SCI: Bedside to Bench and Back</u>		

The objective of this proposal is to understand the role of cardiovascular variables in the recovery process after acute spinal cord injury using clinical data to model the range of variations, then testing methods to determine the how to achieve the best outcome.

AIMS: 1) Examine the available evidence for a correlation between early BP management and vasopressor use, and later outcomes, including outcomes on autonomic, bladder and bowel function; 2) Provide detailed reports and physiological monitoring in the ED and ICU to identify cardiovascular parameters and (events) during early management of SCI that may be associated with poor outcome, including bowel and bladder function; 3) Determine the effects of episodes of hypotension and hypertension on the recovery of locomotor, bladder and bowel function in our rat model of high thoracic contusion SCI.

Role: Co-Investigator

U01NS086090 (PI: Manley-Contact PI)	09/30/2013-08/31/2018	2.26 calendar
NIH/NINDS	\$2,089,213	(Effort reduced)
Agency Point of Contact: Joanna Vivalda	Email: joanna.vivalda@nih.gov	
<u>Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TBI)</u>		

The goal of this multicenter study is to create a high quality TBI database that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers for 3,000 patients that will be enrolled across the spectrum of mild to severe TBI. Analytic tools will be developed to establish more precise methods for TBI diagnosis and prognosis, improve outcome assessment, and compare the effectiveness and costs of tests, treatments, and services.

AIMS: 1) To create a widely accessible, comprehensive TBI Information Commons that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers from subjects across the age and injury spectra, and provides analytic tools and resources to support TBI research; 2) To validate imaging, proteomic, and genetic biomarkers that will improve classification of TBI, permit appropriate selection and stratification of patients for clinical trials, and contribute to the development of a new taxonomy for TBI; 3) To evaluate a flexible outcome assessment battery comprised of a broad range of TBI common data elements that enables assessment of multiple outcome

domains across all phases of recovery and at all levels of TBI severity; 4) To determine which tests, treatments, and services are effective and appropriate for which TBI patients, and use this evidence to recommend practices that offer the best value.

Role: Co- Principal Investigator

Antwerp University Hospital subcontract (PI: Andrew Maas) 10/01/13-03/31/20 0.12 calendar
European Commission 7th Framework Programme (PI: Maas) \$14,441
Agency Point of Contact: Annina Sorgner Email: Annina.Sorgner@gabo-mi.com

CENTER-TBI: Collaborative European NeuroTrauma Effectiveness Research in TBI

UCSF will contribute to this international effort through participation in the management committee, harmonizing data collection forms, and by facilitating collaboration with TRACK-TBI. CENTER-TBI aims to advance the care for patients with traumatic brain injury (TBI), a field in medicine with one of the greatest unmet needs. The project will be based upon a prospective longitudinal data collection in 60 centres from 20 countries including approximately 6000 patients (CENTER-TBI Core Study). Data will be collected from ictus up to 2 years after injury, thus bridging the acute and post-acute care phases. The core study cohort will include detailed data on the entire clinical course on injury details, treatment, outcome and health costs. Moreover, information on provider profiles will be captured. These data sets will be subjected to extensive analyses aimed at 1) improving characterization of injury and outcome and 2) identify the most effective (and cost-efficient) clinical interventions taking into consideration the type of brain injury and the history of the TBI patient (comparative effectiveness research, CER).

Role: Principal Investigator

W81XWH-14-2-0176 (PI: Manley, Contact-PI) 09/30/14 – 09/29/19 1.20 calendar
Department of Defense \$2,421,187 (NEW)
Agency Point of Contact: Joshua D. McKean Email: joshua.d.mckean3.civ@mail.mil

TBI Endpoints Development (TED)

To identify and validate candidate COAs and biomarkers for future DDT qualification.

AIMS: Stage I (Years 1-2) Technical Objective 1: Establish a collaborative, multidisciplinary team to advance the identification and validation of clinical outcome assessments (COAs) and biomarkers for use as potential FDA-qualified drug development tools (DDTs), and initiate development of CDISC data standards for trials involving diagnosis and treatment of mTBI to modTBI. Stage II (Years 3-5) Technical Objective 2: Validate candidate COAs and biomarkers selected in Stage I, leveraging the existing research infrastructure and clinical study networks of TRACK-TBI, CENC and CRC for potential qualification as DDTs.

Role: Co- Principal Investigator

R21NS087458 (PI: Rosi) 09/01/14 – 08/31/16 0.12 calendar
NIH \$150,000 (NEW)
Agency Point of Contact: Yvonne C Talley Email: alleyy@mail.nih.gov

Contribution of infiltrating macrophages on synaptic function after TBI

We will gain critical and novel information in regard to the contribution of peripheral macrophage accumulation in the pathogenicity of TBI-induced neuroinflammation and potentially a novel therapeutic target and optimal time point for its treatment

AIMS: 1) Will examine if genetic and pharmacological deletion of CCR2 signaling ameliorates TBI-induced synaptic and cognitive dysfunction. TBI will be induced using controlled cortical impact on both wild type and CCR2RFP/RFP mice. We will examine hippocampal-dependent cognitive function as well as homeostatic synaptic function, 28 days after injury. Preliminary studies indicate that CCR2 deletion abrogates TBI-induced hippocampal cognitive dysfunction compared to WT mice. 2) Will determine the temporal kinetics and inflammatory profile of TBI-induced Ly6ChiCCR2+ monocytes/macrophages into the brain parenchyma. TBI will be induced as in Aim 1 except using CX3CR1+/GFPCCR2+/RFP mice. Multiple time points following injury will be examined to include acute, subacute, and chronic phases. Preliminary data shows that 48 hours after injury, TBI-treated mice had a significant increase in macrophage infiltration and that a specific subset of those resembled resident microglia.

Role: Co-Investigator

PCORI: ME-1306-02735 (Hubbard, PI) 04/01/14-03/31/17 0.12 calendar
University of California, Berkeley/PCORI \$82,452 (subaward only) (NEW)
Agency Point of Contact: Deborah Howard Email: subcontracts@berkeley.edu

Semiparametric Causal Inference Methods for Adaptive Statistical Learning in Trauma Patient-Centered Outcomes Research

Combine the expertise physicians/surgeons in critical care facilities, along with computational biostatistics to develop methods for targeting patient-centered parameter estimation.

AIMS: To leverage new advances in statistical theory for creating real-time decision-tools calibrated for individual patients based on their characteristics, which can provide continuously updated prognosis information along with estimated outcomes of potential treatment decisions.

Role: Co-Investigator

Grant (PI: Manley) 03/01/14-08/31/18 0.0 calendar months (effort included in U01) One Mind
for Research Inc. \$55,000 (NEW)
Agency Point of Contact: : Joan Demetriades Email: joan.demetriades@onemind.org

Supplemental Funding for TRACK TBI

This grant is designated to supplement the research of the TRACK-TBI U01 study by providing funds for patient stipend payments and travel reimbursements.

AIMS: To supplement the TRACK TBI study exclusively for patient and travel costs.

Role: Principal Investigator

Subcontract (PI: Michael McCrea, PhD) 11/1/14-9/14/17 0.84 calendar
Medical College of Wisconsin/ DOD-USAMRAA \$60,882 (subaward only) (NEW)
Agency Point of Contact: Jennifer R. Ward Email: jward@mcw.edu
The NCAA-DOD Grand Alliance- Concussion Assessment, Research and Education (CARE)

The Advanced Research Core (ARC) will leverage the progress and discoveries from the NIH-funded TRACK-TBI study, including innovative platforms and procedures for the acquisition, processing, analysis, storage and quality control for the neuroimaging and neurobiological studies included in the ARC.

AIMS: To harmonize the data collection in ARC with the TRACK-TBI and the TBI Common Data Elements (TBI-CDEs).

Role: Subcontract PI

W911QY-14-C-0070 (Contact PI: David Okonkwo) 0.0 calendar months (effort included in U01)
University of Pittsburgh/Naval Health Research Center 09/05/14-09/04/18 \$153,291 (subaward only) (NEW)
Agency Point of Contact: Heather Bragg Email: hmb30@pitt.edu
Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) - High Definition Fiber Tracking

Neuroimaging, Biospecimen and Data Informatics Repositories

To deliver over four years on three core missions that will harmonize TRACK-TBI resources and infrastructure with ongoing DoD-funded initiatives, broadening the impact to military health priorities.

AIMS: To build a legacy database with analytic tools and resources to support the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) initiative.

Role: Co-Principal Investigator

Private Contract (PI: Manley) 12/18/14-12/18/15
Abbott Laboratories \$302,256 direct 0.0 calendar months (effort included in U01)
Agency Point of Contact: Beth A Schodin, PhD Email: Beth.Schodin@abbott.com (NEW)
Abbott - TRACK-TBI biospecimen collection and transfer

The TRACK-TBI Investigators will add an additional blood collection as well as tubes to the study and provide them to Abbott for use in the TBI Biomarker program.

AIMS: To create a large, high quality database that integrates clinical, imaging, proteomic, genomic and outcome biomarkers to establish more precise methods to TBI diagnosis and prognosis, refine outcome assessment and compare the effectiveness and costs of TBI care.

Role: Principal Investigator

OVERLAP

None, pending applications will leverage the TRACK TBI datasets. DoD Award W81XWH-13-1-0441 will also leverage the TRACK-TBI dataset; however, this work is focused on the advance imaging and biomarker analytics for modeling outcomes in the patients enrolled into the original TRACK-TBI Pilot study (RC2NS069409). The work on the NIH/NINDS InTBIR Initiative (U01NS086090) involves enrollment of 3,000 new patients at additional sites and there is no overlap of analytic efforts. The funds in Years 3-5 of DoD PT130798 will allow for the NIH/NINDS InTBIR subjects to undergo more comprehensive assessments to include neuroimaging and outcomes testing to validate TBI endpoints.

MUKHERJEE, PRATIK

R01 HD072074 (Xu) 01/04/13-11/30/17 0.6 calendar
NIH/NIBIB \$382,397

Mario Martinez, Grants Management Specialist

6100 Executive Blvd., BG 6100 Room 8A07D, Rockville, MD 20852

Towards Baby Brain Connectome: A study of Newborn Brain Networks

Goals: The goal of this Bioengineering Research Grant is to investigate the development of structural and functional connectivity networks in the newborn brain from 26 weeks of gestational age to 1 year of life and correlating with clinical outcome.

Aims: 1. To optimize our current MRI data acquisition for robust structural and functional connectivity network analysis in newborns. Through modeling and empirical studies in infants, we aim to investigate the impact of diffusion and resting state fMRI acquisition parameters and cortical parcellation methods on network metrics in to acquire data suitable for robust network construction in a clinically feasible imaging time.

2. To estimate the magnitude of quantitative changes in structural and functional network metrics that can

be expected from birth to 12 months. The inherent biological variability of derived network parameters is unknown. Because the practical application of network techniques will require an understanding of this variance, we aim to quantify the range of expected network parameters in a cohort of infants with and without neurologically abnormal outcomes.

3. To determine the correlation between network metrics and neurodevelopmental outcome in the first year of life. In this aim, we will study the relationship between network parameters and clinical phenotypes in the individual patient by correlating derived network measures with neurological outcome at birth and then again at the age of 1 year. This aim will not only serve to validate methods proposed in Aims 1 and 2, but also provide preliminary data to design a large study to gain knowledge in normal and abnormal neurodevelopment, as well as possible pharmaceutical and enhanced learning interventions.

Role: Co-Investigator

U01 NS086090 (PI :Mukherjee, Manley-Contact PI)	09/30/13 - 08/31/18	1.35 calendar
NIH/NINDS/NIBIB/NICHD/NIDCD	\$2,089,213	

Yvonne C. Talley, Grants Management Specialist
6001 Executive Blvd. NSC/Rm. 3252, Bethesda, MD 20892-9537

Transforming Research and Clinical Knowledge in Traumatic Brain Injury

Goal: The goal is to create a large, high quality TBI database that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers, and provides analytic tools and resources to establish more precise methods for TBI diagnosis and prognosis, improve outcome assessment, and compare the effectiveness and costs of tests, treatments, and services.

Aims: 1. To create a widely accessible, comprehensive TBI Information Commons that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers from subjects across the age and injury spectra, and provides analytic tools and resources to support TBI research

2. To validate imaging, proteomic, and genetic biomarkers that will improve classification of TBI, permit appropriate selection and stratification of patients for clinical trials, and contribute to the development of a new taxonomy for TBI

3. To evaluate a flexible outcome assessment battery comprised of a broad range of TBI common data elements that enables assessment of multiple outcome domains across all phases of recovery and at all levels of TBI severity

4. To determine which tests, treatments, and services are effective and appropriate for which TBI patients, and use this evidence to recommend practices that offer the best value.

Role: Principal Investigator (MPI Grant)

W81XWH-13-1-0494 (Cheung)	09/30/13 – 09/29/16	0.06 calendar
DOD US Army Med. Res. Acq. Activity	\$142,121	

Jeffrey Flook, Grants Officer
820 Chandler Street, For Detrick, MD 21702

Tinnitus Multimodal Imaging

Goals: This is an interdisciplinary three-year research project on human subjects to assess predictions arising from a physiologically-based basal ganglia-centric model of tinnitus. Specifically, the project proposes to perform morphological analysis of the striatum, functional connectivity analysis of the striatum and auditory cortex, and spectroscopic imaging analysis of the striatum and auditory cortex in tinnitus

Aims: 1. Specific aims 1 will assess basal ganglia and auditory cortical functional connectivity in tinnitus and its association with level of distress using resting-state fMRI.

1a. To determine if the dorsal striatum has abnormal functional connectivity with auditory cortex in tinnitus.

1b. To determine if the ventral striatum has abnormal functional connectivity to limbic structures that is related to tinnitus distress.

2. Specific aim 2 will examine the profile of functional connectivity of auditory cortical oscillations with the rest of the brain in tinnitus using MEG.

2a. To determine if functional connectivity relationships of neural oscillations in auditory cortex are abnormal in tinnitus.

3. Specific aim 3 will assess the balance of neurotransmitter levels of the basal ganglia and auditory cortex using MRSI and the microstructure of the basal ganglia using structural MRI in tinnitus.

3a. To determine if the striatum and auditory cortex have an abnormal balance of excitation and inhibition in tinnitus by measuring GABA and Glutamate levels.

3b. To determine if the microstructure of the dorsal or ventral striatum is abnormal in tinnitus.

Role: Co-Investigator

114-2014-GES-0001	07/01/14-12/31/15	0.75 calendar
General Electric Company	\$152,123	

Amy Gallenberg, Program Manager

3200 N. Grandview Blvd., W-8976, Waukesha, WA 53188

Advanced MRI Applications for Mild Traumatic Brain Injury

Goal: To determine association between clinical neurological assessments and evaluations of primary and post processed MR image data from MR scans using the Nova Coil or commercial equivalent that indicate biomarkers of mTBI

Role: Principal Investigator

R24 MH106096 (Mukherjee)	09/26/14-06/30/17	0.84 calendar
NIH	\$25,000	

Grant Manager/Officer Name:

Email or Address:

MRI Corticography: Micro-scale Human Cortical Imaging

Goals: This is a project to produce order of magnitude improvements in the spatial resolution of MRI for noninvasive imaging of the cerebral cortex *in vivo* that promises to transform human neuroscience and accelerate the next generation of diagnostic neuroimaging.

Role: Principal Investigator (MPI Grant)

KRAMER, JOEL

Subcontract (Jagust)	01/01/2015-12/31/2015	0.12 cal mos
University of California, Berkeley (125492A)	\$138,268 Yr01 DC	

Tau Imaging in Parkinson's Disease

The UCSF team is responsible for recruit a sample of 30 patients with idiopathic PD over 2 years, clinically characterize their motor and cognitive functioning, work with UCB to schedule the PIB and MRI scans, schedule and carry out follow-up motor and cognitive assessments 12-months after the baseline visit, and assume responsibility for all administrative, budgetary, IRB, and data management requirements specific to the UCSF site. Role: PI of UCSF subcontract

R01 AG048234 (Kramer)	04/15/2015-1/31/2020	1.62 cal mos
NIH/NIA (125168A)	\$391,509 Yr01 DC	

Effects of Chronic Inflammation on Brain Structure and Function

The overarching goal of this proposal is to better define the longitudinal impact of chronic inflammation on brain structure and function in the elderly by employing imaging biomarkers of white matter injury and Alzheimer's disease. Because inflammation is potentially treatable, this study can contribute to public health by establishing the nature and mechanisms of brain changes, and identifying the best biomarkers of inflammation and neurological functioning for clinical trials. Role: Principal Investigator.

2P50 AG23501 (Miller)	04/1/2014-3/31/2019	0.48 cal mos
NIH/NIA (123288B)	\$1,342,065 Yr12 DC	

New Approaches to Dementia Heterogeneity: Alzheimer's Disease Research Centers, Core B

The main goal of this project is to integrate science and clinical resources to investigate Alzheimer's disease (AD), non-AD dementias, and mild cognitive impairment. Role: Co-Investigator.

R01AG045611 (Rabinovici)	05/01/2014-01/31/2019	0.60 cal mos
NIH (123275A)	\$451,751 Yr02 DC	

Early Age-of-Onset AD: Clinical Heterogeneity and Network Degeneration

This project applies cutting-edge brain imaging techniques to facilitate an early and accurate diagnosis of early onset AD, and to study how the disease can cause such diverse symptoms. Findings from this study will improve the care of early-onset AD patients, and further our understanding of how symptoms relate to different elements of AD biology. Role: Co-Investigator.

	01/01/2015 – 12/31/2018	0.60 cal mos
2014-A-004-NET (Kramer)		
The Larry L. Hillblom Foundation (124634A)	\$270,000 Yr01 DC	
<u>Hillblom Network for the Prevention of Age-Associated Cognitive Decline</u>		

The overarching goal of this Hillblom Network is to unite University of California researchers from across the state toward the goal of understanding, predicting, preventing and treating age-associated cognitive decline. Role: Principal Investigator.

P01 AG019724 (Miller)	07/01/2002 – 5/31/2017	0.48 cal mos
NIH/NIA (120391B)	\$1,345,108 Yr13 DC	

Frontotemporal Dementia: Genes, Images and Emotions, Core A

Frontotemporal Dementia: Genes, Images and Emotions, Core A and Project 4

The goal is to determine the genetic, imaging, and emotional and diagnostic features of frontotemporal lobar degeneration. Role: Co-Investigator.

R01 AG022983 (Kramer)	12/01/2003 – 2/29/2016	1.14cal mos
NIH/NIA (116802A)	\$221,057 Yr10 DC	

Cognitive and Behavioral Control in FTD

The overarching goal of this project is to determine the cognitive, neuroanatomic and physiological underpinnings of the profound deficits in behavioral regulation exhibited by patients with behavioral variant frontotemporal dementia (bvFTD). Role: Principal Investigator.

	07/01/2015 – 06/30/2018	0.06 cal mos
15-10298 (Rosen)		
CALIF H&W Dept. of Public Health (125556A)	\$260,926 Yr01 DC	
<u>Alzheimer's Disease Research Centers of California</u>		

The goal of this this project is to provide expert and comprehensive specialty clinical care to patients with dementia. Follow-up will be provided where clinically indicated through several modalities which include telephone, letters and in-person clinic visit. The specific objective of the clinical service goal is to provide state-of-the-art care for all patients Role: Neuropsychologist.

1U01NS086090-01 (Manley)	09/30/2013 – 08/31/2018	0.60 cal mos
NIH/NINDS (122283A)	\$5,129,282 Yr02 DC	
<u>Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TBI)</u>		

To create a large, high quality TBI database that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers, and provides analytic tools and resources to establish more precise methods for TBI diagnosis and prognosis, improve outcome assessment, and compare the effectiveness and costs of tests, treatments, and services. Role: Co-Investigator.

Contract (Miller)	10/12/2014 – 07/31/2015	0.60 cal mos
Quest Diagnostics Incorporated (124533A)	\$206,145 Yr01 DC	

SIM (Strategy, Integration, Management)-Phase 1A

The Strategic, Integration and Management (SIM) Core will be responsible for providing the focus and key decision-making required for the collaboration on the Dementia Care Pathway project. Leadership in this core will take responsibility for oversight of the enhanced Dementia Care Pathway as a whole, ensuring that all the elements from the current six subprojects are effectively integrated, and that the decision-making process underlying the dementia care pathway is specified and adaptable within the broader community.

Role: Neuropsychologist.

Contract (Possin)	01/05/2015 – 12/05/2015	0.60 cal mos
Quest Diagnostics Incorporated (124865A)	\$261,028 Yr01 DC	

Neurobehavioral Screen Phase 1A Role:

The intent of this core will be to develop and validate a tablet-based neurobehavioral tool: the Brief Neurobehavioral Screen, and begin development of the Comprehensive Neurobehavioral Assessment. The aim will be that the Brief Neurobehavioral Screen meets recommendations by the Alzheimer's Association for the Medicare Annual Wellness Visit in primary care (Cordell et al., 2013) and is specifically tailored to be part of the Quest Dementia Care Pathway. Role: Co-Investigator.

R21AG048456 (Leung)	04/01/2015-03/31/2017	0.36 cal mos
NIH/NIA (125181A)	158,713 Yr01 DC	

The Effects of Light vs Deep Anesthesia on Postoperative Cognitive Outcomes

Delirium is a major concern facing older surgical patients due to its potential severe impact on patients' long term outcomes. Recent limited evidence suggests that anesthetic depth may influence postoperative cognitive outcomes. We propose an exploratory clinical trial to randomizing patients into receiving light vs. deep anesthesia to determine the feasibility and safety of such an approach, and to inform the effect size for a future larger trial. Role: Co-Investigator.

2R01AG032289 (Kramer)	09/01/2015-05/30/2020	1.62 cal mos
NIH/NIA (125842A)	\$380,181 Yr01 DC	

Biological predictors of brain aging trajectories

The overarching goal of this proposal is to better understand the inflammatory, vascular, and neurodegenerative mechanisms that contribute to this clinically important diversity in brain aging trajectories since more precise specification of these relationships will lead to better prediction and prevention of adverse cognitive aging and inform person-specific interventions.

Role: Principal Investigator.

YAFFE, KRISTINE

5K24 AG031155 (Yaffe)	06/13 – 11/19	3.0 cal mos.
NIH: National Institute on Aging	\$796,095 TDC	
Molly Wagster, Chief, Behavioral and Systems Neuroscience Branch		
31 Center Drive, MSC 2292, Bethesda, MD 20892		

Predictors of Cognitive Aging across the Lifecourse

Goals: This K24 Midcareer Investigator Award renewal is being used for aging-related patient-oriented research as well as mentorship. The goal of this project is to identify the predictors of cognitive aging and structural brain integrity across the lifecourse among a biracial cohort of adults.

Aims: 1. To perform rigorous patient-based research studies in a new direction aimed at the identification of the predictors of cognitive aging and structural brain integrity across the lifecourse among biracial adults.

2. To use the applicant's research as a platform for the mentorship of patient-oriented researchers in the epidemiology of cognitive aging.

3. To enable the applicant to pursue new research directions and to continue to support her development as an internationally recognized mentor for trainees from a wide range of disciplines interested in cognitive aging. Role: PI

81XWH-13 (Yaffe)	10/14-09/17	0.6 cal mos.
Department of Defense	\$593,534 TDC	

Blossom J. Widder, Grants Officer
MRPRA CSRA

820 Chandler Street, Fort Detrick, MD 21702-0514

Blood Biomarker Profile of TBI-associated Cognitive Impairment Among Old and Young Veterans

The goal of this project is to define the biomarker profile of late-life cognitive impairment in veterans who have been exposed to TBI.

Aim 1: To establish a unique new cohort of older veterans with AD, TBI-associated CI and healthy controls living in veterans homes at two sites.

2: We will conduct a state-of-the-art study of the blood biomarker profile of TBI-associated CI compared to that of AD and normal aging

Role: PI

R01 AG026720 (Multiple PI: Stone/Yaffe) 10/1/12 – 03/30/17 1.2 cal mos.

NIH: National Institute on Aging \$2,068,666 TDC

Mirosław Mackiewicz, Program Director

31 Center Drive, MSC 2292, Bethesda, MD 20892

Change in Sleep & Cognition in Older Women

Goals: The goal of this renewal is to determine the association between sleep dysfunction and cognitive impairment in a large ongoing prospective study.

Aims: 1. To identify candidate -regions, -genes, and -pathways for both sleep characteristics and cognitive outcomes using recently obtained phenotypic and genome-wide genetic data from the SOF cohort.

2. To test the hypothesis that poor sleep is associated with metabolic dysfunction among older women, and that metabolic dysfunction mediates associations between poor sleep and cognitive outcomes.

3. To determine the associations of sleep characteristics (among older women with and without cognitive impairment) with incident age-related outcomes assessed every six months during 5 years of follow-up.

Role: Multiple-PI

2P01 AG019724 (Miller/Yaffe) 09/1/12 – 08/31/17 0.6 cal mos

NIH: National Institute on Aging \$663,642 TDC (Core)

John Hsiao, Director, Diagnosis and Biomarkers Program, Dementias of Aging Branch 31

Center Drive, MSC 2292, Bethesda, MD 20892

Frontotemporal Dementia: Genes, Images, and Emotions: Data Management and Biostatistics Core

Goal: The goal of this program project is to test new international research criteria for frontotemporal dementia and to determine the value of imaging and biomarkers for diagnosis.

Aims: 1. To develop and maintain centralized, integrated data management systems and procedures that ensure the accuracy, availability, and confidentiality of administrative, clinical, and research data from PPG cores and projects.

2. To provide high-quality biostatistical consultation to all PPG cores and projects in order to systematically unify and focus research design and statistical analysis.

3. To promote research methods integration and collaboration among PPG cores, projects, and related research protocols through efficient data sharing, coordinated data analysis plans, and regular meetings to discuss research process and data integration.

Role: Dr. Yaffe is the PI of the Data Management and Biostatistics Core

R01 AG05407 (Multiple PI: Yaffe/Cummings) Yrs26-30 09/1/11 – 08/31/16 1.92 cal mos

NIH: National Institute on Aging \$3,706,144 TDC

Sherry Sherman, Project Officer

31 Center Drive, MSC 2292, Bethesda, MD 20892

Study of Osteoporotic Fractures

Goals: The goal of this multicenter prospective study is to investigate aging outcomes.

- Aims: 1. Determine the association of age-related parameter trajectories with longevity and active lifespan in older women.
2. Determine the association of age-related parameter trajectories with exceptional healthspan in older women.
3. Among older women, determine the association of age-related parameter trajectories with inpatient and residential health care use. 4. Sustain and actively use the extensive SOF biologic repository of serum, urine and DNA specimens.

Role: Multiple-PI

5R01 DK069406 (Multiple PI: Yaffe/Kurella) 09/1/11-05/31/16 1.2 cal mos

NIH: NIDDK \$2,867,726 TDC

John Kusek, Program Director, Division of Kidney, Urologic and Hematologic Diseases, NIDDK 6707 Democracy Boulevard, MSC 5450, Bethesda, MD 20892-5450

Cognitive Decline in Chronic Renal Insufficiency

Goals: The goal of this project (a competitive renewal of R01-DK069406) is to investigate cognitive trajectories of individuals transitioning from CKD to ESRD.

- Aims: 1. To determine the long-term trajectory of cognitive function in adults with CKD.
2. To determine the clinical significance of cognitive decline among adults with CKD by evaluating its association with CKD management strategies and geriatric outcomes.
3. To characterize the trajectory of cognitive function during the transition from advanced CKD to ESRD.
4. To determine if several novel biomarkers associated with CKD and aging may also predict cognitive decline, thereby informing about mechanisms linking these disorders.

Role: Multiple PI

R01 (Sidney/Yaffe) 12/14 – 11/18 1.08 cal mos

NIH: NHLBI \$2,608,740 TDC

Jared Reis, Program Official
31 Center Drive, MSC 2292, Bethesda, MD 20892

Determinants of Midlife & Longitudinal Change in Cognitive Function: CARDIA Study

Goal: The goal of this project is to better understand young adult risk factors and their effect on cognition in midlife and later.

- Aims: 1. To determine the rate and correlates of 5-year change in cognitive function at mid-life with regard to gender, education, literacy, socio-economic status and race among approximately 3100 black and white adults.
2. Using carefully collected repeated measures over 30 years, to determine the association between cardiovascular and metabolic risk factors (such as diabetes, insulin, dyslipidemia, blood pressure, adiposity, inflammation) in young adulthood and cognitive function and its 5- year change at mid-life with consideration of whether there are "critical windows" and cumulative effects of exposure.
3. Using carefully collected repeated measures over 30 years, to determine the association between measures of "modifiable" behavioral and psychosocial risk factors (such as physical activity, diet, depression, social support) on cognitive function and 5-year change at mid-life with consideration of whether there are "critical windows" and cumulative effects of exposure.
4. To use already collected genome-wide genetic data from CARDIA to investigate the association of genetic variants, which are known to influence the cardiovascular, metabolic and behavioral risk factors (Aims 2 and 3), with cognitive outcomes and to further investigate causal associations for these risk factors.

Role: Multiple-PI

COL Dallas Hack, Director of Combat Casualty Care Research Program/ Stuart Hoffman (VA), Scientific Program Manager for the Brain Injury Portfolio

810 Vermont Avenue, NW, Washington, DC 20420

Chronic Effects of Neurotrauma Consortium: Epidemiology Project

The goals of this study are to capitalize on a variety of existing data sources by integrating and analyzing them in novel ways to examine trajectories and neurosensory outcomes of mild traumatic brain injury (mTBI) in Veterans over time.

Aim 1. Among OEF/OIF/OND Veterans, to determine the association of mTBI and mental health disorders with adverse clinical outcomes with the goal of understanding why some Veterans with mTBI are more resilient than others.

Aim 2: Among Veterans from any era, to determine whether mTBI is independently associated with adverse neurosensory outcomes and mortality across the life course and whether treatment of comorbid conditions reduces risk.

Aim 3: Among OEF/OIF/OND Veterans with mTBI who received five or more years of VA care, we will identify trajectories of neurosensory, psychiatric, and pain comorbidity.

Aim 4: We propose to develop an architectural plan to create the *National CENC Data Repository (NCDR)*. We will complete the initial foundational steps toward creating the NCDR, which will ultimately integrate several existing DoD- and VA-affiliated TBI databases that are not currently interconnected, harmonize the data structure and content using the NINDS TBI CDE, and leverage the infrastructure of the FITBIR to archive the centralized repository.

Role: Project PI

P50 AG023501 (Miller/Yaffe)

04/01/14 – 03/31/19

0.6 cal mos.

NIH: National Institute on Aging

\$528,482 TDC (Core)

Creighton Phelps, Deputy Director

31 Center Drive, MSC 2292, Bethesda, MD 20892

New Approaches to Dementia Heterogeneity: Alzheimer's Disease Research Centers: Data and Statistical Core

Goals: The goal is to integrate science and clinical resources to investigate Alzheimer's disease (AD), non-AD dementias, and mild cognitive impairment.

Aims 1. Explore the heterogeneous features of AD, FTD-spectrum disorders, and CJD in the early stages with the goal of predicting their physiological, genetic, and molecular underpinnings. This aim will be facilitated via our Clinical; Data Management and Statistical (DMS); Neuropathology, Biospecimens, and Genetics (Neuropath); Education and Imaging Cores.

2. Leverage the valuable cohorts in the ADRC and the powerful neuroscience community at UCSF and beyond to stimulate new diagnostic and treatment efforts for AD, FTD and CJD. Drs. Mucke and Miller from the Administrative Core will lead the ADRC's effort for this aim.

3. Increase understanding of the unique cultural and biological features of aging Chinese-Americans with neurodegenerative disease, while educating this community with lectures and web-based presentations.

4. Develop innovative approaches to data management and biostatistics that we will share across the ADRC infrastructure and will use to better understand our own cohorts. The DMS will accomplish these aims.

5. The Education Core will be responsible for training new dementia leaders, while educating the medical and lay communities regarding the non-AD dementias and non-amnesic subtypes of AD with conferences and web-based presentations.

Role: PI of Data and Statistical Core C

P30 AG044281 (Covinsky) 07/15/2013 – 06/30/18 0.36 cal mos
NIH: National Institute on Aging \$3,429,089 TDC (Overall)
Basil Eldadah, Program Officer
Gateway Building, Suite 3C-307, 7201 Wisconsin Avenue, Bethesda, MD 20892 UCSF
Older American Independence Center

Goals: The goal of this project is to improve the health care and quality of life of vulnerable older adults with or at risk for disability

Aims:

1. Catalyze research on disability in vulnerable older persons at UCSF by serving as a hub that brings together scholars and leverages resources
2. Provide tangible, high-value support to funded projects at UCSF that stimulate new research on disability, and lead to new research opportunities for senior and junior investigators
3. Support pilot studies that accelerate science and lead to research funding in late life disability
4. Identify the future leaders of geriatrics research and support them with career development funding and exceptional mentoring
5. Develop a leadership and administrative structure that spurs interdisciplinary collaboration, making the OAIC greater than the sum of its parts

Role: Co-Investigator

PITTSBURGH

WISNIEWSKI, STEPHEN

Nothing to Report

OKONKWO, DAVID

Nothing to Report

BELL, MIKE

Nothing to Report

HMJF

DIAZ-ARRASTIA, RAMON

Title: Chronic Effects of Neurotrauma Consortium (CENC) (Diaz-Arrastia- Co-PI (with David Cifu, MD (VCU) and Rick Williams, PhD (RTI)

Time Commitment: 2.0 calendar months

Supporting Agency: DoD/VA

Program Officials: COL Dallas Hack (DoD)/Stuart Hoffman (VA)

Period of Performance: 07/01/13-06/30/18

Level of Funding: \$62,500,000 overall (\$489,387 USUHS budget)

Project Goals: To conduct a prospective observational study of military service members and veterans to identify the chronic effects of Neurotrauma.

Specific aim: Carry out 5 research projects, supported by 5 Cores, with the goal of characterizing the long-term consequences of traumatic brain injury.

(1). Longitudinal Cohort Study: A large, prospective, longitudinal investigation of Veterans with OEF/OIF combat-related mTBI and combat-exposed controls, from 2003 to the present, with varying degrees of chronic symptoms and comorbidities. These Veterans will be comprehensively evaluated on a regular basis for changes in status and performance using clinical testing, neuroimaging, genomics, biomarkers, and neuropathology.

- (2). Telehealth Intervention Study: A multi-arm, randomized, controlled trial of telehealth interventions targeted at OEF/OIF Veterans with and without mTBI, who have chronic symptoms and/or comorbidities.
- (3). Military Retirement Home Study: A large, prospective, longitudinal clinicopathologic study of older Veterans with and without a history of distant TBI to assess for late neurodegeneration using clinical testing, neuroimaging, genomics, biomarkers, and neuropathology.
- (4). Integrated Dataset Study: A coordinated and comprehensive analysis and rapid dissemination of existing VA, DoD, and other federal (National Institutes of Health [NIH], NIDRR, Medicare) datasets of individuals with TBI and comorbid conditions.
- (5). Tau Dysregulation Study: A basic science project to identify the key molecular events in the processing of tau after TBI in rodents and humans, with the goal of developing novel biomarker tools to assess tau dysregulation after TBI.

Overlap: NA

Title: Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Diaz-Arrastia Co-PI (with Geoff Manley, MD (UCSF))-Biomarkers Core Director

Time Commitment: 1.5 calendar months

Supporting Agency: NIH/NINDS

Program Official: Ramona Hicks, PhD (HicksRA@ninds.nih.gov)

Performance Period: 9/1/2013 – 8/30/2018

Level of Funding: \$19,000,000 overall (\$44,414 USUHS budget)

Project Goals: To conduct a prospective observational study of TBI in 10 civilian level I trauma centers to identify imaging and biochemical biomarkers prognostic of outcome and indicative of injury mechanisms.

Specific aim: (1). To create a widely accessible comprehensive TBI Information Commons that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers from subjects across the age and injury spectra, and provides analytic tools and resources to support TBI research.

(2). To validate imaging, proteomic, and genetic biomarkers that will improve classification of TBI, permit appropriate choice and stratification of patients for clinical trials, and contribute to the development of a new taxonomy for TBI.

(3). To evaluate a flexible outcome assessment battery comprised of a broad range of TBI common data elements that enables assessment of multiple outcome domains across all phases of recovery and at all levels of TBI severity.

(4). To determine which tests, treatments, and services are effective and appropriate for which TBI patients, and use this evidence to recommend practices that offer the best value.

Overlap: None

Title: Administration of recombinant erythropoietin to improve neovascularization and decrease neuroinflammation after TBI, (Diaz-Arrastia-PI)

Time Commitment: 1.0 calendar month

Supporting Agency: USUHS/CNRM, 4301 Jones Bridge Road, Bethesda, MD 20814

Program Official: Walter Tinling (walter.tinling@usuhs.edu)

Performance Period: 7/1/2012 – 6/30/2016

Level of Funding: \$449,705

Project Goals: To carry out a Phase II randomized controlled trial to determine if administration of rHuEPO for 8 weeks is effective in increasing the number of circulating endothelial progenitor cells and improving cerebrovascular reactivity when administered in the subacute period after TBI.

Specific aim: (1) To validate and modify the method of isolation of EPC from the minimal blood volume to be taken multiple time from the same research participant.

(2). To study the feasibility of EPC and other BM as outcome measure in clinical trials.

(3). To conduct a randomized (2:1) placebo-controlled pilot study to explore efficacy of EPO with a fixed dose of 40,000 IU i.m once weekly for 8 weeks TBI patients to TBI patients with persistent post-concussive symptoms initiated 14 - 90 days after the injury.

Overlap: None

Title: Dopamine Receptor Imaging to Predict Response to Stimulant Therapy in Chronic TBI, (Diaz-Arrastia- PI)

Time Commitment: 0.3 calendar months

Supporting Agency: USUHS/CNRM, 4301 Jones Bridge Road, Bethesda, MD 20814

Program Official: Walter Tinling (walter.tinling@usuhs.edu)

Performance Period: 7/1/2013 – 6/30/2016

Level of Funding: \$463,987

Project Goals: To image dopamine receptor occupancy with [11C]-raclopride PET to identify deficits in dopaminergic transmission in the chronic stage after TBI, and to determine if such deficits are associated with positive response to stimulant therapy

Specific aim: (1). We will recruit 30 subjects who experience deficits in neuropsychological function from TBIs incurred between 6 months and 12 years prior. Each will be evaluated using psychometric measures adapted from the TBI Common Data Elements, and information about details of the injury and experience of post-concussive symptoms recorded.

(2). Subjects will be studied with [11C]-raclopride PET in two imaging sessions. One session will be after administration of methylphenidate, 60 mg by mouth, and the other after administration of an inactive placebo. The binding potential relative to a non-displaceable reference (cerebellum), BPND, is used as a measure of D2/D3 receptor availability. The difference in BPND between methylphenidate and placebo (BPND) is used as a measure of phasic DA release.

Specific aim 3: Subjects will then be treated with a titrated regimen of oral methylphenidate for 12 weeks. At that point the neuropsychologic tests are repeated. The primary outcome is change in processing speed.

Overlap: None

Title: Fieldable Multiplex Test for TBI Assessment (Diaz-Arrastia PI)

Time Commitment: 0.3 calendar months

Supporting Agency: DoD/Broadband Agency Announcement

Program Official: Meso Scale Diagnostics, LLC

Performance Period: 10/1/2013 – 3/30/2016 (NCE)

Level of Funding: \$920,606 USUHS budget

Project Goals: To conduct the synthesis of the biomarker, imaging and neuropsychological data to create a biomarker signature for TBI.

Specific aim: (1) Identification and Confirmation of Novel TBI Biomarkers. A focused discovery effort will investigate the class of brain proteins that undergo TBI-induced citrullination

(2). Development of Assays for TBI Biomarkers. Immunoassays will be developed for known TBI markers and new candidate markers on the MSD MULTI-ARRAY platform. These will include markers that have shown promise in our work and in the TBI field.

(3). Identification of an Optimal TBI Biomarker Panel and Algorithm. Serum from TBI patients will be used to screen the new and known biomarkers for their diagnostic utility.

(4). Optimization and Verification of Fieldable Platform. The MSD cartridge reader will undergo software upgrades to allow processing of the TBI cartridges and eight readers will be built.

(5). Validation of Accurate Assessment of TBI. A large and diverse set of clinical samples will be measured with the final platform, with the goal of validating the test's ability to classify TBI as compared to current TBI diagnostic methods.

Overlap: None

Title: Blood Biomarker Profile of TBI-Associated Cognitive Impairment among Old and Young Veterans (Diaz-Arrastia PI) (NCIRE2)

Time Commitment: 1.0 calendar month

Support Agency: DoD/MRMC

Program Official: Pending notification from prime award

Performance Period: 12/01/2014-09/29/2017

Level of Funding: \$47,783

Project Goals: The goal of this project is to assess post-concussive symptoms and PTSD on retired military personnel using a uniform evaluation.

Specific Aims: (1): Identify and enroll 80 older veterans with TBI-associated cognitive impairment (CI) and 80 normal controls.

(2): Identify and enroll 80 older veterans with Probable (or Possible) Alzheimer Disease (AD) at AFRH and VHC-Yountville.

(3): Identify blood biomarkers of TBI-associated CI.

(4): Identify younger veterans with mTBI with cognitive impairment and those with mTBI and no cognitive impairment (controls).

(5): Using the biomarker profile identified among older veterans with TBI-CI, we will validate the profile in younger veterans.

Overlap: None

Title: Neuropathology of Chronic Traumatic Encephalopathy and Late Effects of TBI: Towards in-vivo diagnosis, (Diaz-Arrastia Collaborator (Wayne Gordon, MSSM, and Dan Perl, USUHS, PIs)

Time Commitment: 0.9 calendar months

Supporting Agency: NIH/NINDS

Program Official: Ramona Hicks, PhD (HicksRA@ninds.nih.gov)

Performance Period: 10/1/2013 – 9/30/2017

Level of Funding: \$10,000,000 overall (\$957,129 USUHS budget)

Project Goals: To establish a brain bank of civilians who have suffered mild, moderate, or severe TBI in the past and who have been well-characterized during life with clinical, neuropsychologic exams, and neuroimaging.

Specific aim: (1). To apply neuropathological methods to: a). Fully characterize the neuropathology associated with CTE and the late effects of TBI, and distinguish the neuropathological signatures of single and repetitive brain trauma from known types of neurodegeneration; b). Apply state of the art neuropathological methods, including the Histelide approach, to quantify pathologic tau and A β species, and to elucidate the tissue substrate of CTE and the late effects of TBI; c). Document the distribution of lesions using whole brain serial-sectioning; and d). Develop and validate neuropathological criteria for posttraumatic neurodegeneration.

(2). To identify neuroimaging signatures of the neuropathology of CTE and the late effects of TBI as a basis for the development of *in vivo* diagnostic tools. We will accomplish this by correlating premortem 3T MRI data and two modalities of high resolution post-mortem imaging data with neuropathological data.

(3). To extend the existing ACT population-based brain-donor program to include subgroups with moderate-severe TBI and athletes with multiple brain injuries, all of whom will be characterized with uniform behavioral and cognitive information that will be linked with pre and post-mortem imaging, and neuropathology.

(4). To promote data and tissue sharing to maximize the value of the brain donation by leveraging current well-established mechanisms to distribute biospecimens and other relevant information to qualified investigators.

(5). To use appropriate statistical techniques to estimate the incidence and prevalence of CTE and posttraumatic neurodegeneration.

Overlap: None

Title: Targeted Alteration of dietary omega-3 and omega-6 fatty acids for the treatment of post-traumatic headaches (Diaz-Arrastia PI)

Time Commitment: 1.0 calendar month

Supporting Agency: DoD/CDMRP/PRMRP-CTA

Program Official: Pending

Performance Period: 07/01/2015-06/30/2019

Level of Funding: 3,252,840

Project Goals: The goal of this project is to conduct a pilot clinical trial of dietary manipulation lowering omega-6 and increasing omega-3 fatty acids in patients with post-traumatic headaches, to determine if it is effective in decreasing severity and frequency of post-traumatic headaches and increasing plasma levels of bioactive lipids. **Specific Aims:** (1): To compare the efficacy of the H3-L6 dietary intervention to the Control Diet, in reducing headache pain and improving headache-related quality of life.

Hypothesis 1: Compared to the Control Diet, the H3-L6 intervention will produce significant improvement in (1a) the Headache Impact Test—a headache-specific quality of life measure-Primary Clinical Outcome); (1b) mean total Headache Hours per day; and (1c) mean Severe Headache Hours per day.

(2): To evaluate whether the H3-L6 dietary intervention can increase circulating anti-nociceptive n-3 DHA metabolites, and reduce pro-nociceptive n-6 AA metabolites, in patients with Posttraumatic Headaches.

Hypothesis 2: Compared to the Control Diet, the H3-L6 intervention will produce significant increases in anti-nociceptive n-3 metabolites including 17-hydroxy DHA (Primary Biochemical Aim), and reductions in pro-nociceptive n-6 metabolites. Lipid mediators will be assayed in the NIH Clinical Center.

(3): To explore the potential of the H3-L6 intervention for improving non-headache TBI outcomes. **Hypothesis 3:** Compared to the Control Diet, the H3-L6 intervention will produce significant improvement in (3a) non-headache pain; (3b) depression/anxiety; (3c) symptoms of post-traumatic stress disorder; and (3d) cognitive function; and (3e) will significantly reduce their use of medications for acute headache treatment.

Overlap: None

Title: Cerebrovascular Reactivity (CVR) Assessed with Functional Near InfraRed Spectroscopy (fNIRS) as a Biomarker of Traumatic Micro Vascular Injury (TVI) Measured (MNCoe)

Time Commitment: 0.6 calendar months

Supporting Agency: USUHS, 4301 Jones Bridge Road, Bethesda, MD 20814

Program Official: Fabio Leonessa

Performance Period: 8/01/2011-12/31/2017

Level of Funding: \$197,517

Project Goals: To conduct a prospective, longitudinal, observational study of 30 acute TBI patients and 10 healthy controls.

Specific Aims: We will enroll 10 healthy controls and 30 TBI patients from WRNMMC and perform initial fNIRS testing within 1 week of TBI. At baseline, each subject will also undergo neurological examination, neurocognitive testing, research blood draw and survey questionnaires. We will perform repeat fNIRS, blood draw, and surveys 1,3 and 6 months and cognitive testing 6 months after TBI. (1) The primary outcome measure will be the CVRx measurement in the first 6 months after TBI. (2) Secondary outcome measures will be the effect of sildenafil on CVRx and clinical/CVRx correlations.

Overlap: None

Title: Acute Low-Level Laser Therapy for the treatment of moderate TBI. (Diaz-Arrastia Collaborator (B. Vakoc, MGH/Harvard, PI)

Time Commitment: 0.9 calendar months

Supporting Agency: DoD/MRMC (Subcontract with Mass General Hospital)

Program Official: Paul Hague

Performance Period: 7/1/2013 – 09/14/2015 (Per prime, currently on hold)

Level of Funding: \$31,060

Project Goals: To conduct preclinical and clinical study of low-level laser light therapy to promote angiogenesis and neurogenesis after TBI.

Specific aim: (1a). We will acquire two LLLT device helmets from Photomedex based on existing prototypes. The optical performance of the helmets will be confirmed using a custom-build light fluence measurement apparatus.

(1b) We will begin enrollment on a double-blinded placebo-controlled 82 patient study of acute LLLT for TBI including collection of neuroimaging, biochemical, and clinical outcome data.

(2a) We will complete an investigation into the effect of LLLT on microglial activation in mouse models of TBI.

(2b) We will perform an intermediate analysis of neuroimaging data from the patients enrolled into the clinical study.

(3) We will complete our investigation into how LLLT affects cerebrovascular dysfunction in chronic models of TBI.

(4) We will complete an investigation into the effect LLLT has on neurogenesis.

Overlap: None

Title: Sildenafil for the Treatment of Cerebrovascular Dysfunction during the Chronic Stage after Traumatic Brain Injury (TBI) and the Exploration of Novel Diagnostic Markers of Cerebrovascular Dysfunction after TBI and Dementia after TBI in Retired Military Service Members (SM)

Time Commitment: 0.6 calendar months

Supporting Agency: USUHS/MNCoE, 4301 Jones Bridge Road, Bethesda, MD 20814

Grant Officer: Walter Tingling, Vice President for Finance and Administration

Period of Performance: 10/01/2011-12/30/2015

Level of Funding: \$1,488,844

Role: PI (Grimes) HU0001-11-1-0007

Goals: To research the diagnosis and treatment of microcerebrovascular injury after traumatic brain injury (TBI) and to perform a preliminary study investigating biomarkers of dementia developing after TBI in retired service members (SM).

Specific Aims: (1) To generate pilot data that will be informative for the design of a clinical trial of sildenafil (Viagra) to treat patients with traumatic vascular injury in the chronic state after TBI. (2) To assess the ability of Near infrared Spectroscopy (NIRS) to detect cognitive and cerebrovascular dysfunction after TBI. (3) To examine serum, saliva and neuroimaging in retired Military SM with and without dementia as well as those with and without a history of TBI to determine if there are biomarkers associated with the dementia that occurs in those with a history of TBI compared to those without.

Overlap: None

UWASHINGTON
TEMKIN, NANCY

1U01NS086090-01 (Manley CPI, Temkin MPI) 09/30/13 – 08/31/18 1.2 cal mos
NIH/NINDS \$3,735,917

Yvonne Talley, Grants Management Specialist

6001 Executive Boulevard, Suite 3262, Bethesda, MD 20892-9537

Project Title: Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TBI)

Goals: To create a large, high quality TBI database that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers, and provides analytic tools and resources to establish more precise methods for TBI diagnosis and prognosis, improve outcome assessment, and compare the effectiveness and costs of tests, treatments, and services

Aims: 1. To create a widely accessible, comprehensive TBI Information Commons that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers from subjects across the age and injury spectra, and provides analytic tools and resources to support TBI research.

2. To validate imaging, proteomic, and genetic biomarkers that will improve classification of TBI, permit appropriate selection and stratification of patients for clinical trials, and contribute to the development of a new taxonomy for TBI.

3. To evaluate a flexible outcome assessment battery comprised of a broad range of TBI common data elements that enables assessment of multiple outcome domains across all phases of recovery and at all levels of TBI severity.

4. To determine which tests, treatments, and services are effective and appropriate for which TBI patients, and use this evidence to recommend practices that offer the best value.

Role: Multiple PI (MPI)

W81XWH-0802-0159 (Stein, Site PI Temkin) 9/15/08 - 9/30/14 3.0 cal mos
DoD \$336,336

Supporting Agency: U.S. Army Medical Research & Materiel Command Department of Defense (subcontract from UCSD)

Grants Officer: Angel Davey. Congressionally Directed Medical Research Programs

1077 Patchel Street, Fort Detrick MD 21702-5024

Project Title: University of Washington Clinical Consortium Study Site

Psychological Health/TBI Clinical Consortium

Brief Description of the Project's Goals: One of 10 sites in the Department of Defense Psychological Health/Traumatic Brain Injury Clinical Trials Consortium, (INTRuST) which conducts clinical trials and observational studies relevant to treatment of those with post-traumatic stress disorder or traumatic brain injury.

Role: Site Principal Investigator

1 R01 NS077913 (Thompson) 3/1/12-2/28/17 0.6 cal mos
NINDS/NIH, \$387,054

Grants Officer: Patrick Bellgowan. 9000 Rockville Pike, Bethesda, MD 20892

Project Title: Impact of Aging on the Immune Response to Traumatic Brain Injury

Brief Description of the Project's Goals: The aims of this prospective cohort study are to: 1) Compare cellular immune responses, plasma inflammatory biomarker concentrations, and measures of impairments, disability and health-related quality of life up to 6 months post-injury in young and older adults with and without mild TBI (75 per group) and 2) Determine the association between selected cellular immune and plasma biomarkers and impairments, disability and health-related quality of life at 3 and 6 months post-injury in older adults with mild TBI.

Role: Investigator

R01HD083126 (Mac Donald) 7/1/2015 - 6/30/2020 1.2 cal mos
NIH/NINDS

Grants Officer: Patrick Bellgowan. 9000 Rockville Pike, Bethesda, MD 20892

EVALUATION Of Longitudinal outcomes in mild TBI Active-Duty Military and Veterans – The EVOLVE Study
The goal of this study is to evaluate the long term impact of concussive TBI in four distinct groups of US Military service members, blast-TBI, non-blast TBI, blast-exposed control, and non-blast-exposed control and leverage existing early clinical and imaging data in these subjects to develop complex models of predictive outcome.

Role: Investigator

H133G110028(Hoffman) 10/01/12 – 09/30/15 0.6 cal mos

NIDRR/DOE \$597,456 /total

Grant Officer: Cate Miller, 400 Maryland Avenue, S.W. , Mailstop PCP-6038 , Washington, DC 20202

Project Title: Amitriptyline to Prevent Headache after Traumatic Brain Injury

Brief Description of the Project's Goals: This is phase II study examining the effect of preventative treatment with amitriptyline on the frequency and severity of headache after mild TBI

Role: Investigator

5U48 DP00191104 (SIP-12-057) (Fraser) 9/30/12 - 9/29/14 0.24 cal mos

CDC \$120,000Grants Officer: Hector Buitrago, Grants Management Officer,

Centers for Disease Control and Prevention

Procurement and Grants Office, Koger Center, Colgate Bldg., 2920 Brandywine Rd., Mail Stop E-09, Atlanta, GA 30341

Project Title: Managing Epilepsy Well (MEW) Collaborating Center

Brief Description of the Project's Goals: To develop an intervention to assist people with epilepsy in improving their self-management skills

Role: Investigator

PT110602 (Hoffman) 9/30/12 - 9/29/16 1.2 cal mos

CDMRP/DoD \$1.96 Million/4 years

Grants Officer: B. Christie Vu

Project Title: Telephone Delivered Cognitive Behavioral Therapy for Chronic Pain after Traumatic Brain Injury

Brief Description of the Project's Goals: This study is a randomized controlled study examining the efficacy of a manualized cognitive behavioral therapy intervention for veterans with chronic pain after TBI compared to a telephone delivered educational intervention. The primary aim is to reduce pain intensity with secondary aims of improving co-morbid diagnoses, function, and satisfaction with life.

Role: Co-Investigator

1R01NS080648 (CPI Chesnut, Temkin MPI) 9/30/12-7/31/17 1.2 cal mos

NIH/NINDS and Fogarty \$2,516,005

Grants Officer: Joanne Odenkirchen, 9000 Rockville Pike, Bethesda, MD 20892

Project Title: Managing severe TBI without ICP monitoring - guidelines development and testing

Brief Description of the Project's Goals: The objective of this project is to create guidelines for the treatment of severe TBI in the absence of ICP monitoring and test them.

Role: Multiple PI

1U01CE002196 (Rivara) 9/30/12-9/29/17 0.6 cal mos

CDC \$504,681

Grant Officer: Victor Coronado vgc1@cdc.gov

Project Title: Effect of treatment on outcome after TBI in children & adolescents

Brief Description of the Project's Goals: This study will address many of the unanswered questions on pediatric TBI. It is innovative in many ways. It is a multi-centered study bringing together leading expertise in the United States on pediatric TBI. It will employ the newly developed Common Data Elements for characterizing injuries and the newly

developed quality of care indicators for characterizing their inpatient rehabilitation care. The study will utilize the new PROMIS outcome measures and collect data in a longitudinal fashion from both caregivers and patients using web-based technology. By applying novel statistical approaches designed to assess causal effects in observational designs, it will provide critical information on the effects of treatment at different stages of care on functional outcomes after TBI

Role: Investigator

H133A980023 (Hoffman) 10/01/12 – 09/30/17 0.6 cal mos

NIDRR/DOE \$2, 237,046

Grants Officer: Cate Miller, 400 Maryland Avenue, S.W. Mailstop PCP-6038 Washington, DC 20202

Project Title: University of Washington Traumatic Brain Injury Model System

Brief Description of the Project's Goals: 1) Operate a comprehensive multidisciplinary system of care specifically designed to serve persons with TBI from injury through maximal community integration and participation. 2) Perform innovative and rigorous site-specific and multi-site research projects that are responsive to priorities specified by NIDRR 3) Participate in the continued assessment of long-term outcomes of TBI by contributing to a uniform, standardized national database. 4).Promote dissemination of research finding to clinicians, persons with TBI and their families, and the community at large through site-specific dissemination efforts and collaboration with the Model Systems Knowledge Translation Center. 5) Collaborate with other model system sites and other academic, government, and community systems in addressing issues related to TBI.

Role: Investigator

W81XWH-13-2-0095 (Cifu, site PI Temkin)09/01/13 – 08/31/18 3.0 cal mos

DoD/VA (Subcontract from VCU) \$62,500,000 overall

Title: Chronic Effects of Neurotrauma Consortium (CENC)

Brief Description of the Project's Goals: To conduct a prospective observational study of military service members and veterans to identify the chronic effects of Neurotrauma.

Specific aim: Carry out research projects, supported by 5 Cores, with the goal of characterizing the long-term consequences of traumatic brain injury.

(1). Longitudinal Cohort Study: A large, prospective, longitudinal investigation of Veterans with OEF/OIF combat-related mTBI and combat-exposed controls, from 2003 to the present, with varying degrees of chronic symptoms and comorbidities. These Veterans will be comprehensively evaluated on a regular basis for changes in status and performance using clinical testing, neuroimaging, genomics, biomarkers, and neuropathology.

(2). Tau Dysregulation Study: A basic science project to identify the key molecular events in the processing of tau after TBI in rodents and humans, with the goal of developing novel biomarker tools to assess tau dysregulation after TBI

Role: Site PI, Lead biostatistician

No grant number (Bombardier) 10/01/13 – 09/30/18 0.12 cal mos

National Multiple Sclerosis Society \$1,466,730

Grant Contact Nicholas LaRocca, Ph.D. Nicholas.larocca@nmss.org, 212-476-0414

Project Title: The effect of aerobic exercise on cognition in multiple sclerosis

Brief Description of the Project's Goals: The long term goal of our research agenda is to identify activity-based interventions that can improve neurocognitive outcomes in people with MS. Associated goals include elucidating effective intervention characteristics (e.g., frequency, intensity, duration, timing and type of activity), identifying patient characteristics that predict response to treatment, the durability of effects and uncovering mechanisms by which exercise interventions influence cognitive outcomes. This line of research could transform the standard of care for treatment of cognitive impairment in MS.

List of specific aims:

Aim1: To determine whether aerobic exercise training significantly improves cognitive functioning in adults with MS.

Aim 2: To explore whether improvement in cognitive functioning is positively associated with improvement in cardiorespiratory fitness.

Aim 3: To explore whether improvement in cognitive functioning is associated with baseline fitness, baseline cognitive functioning, or cognitive reserve, as indicated by years of education.

Aim 4: To determine whether there is greater improvement in cognitive functioning and fitness in the aerobic exercise vs. minimal exercise group from baseline to 3 months after the end of treatment.

DIKMEN, SUREYYA

1U01NS086090-01 (Manley CPI, Temkin MPI) 09/30/13 – 08/31/18 1.2 cal mos
NIH/NINDS \$3,735,917

Yvonne Talley, Grants Management Specialist

6001 Executive Boulevard, Suite 3262, Bethesda, MD 20892-9537

Project Title: Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TBI)

Goals: To create a large, high quality TBI database that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers, and provides analytic tools and resources to establish more precise methods for TBI diagnosis and prognosis, improve outcome assessment, and compare the effectiveness and costs of tests, treatments, and services

Aims: 1. To create a widely accessible, comprehensive TBI Information Commons that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers from subjects across the age and injury spectra, and provides analytic tools and resources to support TBI research.

2. To validate imaging, proteomic, and genetic biomarkers that will improve classification of TBI, permit appropriate selection and stratification of patients for clinical trials, and contribute to the development of a new taxonomy for TBI.

3. To evaluate a flexible outcome assessment battery comprised of a broad range of TBI common data elements that enables assessment of multiple outcome domains across all phases of recovery and at all levels of TBI severity.

4. To determine which tests, treatments, and services are effective and appropriate for which TBI patients, and use this evidence to recommend practices that offer the best value.

Role: Investigator

W81XWH-0802-0159 (Stein) 9/15/08 - 9/30/14 2.0 cal mos
DoD \$336,336

Supporting Agency: U.S. Army Medical Research & Materiel Command Department of Defense (subcontract from UCSD)

Grants Officer: Angel Davey. Congressionally Directed Medical Research Programs

1077 Patchel Street, Fort Detrick MD 21702-5024

Project Title: University of Washington Clinical Consortium Study Site

Psychological Health/TBI Clinical Consortium

Brief Description of the Project's Goals: One of 10 sites in the Department of Defense Psychological Health/Traumatic Brain Injury Clinical Trials Consortium, (INTRuST) which conducts clinical trials and observational studies relevant to treatment of those with post-traumatic stress disorder or traumatic brain injury.

Role: Investigator

R01HD083126 (Mac Donald) 7/1/2015 - 6/30/2020 1.2 cal mos
NIH/NINDS

Grants Officer: Patrick Bellgowan. 9000 Rockville Pike, Bethesda, MD 20892

EVALUATION OF Longitudinal outcomes in mild TBI Active-Duty Military and Veterans – The EVOLVE Study

The goal of this study is to evaluate the long term impact of concussive TBI in four distinct groups of US Military service members, blast-TBI, non-blast TBI, blast-exposed control, and non-blast-exposed control and leverage existing early clinical and imaging data in these subjects to develop complex models of predictive outcome.

Role: Investigator

H133G110028(Hoffman)	10/01/12 – 09/30/15	0.6 cal mos
NIDRR/DOE	\$597,456 /total	
Grant Officer: Cate Miller, 400 Maryland Avenue, S.W. , Mailstop PCP-6038 , Washington, DC 20202		
Project Title: Amitriptyline to Prevent Headache after Traumatic Brain Injury		
Brief Description of the Project's Goals: This is phase II study examining the effect of preventative treatment with amitriptyline on the frequency and severity of headache after mild TBI		
Role: Investigator		
PT110602 (Hoffman)	9/30/12 - 9/29/16	1.2 cal mos
CDMRP/DoD	\$1.96 Million/4 years	
Grants Officer: B. Christie Vu		
Project Title: Telephone Delivered Cognitive Behavioral Therapy for Chronic Pain after Traumatic Brain Injury		
Brief Description of the Project's Goals: This study is a randomized controlled study examining the efficacy of a manualized cognitive behavioral therapy intervention for veterans with chronic pain after TBI compared to a telephone delivered educational intervention. The primary aim is to reduce pain intensity with secondary aims of improving co-morbid diagnoses, function, and satisfaction with life.		
Role: Investigator		
1R01NS080648 (CPI Chesnut,)	9/30/12/12-7/31/17	1.2 cal mos
NIH/NINDS and Fogarty	\$2,516,005	
Grants Officer: Joanne Odenkirchen, 9000 Rockville Pike, Bethesda, MD 20892		
Project Title: Managing severe TBI without ICP monitoring - guidelines development and testing		
Brief Description of the Project's Goals: The objective of this project is to create guidelines for the treatment of severe TBI in the absence of ICP monitoring and test them.		
Role: Investigator		
H133A980023 (Hoffman)	10/01/12 – 09/30/17	0.6 cal mos
NIDRR/DOE	\$2, 237,046	
Grants Officer: Cate Miller, 400 Maryland Avenue, S.W. Mailstop PCP-6038 Washington, DC 20202		
Project Title: University of Washington Traumatic Brain Injury Model System		
Brief Description of the Project's Goals: 1) Operate a comprehensive multidisciplinary system of care specifically designed to serve persons with TBI from injury through maximal community integration and participation. 2) Perform innovative and rigorous site-specific and multi-site research projects that are responsive to priorities specified by NIDRR 3) Participate in the continued assessment of long-term outcomes of TBI by contributing to a uniform, standardized national database. 4).Promote dissemination of research finding to clinicians, persons with TBI and their families, and the community at large through site-specific dissemination efforts and collaboration with the Model Systems Knowledge Translation Center. 5) Collaborate with other model system sites and other academic, government, and community systems in addressing issues related to TBI.		
Role: Investigator		
W81XWH-13-2-0095 (Cifu)	09/01/13 – 08/31/18	3.0 cal mos
DoD/VA (Subcontract from VCU)	\$62,500,000 overall	
Title: Chronic Effects of Neurotrauma Consortium (CENC)		
Brief Description of the Project's		
Goals: To conduct a prospective observational study of military service members and veterans to identify the chronic effects of Neurotrauma.		
Specific aim: Carry out research projects, supported by 5 Cores, with the goal of characterizing the long-term consequences of traumatic brain injury.		

(1). Longitudinal Cohort Study: A large, prospective, longitudinal investigation of Veterans with OEF/OIF combat-related mTBI and combat-exposed controls, from 2003 to the present, with varying degrees of chronic symptoms and comorbidities. These Veterans will be comprehensively evaluated on a regular basis for changes in status and performance using clinical testing, neuroimaging, genomics, biomarkers, and neuropathology.

(2). Tau Dysregulation Study: A basic science project to identify the key molecular events in the processing of tau after TBI in rodents and humans, with the goal of developing novel biomarker tools to assess tau dysregulation after TBI

Role: Investigator

MACDONALD,CHRISTINE

R01HD083126 (Mac Donald)

7/1/2015 - 6/30/2020

3.0 calendar months

NIH/NICHHD

Grants Officer: Patrick Bellgowan. 9000 Rockville Pike, Bethesda, MD 20892

EVALUATION OF LONGITUDINAL OUTCOMES IN MILD TBI ACTIVE-DUTY MILITARY AND VETERANS – THE EVOLVE STUDY

The goal of this study is to evaluate the long term impact of concussive TBI in four distinct groups of US Military service members, blast-TBI, non-blast TBI, blast-exposed control, and non-blast-exposed control and leverage existing early clinical and imaging data in these subjects to develop complex models of predictive outcome.

Role: PI

Seattle Children's Hospital (Mac Donald)

12/1/2014-11/30/2015

2.4 calendar months

TBI Research Fund

\$30,600

Pediatric Concussion Research Program

The goal of this study is to conduct advanced neuroimaging techniques on pediatric concussion patients and healthy controls to explore the relationship between imaging changes and outcome.

Role: PI

Department of Defense (Mac Donald)

10/1/2014 - 9/30/2016

3.0 calendar months

Chronic Effects of Neurotrauma Consortium \$1,000,000

Assessment of long term outcome & Disability in Active-duty military Prospectively examined following concussive TBI

The goal of this study is to evaluate the long term impact of blast-related concussive TBI on US military service members.

Role: PI

1U01NS086090 (Temkin MPI, Chesnut Site PI)

9/30/13 – 8/31/18

0.6 calendar months

NIH/NINDS

\$186,302

Yvonne Talley, Grants Management Specialist

6001 Executive Boulevard, Suite 3262, Bethesda, MD 20892-9537

Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI)

The goal of this multicenter study is to create a high quality TBI database that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers for 3,000 patients that will be enrolled across the spectrum of mild to severe TBI. Analytic tools will be developed to establish more precise methods for TBI diagnosis and prognosis, improve outcome assessment, and compare the effectiveness and costs of tests, treatments, and services.

Role: Investigator

NCIRE

WEINER, MIKE

CURRENT

U01AG024904 (Weiner) 09/30/10 – 07/31/16 3.24 calendar
NIH/NIA \$59,000,000 (Increased from 1.92)
Laurie Ryan

GWY BG RM 350, 7201 Wisconsin Ave., MS 9205, Bethesda, MD 20814-9205

Alzheimer's Disease Neuroimaging Initiative 2

Goals: The overall goal of this project is to determine the relationships among the clinical, cognitive, imaging, genetic and biochemical biomarker characteristics of the entire spectrum of Alzheimer's disease (AD), as the pathology evolves from normal aging through very mild symptoms, to mild cognitive impairment (MCI), to dementia.

Aims: 1.) Predictors: Determine and define those biomarkers which best predict future cognitive decline and conversion to MCI/dementia at the various stages of the progression from normal cognition to dementia. These biomarkers may serve as predictive or early diagnostic markers, and could be used for selection of subjects or as covariates in future treatment or prevention trials.
2.) Outcomes: Determine and define those biomarkers that best serve as outcome measures to quantify the rate of progress at the various stages from controls to dementia. These biomarkers may serve as outcome measures in future treatment or prevention trials.
3.) Clinical Trial Design: To improve clinical trials by developing various clinical trial protocol scenarios which use clinical, cognitive, and biomarker measures as selection criteria, as covariates, and as outcome measures, with maximum statistical power to detect treatment effects. Such scenarios would be developed for subjects with dementia, with MCI, with mild symptomatology, and normal healthy controls. Further descriptions of this aim are in the Clinical Core.

Role: Principal Investigator

W81XWH-12-2-0012 (Weiner) 02/21/12-02/20/17 0.60 calendar
DOD \$6,000,000 (reduced from 1.66)
Mary Rico

1054 Patchel St., Fort Detrick, MD 21702

Effects of Traumatic Brain Injury (TBI) and Post Traumatic Stress Disorder (PTSD) on Alzheimer's Disease (AD) in Veterans Using Imaging and Biomarkers in the AD Neuroimaging Initiative (ADNI)

Goals: This study will provide novel data to test the hypothesis that Combat associated TBI and/or PTSD increase the risk for AD, and decrease cognitive reserve, determined with imaging/biomarkers, in Veteran subjects, after accounting for age and APOE genotype.

Aims: 1.) Using military and VA records, identify Vietnam War Veterans with well documented history of moderate/severe TBI or evidence of ongoing PTSD, and comparable Veteran controls. Subjects meeting criteria for mild cognitive impairment and dementia will be excluded.
2.) Contact the subjects, screen them, and enroll them in the study. Perform Structured Diagnostic Interview for DSM-IV and the Clinician Administered PTSD Scale (CAPS) by telephone prior to referral to ADNI clinics.
3.) Subjects will be referred to and enrolled in the existing network of the Alzheimer's Disease Neuroimaging Initiative (ADNI).
4.) Baseline measurements of cognition, function, blood and cerebrospinal fluid analyses, MRI (structural, diffusion tensor, and resting state BOLD fMRI) and amyloid PET imaging with Florbetapir and 1 yr follow-up measurements will be obtained.
5.) Analyze the data to test the primary and secondary hypotheses as stated, as well as exploratory analyses.

Role: Principal Investigator

W81XWH-13-1-0259 (Weiner) 9/30/13-9/29/16 0.60 calendar
DOD \$6,400,000 (increased from 0.35)
Blossom Widder

820 Chandler Street, Fort Detrick, MD 21702-5012

Effects of traumatic brain injury and post traumatic stress disorder on Alzheimer's disease (AD) in Veterans with mild cognitive impairment using ADNI

Goals: The overall long-term goal of this project is to prevent Alzheimer's Disease. This study targets veterans who have suffered PTSD and TBI and show mild cognitive impairment to assess their risk for Alzheimer's Disease.

Aims: 1.) Using military and VA records, identify Vietnam War Veterans with well documented history of moderate/severe TBI or evidence of ongoing PTSD, and comparable Veteran controls. Only subjects meeting criteria for mild cognitive impairment will be included.
2.) Contact the subjects, screen them, and enroll them in the study. Perform Structured Diagnostic Interview for DSM-IV and the Clinician Administered PTSD Scale (CAPS) by telephone prior to referral to ADNI clinics.
3.) Subjects will be referred to and enrolled in the existing network of the Alzheimer's Disease Neuroimaging Initiative (ADNI). 4) Baseline measurements of cognition, function, blood and cerebrospinal fluid analyses, MRI (structural, diffusion tensor, and resting state BOLD fMRI) and amyloid PET imaging with Florbetapir and 1 year follow-up measurements will be obtained.
5.) Analyze the data to test the primary and secondary hypotheses as stated, as well as exploratory analyses.
6.) Perform neuropathology on brains of subjects who come to autopsy.

Role: Principal Investigator

W81XWH-14-1-0462 (Weiner) 09/30/14-9/29/17 0.60 calendar
DOD \$5,500,000 (new)

Elena Howell, Grants Specialist,

820 Chandler Street, Fort Detrick, MD 21702-5012

Effects of Traumatic Brain Injury and Post-Traumatic Stress Disorder and Alzheimer's Disease on Brain Tau in Vietnam Veterans using ADNI

The overall goal of this project is to determine the effects of prior traumatic brain injury (TBI), and ongoing post-traumatic stress disorder (PTSD) on brain tau, and the longitudinal change of brain tau, measured with the tau specific ligand [18F]-T807 and positron emission tomography (PET) scanning.

Aims: To determine the baseline and longitudinal relationships between brain tau and cognition, history of TBI, and A β status in Vietnam veterans with history of TBI or PTSD, with a range of cognitive impairments, as well as civilian subjects with a range of cognitive impairments.

Role: Principal Investigator

R01AG10897 (Weiner) 03/15/09 – 02/28/16 4.20 calendar
NIH/NIA \$3,421,090 (increased from 0.6)

John Hsiao, Director, Diagnosis and Biomarkers Program, Dementias of Aging Branch

6001 Executive Blvd Rm 7165, MSC 9635, Bethesda, MD 20892

Prediction of Cognitive Decline with MRI and MRS

Goals: The goal of this project is to determine the pattern of longitudinal, structural, perfusion, and metabolic changes in the brain, which best predict future cognitive decline and dementia due to Alzheimer's disease (AD).

Aims: 1.) To continue to follow the 1.5T cohort of 145 subjects (who already have had scans at baseline, 6 months, 1 and 2 years) with annual clinical/neuropsychological assessments visits, in order to have better determined measures of cognitive decline in these subjects. Furthermore, in response to the Critique, we will enroll all eligible subjects who previously completed the 1.5T study, in the 4T cohort.

2.) To continue to enroll our 4T cohort of non-demented subjects with memory problems or complaints, perform imaging studies, and determine the extent that imaging adds statistically significant predictive value to baseline clinical/neuropsychological evaluation.

Role: Principal Investigator

P01AG19724 (Miller) 09/01/12 - 08/31/17 0.24 calendar
NIH/NIA \$738,237

John Hsiao, Director, Diagnosis and Biomarkers Program, Dementias of Aging Branch

6001 Executive Blvd Rm 7165, MSC 9635, Bethesda, MD 20892

Frontotemporal Dementia: Genes, Images & Emotions: Project 2: Imaging

Goals: The goals of this project are to determine the structural, perfusion, and chemical changes of the brain that: 1) occur in frontotemporal lobar degeneration (FTLD) and progressive supranuclear palsy (PSP) 2) distinguish FTLD and PSP from Alzheimer's Disease (AD); 3) accompany the cognitive and behavioral symptomatology of FTLD and PSP.

Aims: 1.) Use multimodality neuroimaging to distinguish those subjects with non-AD clinical syndromes ((a) bvFTD, (b) nfPPA, svPPA, and lvPPA, (c) CBS, and (d) PSP-S) caused by Alzheimer's amyloid pathology from those without amyloid pathology.

2.) Explore the brain-behavior associations of multimodality neuroimaging for the following cognitive and behavioral profiles: (a) motor speech impairment, (b) executive control, and (c) emotion.

3.) Explore the predictive value of baseline brain-behavior associations for longitudinal decline and identify a combination of multimodality brain-behavior associations that best predicts the decline.

Role: Co-Investigator

R01 MH098062-01 (Mackin) 8/01/13–7/31/18 0.24 calendar
NIH/ NIMH \$647,392 (increased from 0.22)

Jovier Evans, Program Chief

6001 Executive Boulevard, Room 7113, Bethesda, MD 20892 - MSC 9634

Characterizing Cognitive Decline in Late Life Depression: The ADNI-D Project

Goals: The overall goal of this program of research is to identify the neurobiological substrates of cognitive impairment (CI) in late life depression (LLD).

Aims: 1.) To clarify the impact of cerebral blood flow, cortical thickness, and amyloid deposition on CI in LLD, and

2.) To determine the impact of depression on course of cognitive decline in older adults.

Role: Co-Investigator

12-12004 (Carmichael) 6/1/13-6/30/16 0.12 calendar
California Department of Public Health \$156,004 (new)

Julie Parson, Grant Manager

1616 Capitol Avenue #74.420, Sacramento, CA 95814

California Alzheimer's Disease Program – Determinants and Consequences of White Matter Degeneration in Alzheimer's Disease

Goals: Disconnection of distributed cognitive systems is a hallmark of Alzheimer's disease (AD), but limited research has investigated the impact of white matter injury on its natural history. Understanding the impact of white matter injury in AD may extend our understanding of disease pathophysiology and identify new avenues for therapeutics .

Aims: 1.) Relate AD pathology to white matter and gray matter injury.
2.) Characterize associations between mild white matter injury, severe white matter injury, and gray matter atrophy.
3.) Assess the independent contributions of white matter injury and gray matter atrophy to cognitive decline related to AD.

Role: Subcontract Principal Investigator

P50 AG23501 (PI: Miller)

04/01/14–03/31/19

0.24 calendar

NIH/NIA

\$61,415 (Core F Only)

New Approaches to Dementia Heterogeneity: Alzheimer's Disease Research Centers, Core F

The main goal of this project is to integrate science and clinical resources to investigate Alzheimer's disease (AD), non-AD dementias, and mild cognitive impairment.

Aims: The overall long-term goal of this project is to assess the value of multimodality imaging for

- 1.) Classification and early detection of FTD subtypes and related disorders
- 2.) For understanding the changes in the brain responsible for cognitive, linguistic, and emotional dysfunction in FTD and AD, and
- 3) To predict longitudinal changes in cognition and function in FTD.

Role: Subcontract Principal Investigator

R01MH101472 (Tosun-Turgut/Mackin)

06/01/15-02/29/20

0.24 calendar

NIH

\$692,848

(new)

Multimodal MRI Characteristics of Psychotherapy Response in Late Life Depression

Chris Booher, Grants Management Specialist (301)443-3066

The purpose of this project is to identify the impact of cerebral blood flow (CBF), cortical atrophy, and white matter lesions on psychotherapy treatment outcomes in late life depression (LLD) and to determine the degree to which remission of depression is associated with increased CBF in frontal brain regions.

Aims: 1.) To clarify the role of cerebral blood flow (CBF), cortical gray matter (GM) atrophy, and subcortical WM lesion burden as predictors of psychotherapeutic response in LLD after accounting for cognitive function and other clinical characteristics.
2.) To clarify the role of CBF as a biological marker of psychotherapy response in LLD.

Role: Subcontract Principal Investigator

TOSUN, DUYGU

CURRENT

U01AG024904 (Weiner)

09/30/10 – 07/31/16

1.80 calendar

NIH/NIA

\$59,000,000

(new)

Laurie Ryan

GWY BG RM 350, 7201 Wisconsin Ave., MS 9205, Bethesda, MD 20814-9205

Alzheimer's Disease Neuroimaging Initiative 2

Goals: The overall goal of this project is to determine the relationships among the clinical, cognitive, imaging, genetic and biochemical biomarker characteristics of the entire spectrum of Alzheimer's disease (AD), as the pathology evolves from normal aging through very mild symptoms, to mild cognitive impairment (MCI), to dementia.

Aims: 1.) Predictors: Determine and define those biomarkers which best predict future cognitive decline and conversion to MCI/dementia at the various stages of the progression from normal cognition to dementia. These biomarkers may serve as predictive or early diagnostic markers, and could be used for selection of subjects or as covariates in future treatment or prevention trials.
2.) Outcomes: Determine and define those biomarkers that best serve as outcome measures to quantify the rate of progress at the various stages from controls to dementia. These biomarkers may serve as outcome measures in future treatment or prevention trials.
3.) Clinical Trial Design: To improve clinical trials by developing various clinical trial protocol scenarios which use clinical, cognitive, and biomarker measures as selection criteria, as covariates, and as outcome measures, with maximum statistical power to detect treatment effects. Such scenarios would be developed for subjects with dementia, with MCI, with mild symptomatology, and normal healthy controls. Further descriptions of this aim are in the Clinical Core.

Role: Co-Investigator

P01AG19724 (Miller) 09/01/12-08/31/17 1.20 calendar

NIH/NIA

\$738,237

John Hsiao, M.D., Director, Diagnosis and Biomarkers Program, Dementias of Aging Branch

GWY BG RM 350, 7201 Wisconsin Ave., Bethesda, MD 20814

Frontotemporal Dementia: Genes, Images & Emotions Project 2: Imaging (Weiner)

Goals: The goals of this project are to determine the structural, perfusion, and chemical changes of the brain that: 1) occur in frontotemporal lobar degeneration (FTLD) and progressive supranuclear palsy (PSP) 2) distinguish FTLD and PSP from Alzheimer's Disease (AD); 3) accompany the cognitive and behavioral symptomatology of FTLD and PSP.

Aims: 1.) Use multimodality neuroimaging to distinguish those subjects with non-AD clinical syndromes ((a) bvFTD, (b) nfPPA, svPPA, and lvPPA, (c) CBS, and (d) PSP-S) caused by Alzheimer's amyloid pathology from those without amyloid pathology.
2.) Explore the brain-behavior associations of multimodality neuroimaging for the following cognitive and behavioral profiles: (a) motor speech impairment, (b) executive control, and (c) emotion.
3.) Explore the predictive value of baseline brain-behavior associations for longitudinal decline and identify a combination of multimodality brain-behavior associations that best predicts the decline.

Role: Co-Investigator

12-12004 (Carmichael)

6/1/13-6/30/16

2.16 calendar

California Department of Public Health

\$156,004

(reduced from 3)

Julie Parson, Grant Manager

1616 Capitol Avenue #74.420, Sacramento, CA 95814

California Alzheimer's Disease Program – Determinants and Consequences of White Matter

Degeneration in Alzheimer's Disease

Goals: Disconnection of distributed cognitive systems is a hallmark of Alzheimer's disease (AD), but limited research has investigated the impact of white matter injury on its natural history. Understanding the impact of white matter injury in AD may extend our understanding of disease pathophysiology and identify new avenues for therapeutics .

Aims: 1.) Relate AD pathology to white matter and gray matter injury.
2.) Characterize associations between mild white matter injury, severe white matter injury, and gray matter atrophy.
3.) Assess the independent contributions of white matter injury and gray matter atrophy to cognitive decline related to AD.

Role: Co-Investigator

R01AG10897 (Weiner)

03/15/09 – 02/28/16

0.84 calendar

NIH/NIA

\$3,421,090

(reduced from 1.10)

John Hsiao, Director, Diagnosis and Biomarkers Program, Dementias of Aging Branch

6001 Executive Blvd Rm 7165, MSC 9635, Bethesda, MD 20892

Prediction of Cognitive Decline with MRI and MRS

Goals: The goal of this project is to determine the pattern of longitudinal, structural, perfusion, and metabolic changes in the brain, which best predict future cognitive decline and dementia due to Alzheimer's disease (AD).

Aims: 1.) To continue to follow the 1.5T cohort of 145 subjects (who already have had scans at baseline, 6 months, 1 and 2 years) with annual clinical/neuropsychological assessments visits, in order to have better determined measures of cognitive decline in these subjects. Furthermore, in response to the Critique, we will enroll all eligible subjects who previously completed the 1.5T study, in the 4T cohort.
2.) To continue to enroll our 4T cohort of non-demented subjects with memory problems or complaints, perform imaging studies, and determine the extent that imaging adds statistically significant predictive value to baseline clinical/neuropsychological evaluation.

Role: Co-Investigator

W81XWH-14-1-0462 (Weiner)

09/30/14-9/29/17

0.60 calendar

DOD

\$5,500,000

Elena Howell, Grants Specialist,

820 Chandler Street, Fort Detrick, MD 21702-5012

Effects of Traumatic Brain Injury and Post-Traumatic Stress Disorder and Alzheimer's Disease on Brain Tau in Vietnam Veterans using ADNI

The overall goal of this project is to determine the effects of prior traumatic brain injury (TBI), and ongoing post-traumatic stress disorder (PTSD) on brain tau, and the longitudinal change of brain tau, measured with the tau specific ligand [18F]-T807 and positron emission tomography (PET) scanning.

Aims: To determine the baseline and longitudinal relationships between brain tau and cognition, history of TBI, and A β status in Vietnam veterans with history of TBI or PTSD, with a range of cognitive impairments, as well as civilian subjects with a range of cognitive impairments.

Role: Co-Investigator

1I01CX000798-01A2 (PI: Chao) 10/01/13-09/30/17 0.60 calendar
VA Merit \$1,392,809

Longitudinal assessment of Gulf War veterans with suspected Sarin exposure

The overall goal of this study is to determine whether Gulf War (GW) veterans with suspected Sarin exposure have greater rates of cognitive decline and/or faster rates of brain atrophy than GW veterans without suspected Sarin exposure.

Role: Co-Investigator

P50 AG23501 (PI: Miller) 04/01/14 – 03/31/19 0.96 calendar
NIH/NIA \$61,415 (Core F Only)

New Approaches to Dementia Heterogeneity: Alzheimer's Disease Research Centers, Core F

The main goal of this project is to integrate science and clinical resources to investigate Alzheimer's disease (AD), non-AD dementias, and mild cognitive impairment. (Role:Co-Project Lead)

Aims: The overall long-term goal of this project is to assess the value of multimodality imaging for

- 1.) Classification and early detection of FTD subtypes and related disorders,
- 2.) For understanding the changes in the brain responsible for cognitive, linguistic, and emotional dysfunction in FTD and AD, and
- 3.) To predict longitudinal changes in cognition and function in FTD.

Role: Subcontract Co-Investigator

R01MH101472 (Tosun-Turgut/Mackin) 06/01/15-02/29/20 1.68 calendar
NIH \$692,848

Multimodal MRI Characteristics of Psychotherapy Response in Late Life Depression

Chris Booher, Grants Management Specialist (301)443-3066

The purpose of this project is to identify the impact of cerebral blood flow (CBF), cortical atrophy, and white matter lesions on psychotherapy treatment outcomes in late life depression (LLD) and to determine the degree to which remission of depression is associated with increased CBF in frontal brain regions.

- Aims:
- 1.) To clarify the role of cerebral blood flow (CBF), cortical gray matter (GM) atrophy, and subcortical WM lesion burden as predictors of psychotherapeutic response in LLD after accounting for cognitive function and other clinical characteristics.
 - 2.) To clarify the role of CBF as a biological marker of psychotherapy response in LLD.

Role: Subcontract Co-Investigator

RTI

WILLIAMS, RICK- Requested

(GRANT ADDED)

W81XWH-15-2-007

9/30/15-9/29/20

3.6 months

CDMRP

\$7,200,000 (base), \$3,200,000 (optional)

Agency contact:

Email:

Pharmacotherapies for Alcohol and Substance Abuse (PASA) Consortium

Goals:

Aims:

Role: PI

MCW
MCCREA, MICHAEL

(Grant ended)

W81XWH-12-1-0004 (McCrea)	3/1/12-2/28/15	3.00 Calendar Months
USAMRMC	\$1,624,961	

Valerie A. Trabosh, PhD, Senior Scientist, Psychological Health Program Area Manager
810 Schreider Street, Bldg 722, Fort Detrick, MD 21702-5000

An Independent, Prospective, Head to Head Study of the Reliability and Validity of
Neurocognitive Test Batteries for the Assessment of Mild Traumatic Brain Injury

Goals: To investigate and compare the reliability and clinical validity of four candidate
computerized NCATs for acute neurocognitive assessment, tracking cognitive recovery, and
informing clinical management after mTBI.

Aims: 1. To determine and compare the test-retest reliability of the candidate neurocognitive
test batteries over serial administrations and a time course consistent with that typical of a
clinical setting of sport-related concussion and civilian mTBI.

2. To determine and compare the predictive validity of the candidate neurocognitive test
batteries administered during the acute period (within 24 hours) in predicting the time course of
clinical recovery 8, 15 and 45 days after sport-related concussion and civilian mTBI.

3. To determine and compare the sensitivity and specificity of the candidate
neurocognitive test batteries in reliably detecting cognitive impairments in athletes with
concussion and civilians with mTBI who are otherwise self-reporting a complete symptom
recovery and would be potentially cleared for return to activity 24 hours and 8, 15 and 45 days
post-injury.

Role: PI

UCSD
STEIN, MURRAY- REQUESTED

USC
TOGA, ARTHUR

U54EB020406 (Toga)

NIH

James E. Huff, Grants Management Specialist

6707 Democracy Boulevard, Suite 900, Bethesda, MD 20817

Big Data for Discovery Science

Goals: The overarching goal of our BDDS Center is to ease the management and organization of biomedical big data and accelerate data-driven discovery by eliminating or reducing three distinct barriers to effective discovery science: complexity with respect to physical distribution and heterogeneity, scalability of analysis, and ease of access and interaction with big-data and associated analytic methods. These issues are fundamental to discovery science and transcend the specifics of the research question as we span levels of scale from cells to organs to systems, and integrate data from imaging, genetics, “omics,” and phenotypes.

Specific Aims: Under our Big Data for Discovery Science (BDDS) Center, we will accomplish the following aims: Overall Specific Aim #1: We will accelerate data-driven knowledge discovery by addressing complexity, scalability of analysis, and ease of interaction with big-data and associated analytic methods. Overall Specific Aim #2: Training - We will provide an innovative array of training activities directly pertaining to the emerging field of big data science. Overall Specific Aim #3: Administration - Our center will employ a dedicated team of respected biomedical researchers with clear management, communication, and tracking mechanisms in place. Overall Specific Aim #4: Consortium Activities - We will interact closely with the biomedical community and other BD2K Consortium leaders to address the challenges of large-scale research data and its role in discovery science.

Role: PI

09/29/14-09/30/18

\$11,566,693

3.60 calendar

P41EB015922 (Toga)

NIH/NIBIB

Vinay Pai, Program Officer

6707 Democracy Blvd., BG 2DEM RM 213, Bethesda, MD 20817

Laboratory of Neuro Imaging Resource (LONIR)

Goals: The Laboratory of Neuro Imaging Resource (LONIR) develops, validates and disseminates powerful and user-friendly tools and biomedical analysis protocols for studies of various neurological disorders, e.g., HIV, complex behavior, Alzheimer’s disease, and child development. All LONIR data, analysis protocols, computational resources and research findings are openly shared online, enhancing research efforts of a wide community. The research efforts of LONIR investigators and collaborators are centered on the fundamental recognition that the brain is dynamic. LONIR facilitates studies of dynamically changing anatomical frameworks, e.g., developmental, neurodegenerative, traumatic, and metastatic, by providing tools for comprehensive understanding of the nature and extent of these processes.

Specific Aims for Sub-Projects:

TR&D Projects	Aims	Impact
TR&D 1 Image Understanding	Aim 1: Quality assurance and validation Aim 2: Robust image segmentation & registration Aim 3: Diffusion Data	- Develop methods for performing routine evaluation of the image processing algorithms in this project through a combination of quality assurance testing and validation - Address the factors that prevent image segmentation and registration from achieving high-reliability in their routine use by non-experts. - Develop methods for coregistration of tensor and higher dimensional diffusion data into a common space.
TR&D 2: Connectomics	Aim 1: Improved Voxel-Based Assessment of Fiber Integrity using HARDI (TDF-FA) Aim 2: Tract-based statistical analysis by automated clustering of fibers Aim 3: Whole-Brain Connectivity Matrices Aim 4: Genetics of Brain Connectivity	- Advance the study of brain connectivity using diffusion imaging and its powerful extensions beyond the tensor model of diffusion (QBI, multi-shell HYDI, DSI, HARDI-TDF, Q-ball imaging, staggered HYDI, and DSI) - Compare fiber and bundle integrity, properties and statistics across large populations - Create NxN connectivity matrices summarizing the presence and properties of connections between all pairs of brain regions - Develop, test, and disseminate powerful new quantitative genetic approaches for discovering genetic effects on brain integrity and connectivity
TR&D 3:	Aim 1: Develop computational tools to	Allow users to tailor analysis methods to the specific biological

Data Interpretation	assist with data reduction and selection of appropriate statistical models in the multivariate analysis of imaging data • Aim 2: Adapt multivariate statistical methods and model selection criteria so that they are suitable for use with multivariate observations confined to non-Euclidean manifolds • Aim 3: Efficient statistical model to structural and diffusion imaging data	questions of interest. • Involve data reduction and incorporation of non-imaging derived biological measures. • Facilitate the examination of the data for errors and violations of underlying statistical assumptions. • Exploratory and Interactive data and result interpretation • Provide a user-friendly interface for specifying, validating and applying an appropriate statistical model to structural and diffusion imaging data • Enable multivariate statistical analyses of data in non-Euclidean manifolds
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Role: PI

R01MH094343 (Toga)

09/01/13-03/31/17

1.00 calendar

NIH

\$1,527,901

Michelle Freund, Program Officer

6001 Executive Blvd., MS 9645, NSC BG RM 7203, Rockville, MD 20852-9645

Genetic Influences on Human Neuroanatomical Shapes

Goals: This unique large-scale investigation will improve understanding of the complex ways in which genetics exert influence over human neuroanatomy. By providing the larger research community with mathematically sophisticated software tools, we will create opportunities to advance progress in many psychiatric and neurological diseases.

Specific Aims: 1) Heritability of Cortical and Subcortical Gray Matter Shapes. 2) Heritability of White Matter Shapes. 3) Genome-Wide Association Studies (GWAS). 4) Modeling the Influence of Specific Candidate Genes.

Role: PI

003278-00001 (Toga)

09/15/13-09/14/18

0.84 calendar

Alzheimer's Association

\$4,181,820

Dan Parisi, Senior Associate Director, Foundation Relations

225 N. Michigan Avenue, 17th Floor, Chicago, IL 60601

The Global Alzheimer's Association Interactive Network (GAAIN)

Goals: The overall goal of GAAIN is to advance a global cooperative of sharing, investigation and discovery in order to develop effective therapies, prevention methods and a cure for Alzheimer's and other neurodegenerative diseases.

Specific Aims: 1) GAAIN will develop a more extendable and distributable database on LONI's highly successful and mature Integrated Data Archive (IDA). 2) GAAIN will build tools and analytic libraries to share the tools. 3) GAAIN will build a cloud-enabled database infrastructure and federated network composed of nodes. 4) GAAIN will link objectives 1-3—data, tools and network—to build and deploy software. 5) GAAIN will build intuitive and compelling human interfaces for web access and other easy-to-use entry points and develop training materials for all aspects of the data repository. 6) GAAIN will conduct an international awareness campaign to promote the data repository.

Role: PI

003585-00001 (Toga)

09/01/13-12/31/18

0.60 calendar

Michael J. Fox Foundation for Parkinson's Research

\$1,491,998

Sohini Chowdhury, Grants Administrator

Church Street Station, PO Box 780, New York, NY 10008-0780

Parkinson's Progression Markers Initiative (PPMI), Core Study & Sub-Studies

Goals: We will develop the PPMI Database and Dataflow and the PPMI Study Website which will provide a secure and highly interactive environment for archiving, managing and sharing neuroimaging and related data for large, multi-site studies serving research communities investigating Parkinson's disease.

Specific Aims: 1) Development and overall management of a secure Project database housing and correlating various data stream. 2) Development of appropriate infrastructure and protocols for making data available to the broader scientific community. 3) Development of a Project website

Role: PI

A-7059 (Toga)

09/01/13-12/31/19

0.36 calendar

CHDI Foundation, Inc.

\$631,190

Beth Borowsky, Director of Translational Medicine
300 Alexander Park, Suite 110, Princeton, New Jersey 08540
Huntington's Disease Neuroimaging Project: TRACK Database

Goals: We will provide data repository services for raw and processed neuroimaging data, including fMRI biometric data, and associated quality control metadata. We will provide an infrastructure that will de-identify and store Huntington's disease ("HD") magnetic resonance imaging (MRI) data and, hold images in a quarantine area pending review and release from quarantine.

Specific Aims:

Time Objectives	Period 1 (Months 1-4)	Period 2 (Months 5-16)	Periods 3-7 (optional)
Track-On Study Data Archive	- Obtain IRB Approval; - Provide access for Project administrators - Receive raw image data (approx 500 scans); - Integrate metadata elements (optional); - Define processed image metadata elements;	On-going querying and download of raw and processed data to authorized investigators.	On-going querying and download of raw and processed data to authorized investigators.
Track-On Study Quality Control	- Archival, querying and download of data to qualified investigators. - Receive and archive processed images and meta data that has passed a QC analysis by the Foundation;		
Track-On Study Data Integrity Monitoring	Integration of Track-On QC metadata and image status management (quarantine & quarantine release).		
TRACK-HD Study Data Archiving	On-going monitoring of data archival and quarantine/QC status systems and activities.		
Tracking	- On-going querying and download of raw and processed data to authorized investigators. - On-going tracking/logging of data uploads, downloads, edits and deletions.		

Role: PI

Northern California Institute for Res. & Edu. (Toga) 09/01/13-07/31/16 0.30 calendar
Prime: NIH U01 AG024904 (Weiner) \$1,247,837 (Toga's subcontract only)
Jeffrey Ball, Grants Officer
7201 Wisconsin Ave, MS 9205, Bethesda, MD 20814-9205
The Alzheimer's Disease Neuroimaging Initiative

Goals: The goal of this proposed Neuroimaging Core is to provide critical imaging and data-processing resources very rapidly to our clinical and research collaborators and to the public. We will create an infrastructure that will ensure efficient data provenance, reliable processing and interactive data visualization for studies in neurodegeneration.

Specific Aims: 1) Enrichment of the ADNI Database Content and Infrastructure. 2) Incorporation of Processed data and its full Provenance. 3) Enhanced, adaptive and intelligent query. 4) Tools for Efficient Workflow Processing of Data. 5) Database Training.

Role: Subaward PI

Northern California Institute for Res. & Edu. (Toga) 11/01/13-02/20/17 (NCTE) 0.06 calendar
Prime: DOD W81XWH-12-2-0012 (Weiner) \$60,276 (Toga's subcontract only)
John Carney, Grants Officer Representative
820 Chandler St, Fort Detrick, Maryland 21702

Effects of traumatic brain injury (TBI) and post traumatic stress disorder (PTSD) on Alzheimer's disease (AD) in veterans using imaging and biomarkers in the Alzheimer's Disease Neuroimaging Initiative (ADNI)

Goals: AD is the most common cause of dementia. TBI and PTSD are common problems resulting from military service, and both may be associated with increased risk of cognitive decline and dementia due to AD or other causes. The results will have major implications for identifying subjects at increased risk for AD, a possible need for early

detection of AD in military Veterans with histories of TBI and PTSD, and a possible need to employ prevention and treatment measures to avoid accelerated development of AD in US military Veterans. This study is a first step towards a larger, more comprehensive study of dementia risk factors in Veterans. The result will lead to a design and statistical powering of a prevention trial.

Specific Aims: 1) Using military and VA records, identify Vietnam War Veterans with well documented history of moderate/severe TBI or evidence of ongoing PTSD, and comparable Veteran controls. Subjects meeting criteria for mild cognitive impairment and dementia will be excluded. 2) Contact the subjects, screen them, and enroll them in the study. Perform Structured Diagnostic Interview for DSM-IV and the Clinician Administered PTSD Scale (CAPS) by telephone prior to referral to ADNI clinics. 3) Subjects will be referred to and enrolled in the existing network of the Alzheimer's Disease Neuroimaging Initiative (ADNI). 4) Baseline measurements of cognition, function, blood and cerebrospinal fluid analyses, MRI (structural, diffusion tensor, and resting state BOLD fMRI) and amyloid PET imaging with Florbetapir and 1 yr follow-up measurements will be obtained. 5) Analyze the data to test the primary and secondary hypotheses as stated, as well as exploratory analyses

Role: Subaward PI

Northern California Institute for Res. & Edu. (Toga) 09/30/13-09/29/16 0.06 calendar
Prime: DOD W81XWH-13-1-0259 (Weiner) \$155,117 (Toga's subcontract only)

Elena Howell, Grants Specialist/Grants Officer

U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick, MD 21702

Effects of Traumatic Brain Injury and Post-Traumatic Stress Disorder on Alzheimer's Disease (AD) in Veterans with Mild Cognitive Impairment (MCI) using the Alzheimer's disease neuroimaging initiative (ADNI)

Goals: TBI and PTSD are common problems resulting from military service, and both may be associated with increased risk of cognitive decline and dementia due to AD or other causes. The results will have major implications for identifying subjects at increased risk for AD, a possible need for early detection of AD in military Veterans. The result will lead to a design and statistical powering of a prevention trial. Therefore, this project could be first step towards the prevention of AD in Veterans, and in the general population.

Specific Aims: 1) Using military and VA records, identify Vietnam War Veterans with well documented history of moderate/severe TBI or evidence of ongoing PTSD, and comparable Veteran controls. Only subjects meeting criteria for mild cognitive impairment will be included. 2) Contact the subjects, screen them, and enroll them in the study. Perform Structured Diagnostic Interview for DSM-IV and the Clinician Administered PTSD Scale (CAPS) by telephone prior to referral to ADNI clinics. 3) Subjects will be referred to and enrolled in the existing network of the Alzheimer's Disease Neuroimaging Initiative (ADNI). 4) Baseline measurements of cognition, function, blood and cerebrospinal fluid analyses, MRI (structural, diffusion tensor, and resting state BOLD fMRI) and amyloid PET imaging with Florbetapir and 1 year follow-up measurements will be obtained. 5) Analyze the data to test the primary and secondary hypotheses as stated, as well as exploratory analyses. 6) Perform neuropathology on brains of subjects who come to autopsy.

Role: Subaward PI

Northern California Institute for Res. & Edu. (Toga) 09/22/14-09/21/18 0.24 calendar
Prime: DOD W81XWH-14-1-0462 (Weiner) \$404,235 (Toga's subcontract only)

Elena Howell, Grants Specialist/Grants Officer

U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick, MD 21702

Effects of Traumatic Brain Injury and Post-Traumatic Stress disorder and Alzheimer's Disease on Brain Tau in Vietnam Veterans Using ADNI

Goals: The overall goal of this project is to determine the effects of prior traumatic brain injury (TBI), and ongoing post-traumatic stress disorder (PTSD) on brain tau, and the longitudinal change of brain tau, measured with the tau specific ligand [18F]-T807 and positron emission tomography (PET) scanning.

Specific Aims: To determine the baseline and longitudinal relationships between brain tau and cognition, history of TBI, and A β status in Vietnam veterans with history of TBI or PTSD, with a range of cognitive impairments, as well as civilian subjects with a range of cognitive impairments.

Role: Subaward PI

University of California, San Francisco (Toga) 09/30/13-08/31/18 0.24 calendar
Prime: NIH U01 NS086090 (Manley) \$448,993 (Toga's share only)

Yvonne Talley, Grants Management Specialist

6001 Executive Boulevard, Suite 3262, Bethesda, MD 20892-9537

Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TBI)

Goals: To create a large, high quality TBI database that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers, and provides analytic tools and resources to establish more precise methods for TBI diagnosis and prognosis, improve outcome assessment, and compare the effectiveness and costs of tests, treatments, and services.

Specific Aims: 1) To create a widely accessible, comprehensive TBI Information Commons that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers from subjects across the age and injury spectra, and provides analytic tools and resources to support TBI research. 2) To validate imaging, proteomic, and genetic biomarkers that will improve classification of TBI, permit appropriate selection and stratification of patients for clinical trials, and contribute to the development of a new taxonomy for TBI. 3) To evaluate a flexible outcome assessment battery comprised of a broad range of TBI common data elements that enables assessment of multiple outcome domains across all phases of recovery and at all levels of TBI severity. 4) To determine which tests, treatments, and services are effective and appropriate for which TBI patients, and use this evidence to recommend practices that offer the best value.

Role: Subaward PI

Medical University of South Carolina (Toga)

04/01/14-03/31/18

0.36 calendar

Prime: NIH U01 NS087748 (Palesch/Zhao)

\$73,339 (Toga's share only)

Elizabeth E Conklin, Grants Management Specialist:

6001 Executive Boulevard, Suite 3290, MSC 9537, Rockville, MD 20852

NINDS Stroke Trials Network - National Data Management Center

Goals: We will collaborate with the National Data Management Center (NDMC) of the NIH Stroke Trials Network (StrokeNet) in establishing a neuroimaging repository for most, if not all, of the StrokeNet clinical trials.

Specific Aims: 1) In conjunction with the StrokeNet Neuroimaging Core and the NDMC, develop standard operating procedures (SOPs) for neuroimaging processing. 2) Provide relevant user's manual and technical assistance, as needed, to the StrokeNet sites in the imaging upload procedure. 3) In collaboration with the NDMC, program the interface between the LONI and the NDMC's WebDCU™ systems. 4) In collaboration with the Neuroimaging Core, develop a system for central review and adjudication of images. 5) Test and validate the entire process with the Neuroimaging Core and the NDMC prior to the initiation of the first StrokeNet trial.

Role: Subaward PI

BCM

ROBERTSON, CLAUDIA

Nothing to Report

LEVIN, HARVEY

(Grant added)

N6311614MPX083 (Levin)

07/01/2015-60/30/2017

2.4 CM

Department of the Navy

\$212,555

Agency contact: Douglas Oberly

email: doug.oberly@brainscope.com

Objective Brain Function Assessment of MTBI From Initial Injury To Rehabilitation and Treatment

The major goal of this multisite study is to evaluate the sensitivity and validity of a portable EEG device for detecting sports concussions in collegiate athletes. The study will also refine the algorithm developed by the sponsor for detecting concussion.

Role: PI

SRH

GIACINO, JOSEPH- REQUESTED

UFLORIDA
WANG, KEVIN

Nothing to Report

VCU
MERCHANT, RANDALL

Nothing to Report

CIFU, DAVID

Dr. Cifu's percentage of effort on his project, the Chronic Effects of Neurotrauma Consortium increased., and the DRC, and ARRT project ended. See below.

Title: <i>Chronic Effects of Neurotrauma Consortium (CENC)</i>		Time Commitments: 7.2 cal
Supporting Agency: Dept. of the Army—USAMRAA	Name and Address of Funding Agency's Procuring Contracting/Grants Officer: BAA 12-1 820 Chandler Street Fort Detrick, MD 21702-5014	
Performance Period: 9/30/2013 - 9/29/2018	Level of Funding: \$37,175,000	
Brief Description of the Project's Goals: A multicenter collaboration linking basic science, translational, and clinical neuroscience researchers from the VA, military and academia to effectively address the diagnostic and therapeutic ramifications of traumatic brain injury (TBI) and its long-term effects		
List of Specific Aims: The overarching goals of CENC are to examine the critical issues related to the identification and characterization of the anatomic, molecular, and physiological mechanisms of chronic brain injury and potential neurodegeneration, investigate the relationship of comorbidities of trauma and combat exposure to TBI and neurodegeneration, and assess the efficacy of existing and novel treatment and rehabilitation strategies for chronic TBI effects and neurodegeneration.		

Title: <i>DCOE PH/TBI HBO2 Research Support</i>		Time Commitments: 0.24 cal
Supporting Agency: Department of the Navy	Name and Address of Funding Agency's Procuring Contracting/Grants Officer: Christine Garves Lovelace Biomedical and Environmental Research Institute	
Performance Period: 1/2/2012 – 9/27/2014	Level of Funding: \$20,882	
Brief Description of the Project's Goals: To provide consultation regarding the use of Hyperbaric Oxygen in TBI patients.		
List of Specific Aims: Identify valid outcome measures; Provide support in collection of outcome measures; Assist in the analysis of outcome data; & Disseminate Findings		

Title: <i>Epidemiological Study of Mild Traumatic Brain Injury Sequelae Caused by Blast Exposure during Operations Iraq Freedom and Enduring Freedom</i>		Time Commitments: 0.0 cal
Supporting Agency: CDMRP/DCoE	Name and Address of Funding Agency's Procuring Contracting/Grants Officer: Robert Dresch McGuire Research Institute 1201 Broad Rock Boulevard. Richmond VA 23249	
Performance Period: 9/1/2008 – 8/31/2014	Level of Funding: \$568,019	

Brief Description of the Project's Goals: A longitudinal study of OEF/OIF service members with mild TBI.

Title: <i>Virginia Commonwealth Traumatic Brain Injury Model System</i>	Time Commitments: 8% (percent effort)
Supporting Agency: NIDRR	Name and Address of Funding Agency's Procuring Contracting/Grants Officer: Theresa B. San Agustin, MD U.S. Department of Education PCP#4126 LBJ Basement Level 1 400 Maryland Ave., SW Washington, D.C. 20202-270
Performance Period: 10/1/2012-9/30/2017	Level of Funding: \$2,181,000
Brief Description of the Project's Goals: A 16-center collaborative database and clinical trials network for rehabilitation care after moderate and severe TBI.	
List of Specific Aims: clinical trials network for rehabilitation care after moderate and severe TBI	
List of Specific Aims: A longitudinal study of OEF/OIF service members	

UCB

KNIGHT, ROBERT

R37 NS021135 (Knight) 09/09/1985 – 06/30/2017 2.0 summer months
NIH/NINDS \$286,844

Attention, orientation and human prefrontal cortex

This grant examines the contribution of human prefrontal cortex to executive control of goal-directed behavior using neuropsychological, EEG, and ECoG methods.

Role: Principal Investigator

R21 EY023565 (Kastner) 04/01/2014 – 03/31/2016 0.1 calendar month
NIH/NEI (SubK from Princeton) \$24,293

Attention network dynamics in the primate brain

This grant aims to study the neural basis of attention capacity in parallel studies in non-human primates and humans using single unit recordings and LFPs in monkeys and electrocorticography in humans.

Role: Co- Investigator

W911NF-14-2-0043 (Chang) 05/01/2014 – 04/30/2019 0.5 summer month
DoD/DARPA (SubK from UCSF) \$84,024

Unlearning Neural Systems Dysfunction in Neuropsychiatric Disorders

Task 1 aims to establish biologically plausible computational models for each SUBNETS condition.

Role: Consortium PI

2013070 (Deouell) 10/01/2014 – 09/30/18 As needed
US Israel, Binational Science Foundation \$40,348

Object Persistence Over Time – Behavioral, Electrocorticographic and Electroencephalographic Study in Humans

This proposal aims to define which neural signal tracks stimulus perception over time using electrocorticography.

Role: Co-Investigator

N/A (Knight) 05/01/2012 – 4/30/2017
Nielsen \$500,000

Unrestricted Gift Fund

This gift is used to support development of new methods to assess cortical function in humans.

JAGUST, WILLIAM

R01 AG044292 (Jagust) 09/01/2013 – 01/31/2019 1.5 academic month
NIH/NIA \$398,559 (LBNL)

Aging Brain, Cognition, and Dopamine

This project will use a PET imaging agent, FMT, to study the brain dopamine system in aging and examine how cognition, brain activity and resting state networks are altered as a function of age and dopamine loss.

Role: Principal Investigator

R01 AG034570 (Jagust) 09/15/2009 – 08/31/2015 1.32 acad 1 summer
NIH/NIA \$402,522 (LBNL)

Neural and biochemical mechanisms of cognitive aging

This project will use PIB-PET, EDG-PET and structural and functional MRI to define how beta-amyloid deposition produces cognitive decline in normal aging and to understand compensatory mechanisms in the aging brain.

Role: Principal Investigator

P01 AG019724 (Miller) 07/01/2001 – 08/31/2017 0.45 academic month
UC San Francisco (NIH/NIA Prime) \$50,765 (LBNL Subcontract)

Frontotemporal Dementia: Genes, Images, and Emotions – Clinical Criteria (Project 4)

The goal of this program project grant is to determine the imaging, emotional, social-cognitive, language, genetic and diagnostic features of frontotemporal lobar degeneration and related disorders including corticobasal degeneration, progressive supranuclear palsy and amyotrophic lateral sclerosis in contrast to Alzheimer's disease and healthy aging. Dr. Jagust's role as co-investigator is the acquisition and analysis of PIB-PET imaging data on a subgroup of the cohort.

U01 AG024904 (Weiner) NCIRE (NIH/NIA Prime)	09/30/2004 – 07/31/2016 \$291,362 (UC Berkeley Subcontract)	1.00 academic month
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Alzheimer's Disease Neuroimaging Initiative
This is a Multicenter Cooperative Agreement to evaluate longitudinal PET and MRI scanning in the natural history and clinical prediction of Alzheimer's disease. Dr. Jagust is Core Leader of the PET component of the project.

R01 AG032306 (Rosen) UC San Francisco (NIH/NIA Prime)	09/30/2009 – 08/31/2016 \$346,892 (UC Berkeley Subcontract)	1.30 academic month
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The Frontotemporal Lobar Degeneration Neuroimaging Initiative
This is a multicenter study to characterize biomarkers in FTLTD. Dr. Jagust is a co-investigator responsible for PET scanning and analysis and QC of PET images.

R01 DA034685 (D'Esposito) UC Berkeley (NIH Prime)	07/01/2013 – 06/30/2018 \$150,435 (LBNL Subcontract)	1 academic month
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Dopamine & Frontostriatal Function
The goals of this project are to determine the role of dopamine in cognition and to develop improved methods for imaging dopamine.

R01 AG045611 (Rabinovici) UC San Francisco (NIH/NIA Prime)	04/01/2014 – 03/31/2019 \$131,615 (LBNL subcontract)	1 academic month
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Early age-of-onset AD: Clinical heterogeneity and network degeneration
The goals of this project are to define patterns of network degeneration using resting state functional MRI in patients with AD. Dr. Jagust's lab will acquire PET data on the subjects in the project.

W81XWH-14-1-0462 (Weiner) NCIRE (DoD MRPRA Prime)	09/30/2014 – 09/29/2017 \$235,792 (UC Berkeley Subcontract)	1 academic month
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Effects of Traumatic Brain Injury and Post-Traumatic Stress Disorder and Alzheimer's Disease on Brain Tau in Vietnam Veterans Using ADNI
This project will use the ADNI infrastructure to study a number of dementia imaging biomarkers in Veterans with TBI and PTSD. Dr. Jagust leads the PET component of the project.

STANFORD
GHAJAR, JAMSHID

W911QY-14-C-0086 (Ghajar, Jamshid - Project 116140) 09/16/2014-09/15/2017 6.5 calendar
Department of the Army \$3,635,689

Agency contact: SHAWN P. HAUBNER

Contact email:

shawn.p.haubner.ctr@mail.mil

Brain Trauma Evidence-Based Consortium (B-TEC) (Subs: \$2,178,408)

Major Goals: To create a consortium of clinical researchers and methodologists with expertise in evidence-based medicine that will share data, pool resources, and collaborate to answer key questions about brain trauma.

Aims: **Objective #1.** To maximize the utility of current scientific efforts to address the epidemic of concussion and brain trauma, for the purpose of deriving a clinically useful classification system, and evidence-based guidelines for diagnosis, prognosis, treatment, and outcomes.

Objective #2. To create a Consortium among the neurotrauma community that will inspire a commitment to the principles of evidence-based medicine in the design and conduct of brain trauma research.

Objective #3. To establish an Evidence-based Clinical Research Coordinating and Training Center (CTC), integrating “best practice” fundamentals of clinical research with those of evidence-based medicine, which will have the capability to coordinate the next generation of studies required to answer key questions about brain trauma epidemiology, physiology, natural history, treatment, and outcomes.

Role: PI

EMORY
WRIGHT, DAVID

No Award # (Espinoza) 12/01/14 – 12/31/15 1.35 calendar months
Under Armour, Inc. \$500,000

Head Health Challenge II

The overall goal of this project is to develop an all-in-one, comprehensive concussion evaluation platform that can be deployed in real time. The evaluation program will incorporate currently recognized key pillars to concussion assessment within a single unit that is portable, objective, rapid, and simple to use.

Role: Co-Investigator

1R01NS089694 (Bruce) 09/30/14 – 06/30/16 0.30 calendar months
NIH / NINDS \$218,750

Ocular Fundus Abnormalities for Acute Risk Stratification in TIA and Minor Stroke

Using non-mydratic photography, this project is primarily designed to determine whether abnormalities of the ocularfundus are an independent predictor, above and beyond that of other clinical features and neuroimaging studies, of short-term (i.e., within 90 days) clinical outcomes (new stroke, cardiovascular events, and death) in patients presenting with TIA and minor stroke.

Role: Co-Investigator

5 R49 CE001494 (Houry) 08/01/14 – 07/31/16 (NCE) 0.60 calendar months
CDC \$612,582

Grants for Injury Control Research Centers

The Emory Center for Injury Control (ECIC) is a collaborative, multi-disciplinary research center aimed at reducing the burden of violence and unintentional injuries through a focus on research, education and training, and community outreach.

Role: Interim Site PI

1U01NS086607 (Frankel) 09/25/13 – 07/31/18 0.69 calendar months
NIH / NINDS \$250,000

Stroke Trials Network – Regional Coordinating Stroke Centers

The major goal of this project is to build a research network of investigators at metro-Atlanta hospitals for clinical trials to develop effective treatments for patients with stroke.

Role: Co-PI

2R01HL073387 (Richardson) 09/01/13 – 05/31/17 0.48 calendar
months
NIH / NHLBI (via Mt. Sinai) \$42,894
Community VOICES 3

The major goal of this project is to explore community attitudes toward the federal regulations that allow investigators to conduct emergency research without obtaining informed consent from participants.

Role: Co-Investigator

2U10NS059032 (Wright)	09/01/12 – 05/31/17	1.96 calendar months
NIH/NINDS	\$200,000	

Neurological Emergencies Treatment (NETT) Network Clinical Site Hubs

The major goal of this project is to build a research network of investigators at 10 metro-Atlanta hospitals for clinical trials to develop effective treatments for patients with neurological emergencies.

Role: PI

U01NS069498 (Barsan / Johnson)	08/01/2011 – 07/31/2016	0.12 calendar months
NIH / NINDS (via NETT)	Per Subject Payments	

Stroke Hyperglycemia Insulin Network Effort (SHINE)

The purpose of this study is to determine the efficacy and provide further safety data on the use of insulin infusion therapy for glucose control in hyperglycemic acute ischemic stroke patients.

Role: Site Co-Investigator

5R01NS071867 (Frankel)	05/01/11 – 04/30/16	0.30 calendar months
NIH / NINDS	\$217,789	

Biomarkers of Injury and Outcome in ProTECT III (BIO-ProTECT)

The major goal of this study is to determine whether protein biomarkers of traumatic brain injury predict outcome and response to treatment with progesterone,

Role: Co-Investigator

U01 NS062835 (Barsan / Johnston)	02/15/2010 – 08/31/2016	0.12 calendar months
NIH/NINDS (via NETT)	Per Subject Payments	

Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke Trial (POINT) Trial

The purpose of this study is to determine whether clopidogrel 75 mg/day by mouth after a loading dose of 600 mg is effective in improving survival free from major ischemic vascular events (ischemic stroke, myocardial infarction, and ischemic vascular death) at 90 days when initiated within 12 hours of TIA or minor ischemic stroke onset in patients receiving aspirin.

Role: Site Co-Investigator

5U01NS062778 (Wright)	07/01/09 – 06/30/16 (NCE)	2.40 calendar months
NIH/NINDS	\$1,568,850	

ProTECT III

The primary objective is to determine the effect of administering intravenous progesterone (initiated within 4 hours of injury and administered for 72 hours, followed by an additional 24 hour taper) vs. placebo for treating victims of moderate to severe (GCS 12-4) TBI.

Role: National PI

AEHN

WHYTE, JOHN

Nothing to Report

What other organizations were involved as partners?

Critical Path Institute (C-PATH)

Located in Tucson, AZ, C-PATH is an independent, non-profit organization dedicated to bringing scientists from the FDA, industry and academia together to collaborate and improve the drug development and regulatory process for medical products. TED has a binding consultant agreement with C-PATH in which the organization will assist Dr. Manley, the Co-Investigators and their staff (the TED Team) to achieve project objectives by providing consultation as the TED investigators prepare for regulatory evaluation processes. This will include, but is not limited to, preparation of Guidance Documents, Letters of Support, engaging in the Critical Path Innovation Meeting (CPIM) process, providing reviews of Seed Project applications, and responding to formal and informal requests for comment and information.

One Mind for Research

One Mind is an independent, non-profit organization dedicated to benefiting all affected by brain illness and injury through fostering fundamental changes to radically accelerate the development and implementation of improved diagnostics, treatments, and cures — while eliminating the stigma that comes with mental illness. Located in Seattle, WA, One Mind has provided direct salary support for the TED Administrative Core working out of UCSF. One Mind has also proved to be a valuable collaborative partner as demonstrated by their work on assisting with conversion of the TBI CDE's to CDISC standards.

Palantir

Palantir is a leading Silicon Valley data analysis and visualization company with its main office in Palo Alto, CA. Palantir has provided in-kind support to the TED initiative by way of technical and engineering support that is facilitating migration of a test component of the Metadataset to their Gotham platform. This platform allows for disparate datasets to be transformed into meaningfully designed objects and relationships. Analysts from Palantir are currently working with TED's data management team from University of Pittsburgh to harmonize data contained in the Metadataset to be loaded into the Gotham platform. Palantir has also hosted multiple webinars for TED investigators to provide training on the platform.

Clinical Data Interchange Standards Consortium (CDISC)

Located in Austin, TX, CDISC is a global, open, multidisciplinary, non-profit organization that has established standards to support the acquisition, exchange, submission and archive of clinical research data and metadata. TED investigators have been collaborating with CDISC to conform TBI Common Data Elements to CDISC standards for FDA regulatory submission.

Appendix 1

Consensus Conference 1 Agenda



TBI Endpoints Development (TED)

Consensus Conference 1

Agenda | February 2-3, 2015

Natcher Conference Center | NIH Campus

DAY 1 | February 2, 2015

I. Breakfast,
Introductions
& Overview
7:45-9:15am

Continental Breakfast at NIH Natcher Center (7:45 - 8:30am)
Geoff Manley, MD PhD | Introductions and Overview of the TED Technical Objectives and Aims (8:30am)
Col. Dallas Hack | “The TED Initiative’s Mission and Vision”
Q&A

II. Moderated
Tri-Part Panel
Sessions
9:15am-
12:15pm

Segment I Panel | FDA Regulatory Pathways

Co-Moderators | **Diane Stephenson, PhD** C-Path and **Nicholas Kozauer, MD** Quintiles
Rapporteurs | **Raquel Gardner, MD** and **Brian Fabian, MPA**

Lead Speaker | **Douglas Throckmorton, MD** (Center for Drug Evaluation & Research [CDER] Deputy Center Director for Regulatory Programs) “Overview of FDA Innovation”

Panelists | “FDA Divisions’ Roles in the Regulatory Readiness and DDT/MDDT Qualification Processes”

Billy Dunn, MD (Director, Division of Neurology Products, [CDER])

Peter Como, PhD (Lead Reviewer and Neuropsychologist: Division of Neurological and Physical Medicine Devices, Neurodiagnostic and Neurosurgical Devices Branch)

Allison Kumar (Sr. Project Manager: Office of the Center Director - Center for Devices and Radiological Health [CDRH])

Yasmin Choudhry, MD (Medical Officer and Reviewer: Study Endpoints and Labeling Development [SEALD] Office of New Drugs (OND) [CDER])

Christopher Leptak, MD (OND Biomarker Diagnostic Lead and Scientific Lead: Letter of Support) [CDER])

James Kaiser, MD (Medical Officer and Scientific Lead: CDER Critical Path Innovation Meeting [CPIM])

Q&A | **BREAK – 15 minutes**

Segment II Panel | Industry Perspectives on Regulatory Processes

Moderator | **Jam Ghajar, MD PhD** Director, Stanford Concussion and Brain Performance Center

Panelists

Jonathan Murray and team (Victor Miranda, Pam Schaub, Glen Sabin) | GE

Beth McQuiston, MD RD | Abbott Diagnostics

Donna Edmonds | ImmunArray

Dick Moberg | Moberg Research

Mark Lovell, PhD | ImPACT

Q&A | **BREAK – 10 minutes**

Segment III Panel | Regulatory Readiness Case Studies

Moderator | **Ramona Hicks, PhD** One Mind

Panelists | **Diane Stephenson, PhD** C-Path; **Michael Ropacki, PhD** Janssen; **Michael Singer, PhD** BrainScope

Q&A

III. Lunch
12:15-1pm

Box lunches | Self-selected seating in the Atrium and breakout rooms

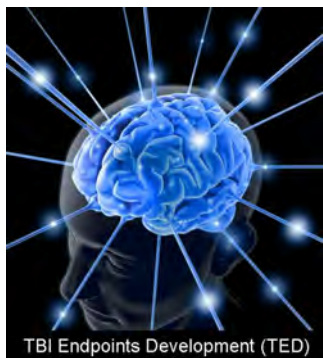
TBI Endpoints Development (TED)

Consensus Conference 1

Agenda | February 2-3, 2015

Natcher Conference Center | NIH Campus

DAY 1 February 2, 2015	
IV. Full Conference, followed by EWG Breakouts 1pm-4:30pm	Geoff Manley, MD, PhD Introduction and charge to Expert Working Groups, Data Aggregation and Integration, and Landscape Analyses Expert Working Group (EWG) Breakouts 1) Landscape Analyses; Identify existing COAs and biomarkers to be analyzed 2) Define roles of EWGs' membership 3) Create workstreams to achieve TED Stage I Aims OUTCOMES EWG Lead Michael McCrea, PhD Co-Leads Murray Stein, MD; Harvey Levin, PhD; Joseph Giacino, PhD; John Whyte, MD PhD Rapporteurs Yelena Guller Bodien, PhD and Sabrina Rose Taylor, PhD BLOOD-BASED BIOMARKER EWG Lead Ramon Diaz-Arrastia, MD PhD Co-Lead Kevin Wang, PhD Rapporteur John Yue, BS NEUROIMAGING BIOMARKER EWG Lead Pratik Mukherjee, MD PhD Co-Lead Arthur Toga, PhD Rapporteur Christine Mac Donald, PhD EMERGING TECHNOLOGIES EWG Lead Jam Ghajar, MD PhD Co-Lead Mona Hicks, PhD Rapporteur Ethan Winkler, MD PhD
V. Day 1 Close 4:45-5:00pm	Geoff Manley Preparation for Day 2



TBI Endpoints Development (TED)

Consensus Conference 1

Agenda | February 2-3, 2015

DAY 2 February 3, 2015	
VI. Breakfast and Welcome 7:45-8:45am	Continental Breakfast at NIH Natcher Center (7:45am-8:30am) Geoff Manley Welcome 8:30am
VII. EWG Reports 8:45-11:00am	EWG Leads Report-back from EWG breakout sessions BREAK 15 mins
VIII. Forward Planning/Adjourn 11:15am-1:00pm	Geoff Manley and EWG Leads Forward plan Execution of remaining Stage I Technical Objectives and Aims Q&A Wrap-up and Forward Plan

Appendix 2

Neuroimaging EWG Response to FDA Request for Information

TRACK-TBI and TED TEAM RESPONSE TO FDA BIOMARKER RFI

DOCKET NO: FDA-2014-N-2187

Written by Pratik Mukherjee, Christine Mac Donald, Diane Stephenson, Ann Robbins, Amy Markowitz, Geoffrey Manley

Introduction

This document is being submitted in response to the Federal Register notice on February 13, 2015; docket FDA-2014-N-2187 requesting comments on ‘Identifying of Potential Biomarkers for Qualification and Describing Contexts of Use To Address Areas Important to Drug Development.’ We appreciate the opportunity to provide public input on this important aspect of future drug development efforts and are pleased to propose the following biomarker for consideration.

A. Information Requirements

In general, submitted information should include the following for each biomarker nominated, as well as any other relevant information:

- **Areas that have a critical need for biomarkers to assist drug development:**

Stratification of Mild Traumatic Brain Injury (mTBI) Patients by Diagnostic Criteria for Therapeutic Intervention

Traumatic brain injury (TBI) affects 1.7 million patients annually in the U.S. alone¹⁻³. To date, there remains a dearth of effective clinical, laboratory and imaging biomarkers of patient outcome after TBI. Over 75% of cases of head injury are considered “mild” based on clinical criteria, defined as loss of consciousness 30 minutes or less, post-traumatic amnesia less than 24 hours, alteration of consciousness less than 24 hours, and unremarkable Computed Tomography (CT) scan (i.e. negative head CT)¹. As a group, mild TBI (mTBI) patients have generally been ascribed a good prognosis. However, there is convincing evidence that many mTBI patients have significant alterations in neuropsychiatric functioning within weeks to months of injury, and approximately 15% have measurable deficits persisting at 1 year post-injury.²⁻⁷ There is also a growing recognition that current classification schemes for TBI based on the Glasgow Coma Scale (GCS), the universal clinical index for head injury severity, has major limitations, with small *mean* effect sizes in long-term impairment potentially obscuring differences among diverse subgroups of TBI patients with very different prognoses.^{11,12} The GCS is by definition limited for mTBI in particular, since mTBI is defined as GCS scores of 13-15, with the majority of cases receiving the highest possible score of 15, indicating the lowest injury severity. As a result, the World Health Organization Collaborating Centre Task Force on mTBI has endorsed an urgent need for well-designed studies that determine risk factors for persistent impairment after mTBI, as a prerequisite for better triage to therapeutic interventions.⁸ Such treatments include early educational intervention, structured cognitive-behavioral therapy, and early mild physical activity, which result in fewer symptoms, lower mean severity of symptoms, less social disability, and fewer days off work.^{13,14} Progress beyond mere

definition of mTBI, toward evidence-based diagnosis, is essential for clinical trials that evaluate potential therapies.⁸⁻¹²

There is a critical need for more definitive diagnostic markers of mTBI for better stratification into therapeutic and rehabilitative interventions, as current diagnostic methods are insensitive to the more subtle underlying pathology following mTBI.

1. Currently, the only **imaging modality** recognized by the FDA for TBI is head computed tomography (CT). However, it is well established that head CT is grossly insensitive to pathology in mTBI, including concussions. Therefore, in many hospitals, in the absence of a lesion demonstrated by head CT, mTBI patients are often discharged without follow-up care. In a geographically diverse study of 878 Emergency Department (ED) visits for mTBI in the U.S.,¹³ 9% of patients received no discharge recommendations; 28% were instructed to return to ED only as needed, without other follow-up; 19% were referred to primary care; and 42% were referred to another, unspecified physician.
2. Best practices regarding intervention and rehabilitation following mTBI vary widely due to these insensitive techniques as it often becomes a judgment call on the part of the clinician as to what should happen next with the patient.
3. There has been a high failure rate of clinical trials for new mTBI therapies and it is believed that much of this failure can be attributed to the crude stratification tools currently in use. Specifically, by basing the inclusion criteria for clinical trials on our current 'gold standard' (i.e., head CT, GCS), it is likely that patients selected for new treatments also included those who would have never benefitted from the drug in the first place. An example of this would be the patient with presentation and/or endorsement of 'altered consciousness' and negative head CT which was in fact unrelated to mTBI as is the case with alcohol or drug use. It is also likely that there have been patients with real underlying pathology who were erroneously excluded or who were erroneously stratified as a 'Control' in the study. An example of this is the patient who did not endorse a change in neurological status following an event for motivational reasons that arise during minimization (i.e., an athlete who wants to return to play and doesn't want to be side-lined due to a concussion). Both scenarios introduce noise into the clinical trial sample that may be masking the true success of the new drug under development.

- **The name of the biomarker:**

We propose the following as a new imaging biomarker for mTBI. Specifically, **pathoanatomic lesions on brain magnetic resonance imaging (MRI)** will provide greater diagnostic sensitivity for better stratification of mTBI patients for therapeutic intervention.

- **The proposed context of use for the biomarker (if known):**

(a) Diagnostic Biomarker: Use of pathoanatomic lesions on brain magnetic resonance imaging (MRI) as a diagnostic tool to evaluate patients with mTBI.

Magnetic resonance imaging (MRI) is a standard imaging technique for the assessment of many brain disorders. Many prior investigations have shown that MRI at both 1.5 Tesla (1.5T) and 3 Tesla (3T) magnetic field strengths has much greater sensitivity to CT for small, focal traumatic intracranial lesions

in TBI¹⁴⁻¹⁸. A recent multicenter study using modern 3T protocols shows that approximately one-third of patients presenting to the ED with head injury, but with no head CT findings of TBI, do demonstrate acute trauma-related pathology on brain MRI, typically small cortical contusions and foci of hemorrhagic and/or non-hemorrhagic axonal shearing injury, also known as traumatic axonal injury (TAI).¹⁹

(b) Prognostic Biomarker: Use of pathoanatomic lesions on brain MRI related to measures of clinical outcome in patients with mTBI.

There is now ample data showing significant clinical and neurocognitive impairments in mTBI patients with intracranial abnormalities on MRI. A study of focal brain lesions in mTBI using 3T MRI found that mTBI patients performed significantly worse on acute neurocognitive tests, with milder but detectable deficits at 1 year³. Other studies demonstrate a correlation between intracranial MRI findings and intermediate-to-long-term outcome in mild-to-severe^{20,21} or moderate-to-severe TBI^{22,23}. However, these studies did not adjust for important, previously validated outcome predictors in moderate-to-severe TBI,^{24,25} including age, GCS, pupillary reactivity, and admission head CT features; thus, the differential predictive power of MRI was unknown.

This shortcoming was addressed in a more recent multicenter study of a cohort of 135 mTBI patients from highly diverse socioeconomic backgrounds and few exclusion criteria¹⁹; thus distinct from studies that have stringently excluded patients with potential confounding influences on outcome, such as history of prior head injury or advanced age. Given the high incidence of these features in the general population, and even greater incidence in those at high risk for TBI, this improves the generalizability of results. These results on a natural cross-section of mTBI patients at three Level I trauma centers is complementary to highly controlled studies of carefully selected patient samples. Factors across a range of domains were analyzed, including socioeconomic, clinical, and demographic factors, using a multivariate approach in order to mitigate any spurious inferences of causality between outcome and any single predictive feature. Also unique about this study is the greater specification of types of lesions that may be predictive, the control for other predictors, the careful use of the NIH TBI Common Data Elements (CDEs)^{26,27} to categorize the imaging findings, and the multicenter nature of the patient sample. The exquisite sensitivity of MRI for small cortical contusions and hemorrhagic axonal injury was demonstrated, and these MRI features improved mTBI outcome prediction after controlling for demographic/socioeconomic, clinical, and CT features. The addition of both CT and MRI pathoanatomic features of SAH, contusion and hemorrhagic axonal injury to a prognostic model of mTBI based on demographic/socioeconomic and clinical predictors alone results in a doubling of the explained variance in the 3-month Glasgow Outcome Scale – Extended (GOS-E), the most widely used endpoint for TBI.

(C) Predictive Biomarker: Use of pathoanatomic lesions on brain MRI as a patient stratification tool to select mTBI patients who are most likely to respond to a specific therapeutic treatment in a clinical trial setting.

Previous work has shown insensitivity of current diagnostic tools to the pathoanatomical underpinnings of mTBI. By including lesions observed on MRI as part of the inclusion criteria, patient selection for new therapeutic intervention will be better focused towards more specifically mTBI patients reducing the variance that can confound findings. In particular new drugs are seeking to target the underlying pathology be it axonal injury, neuroinflammation, edema, etc. will be better targeted toward those with

true underlying pathology by the addition of brain MRI lesion findings as studies will be more assured that those patients, in fact, have sustained injury.

- **The reason why the biomarker should be considered, taking into account its usefulness as a drug development tool:**

- Brain MRI is a **non-invasive** technology widely available in hospitals throughout the country and around the world. It provides greater sensitivity in the identification of brain pathology than head CT. And because it uses existing technology, it does not require significant hardware or software device development. This means that as a new biomarker, it can be quickly operationalized into practice for drug development trials.

- As a medical application, it can be easily ordered by a clinician, billed, and processed without any change to hospital technology systems and/or electronic medical records allowing for rapid dissemination for multi-center therapeutic studies.

- Pathoanatomic lesions on brain MRI have been shown to be associated with clinical outcome providing both diagnostic and prognostic value. There are precise definitions for pathoanatomic lesions on brain MRI from the NIH CDEs for TBI.^{26,27}

- This technique also provides a **non-invasive diagnostic tool** for monitoring the progress of any therapeutic intervention.

- **Any evidence that should be developed to support qualification of the biomarker:**

Current State-of-the-art:

Standardized reporting of pathoanatomic features, employing the TBI CDEs is a key prerequisite for progress in this field, beyond mere definition of mTBI, toward evidence-based diagnosis based on proven correlations of objective biomarkers with patient outcome.²⁶⁻²⁹ As such, uniform adherence to this standardized reporting should be considered to support qualification of pathoanatomic lesions on brain MRI as a diagnostic biomarker.

B. Questions and Requests

The FDA has requested response to the specific questions and requests below:

1. Are there specific aspects of drug development that could be enhanced through the development of biomarkers?

a. Please list the specific applications of biomarkers that address areas important to drug development:

- Use of diagnostic biomarkers for mTBI patient stratification in therapeutic trials, providing greater specificity of patients that might be most responsive to a new treatment. This will, in turn, lead to more robust clinical trial design and likely improve the trial findings.

- Use of prognostic biomarkers for mTBI patient stratification to identify patients who are likely to progress to poor outcome by allowing greater selectivity of 'at risk' populations to target with new

therapeutics. Pathoanatomic lesions on brain MRI in mTBI patients have been shown to portend worse outcome in a multi-center, population-based observational study.¹⁹

b. Please list the specific areas (for example, a specific disease area or an organ toxicity) needed for development of biomarkers important to drug development.

- Diagnostic and prognostic biomarkers for stratification of mTBI patients for therapeutic development (see Section 1)

c. Is there information or efforts which could be leveraged to advance these areas? If yes, please describe.

Prior multi-center studies utilizing magnetic resonance imaging in brain injury research can be leveraged for this purpose. The aforementioned studies above (see Section 1) provide a repository of data to support the notion of utilizing pathoanatomic lesions identified on MRI as a new diagnostic indicator for stratification into therapeutic intervention for drug development.

d. Are there areas that appear to be promising for the development of new biomarkers and for which collaborative engagement from stakeholders offers a path forward? If so, please explain.

We propose that the DOD-funded TBI Endpoint Development (TED) Program (grant #W81XWH-13-PHTBI-TED), an innovative public-private initiative that includes the NIH-funded multi-site TRACK-TBI project studying civilian TBI (Grant #1U01 NS086090-01) (PI Geoffrey T. Manley, UCSF), the Concussion Research Consortium (PI Michael McCrea Medical College of Wisconsin), a large, well-characterized sport TBI cohort, and CENC (W81XWH-12-PHTBI-CENC) (PI, David Cifu, VCU/Co-PI Ramon Diaz-Arrastia, USUHS) an extensive military/veteran TBI cohort, and a committed cadre of pharmaceutical, imaging, and emerging technology industry members, philanthropies, and patient advocacy organizations is uniquely positioned to assist FDA and other TBI public and private stakeholders in the development of utilities and guidelines on the use of diagnostic, MR imaging biomarkers for stratification of mTBI populations as it relates drug development.

d2. Are there groups positioned to accomplish this? If yes, please describe.

See response to d1.

e. Are there barriers that preclude engagement or investment in biomarkers for these priority areas? If yes, please explain.

- Lack of success thus far in TBI drug trials has resulted in fewer new TBI drug trials in which to test biomarkers.

- Additional costs for incorporating MRI-based diagnostics into clinical drug trials that required payment for MRI scans as an additional resource.

2. In each of these priority areas that are important to drug development, please provide the following information:

a. Biomarker: What specific biomarkers do you believe represent the greatest near-term opportunity to establish utility in drug development (i.e., that could be substantially advanced by facilitating discussion and consensus building)?

- Conventional MRI of pathoanatomic lesions following mTBI as a diagnostic and prognostic imaging biomarker for stratification into therapeutic intervention for clinical trials represent the strongest near-term opportunity.

b. Rationale: Why should the biomarker(s) be included on the list, taking into account its usefulness in regulatory decision making as a drug development tool?

Magnetic resonance imaging (MRI) is a standard imaging technique for the assessment of many brain disorders including brain injury. But currently, the only imaging modality recognized by the FDA for TBI is head computed tomography (CT). However, it is well established that head CT is grossly insensitive to pathology in mTBI, including concussions. Therefore, the use of CT findings as diagnostic criteria for drug development trials provides only a crude measure for patient selection and new, more sensitive techniques are warranted. Specifically, the inclusion of pathoanatomic lesions on MRI as an imaging biomarker of mTBI for stratification into therapeutic intervention.

c. Context of use: Can you please describe/propose a specific context of use for the biomarker(s)?

It is proposed that the identification of pathoanatomic lesions by brain MRI is a useful diagnostic tool to assist in the stratification of mTBI patients for clinical trials.

Target Population for Use:

Patients with mild traumatic brain injury based on current standard criteria:

1. Loss of consciousness < 30 minutes
2. Alteration of consciousness < 24 hours
3. Post-traumatic amnesia < 24 hours
4. Unremarkable head computed tomography scan (i.e., negative head CT)

Intended Application:

The intended use of pathoanatomic lesions on brain MRI is to enrich therapeutic trials for mTBI patients who have a high probability of benefitting from drug development aimed at brain injury pathology in which current diagnostic technology (i.e., CT scans) would have yielded negative findings and/or a more ambiguous result.

d. Evidentiary gaps: To support the proposed context of use, what do you see as the largest evidentiary gaps that need to be addressed to permit “fit for purpose” qualification?

- 1) Large-scale observational trial to validate brain MRI following mTBI as a prognostic biomarker using TBI CDEs, with intra-rater and inter-rater reliability measurements for the pathoanatomic analysis of the images as well as correlation of the results with validated patient outcomes using NIH CDEs for TBI outcome assessment.
- 2) Randomized clinical trials to validate brain MRI following mTBI as a predictive biomarker for drug development.
- 3) Sharing of imaging data to enable integration and analyses across studies and systematic collection of TBI CDEs.

e. How can these evidentiary gaps be addressed?

- Leverage existing MRI data from multi-center studies and apply TBI CDEs for the identification of pathoanatomic lesions following mTBI
- Additional federal funding, public-private partnerships
- FDA to incentivize data standardization implementation and data sharing (e.g., Letter of Support)
- Leverage and expand partnerships with relevant stakeholders (industry, non-profit organization, such as Critical Path Institute [C-Path])

f. Collaborative data sharing: Can any of these gaps be addressed by collaborative data sharing of existing data versus prospective studies specifically dedicated to addressing the gap?

Yes, collaborative data sharing can address some of these gaps by providing a large, pre-existing data set of MRI scans on mTBI patients upon which to apply TBI CDEs for the identification of pathoanatomic lesions with the intent of supporting the notion of MRI-based diagnostic biomarkers for better patient stratification in drug development.

3. Please indicate your affiliation from the following list: Academia, pharmaceutical sector, biotechnology sector, government, professional organization, non-profit organization, clinician, patient advocacy group, patient, or other (please provide specifics, if you choose other).

This document was drafted in support of the TRACK-TBI and TBI Endpoint Development (TED) Initiative Investigators led by Principal Investigator, Geoffrey Manley (Academia)

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Appendix 3

Blood-Based Biomarkers EWG Response to FDA Request for Information

TRACK-TBI and TED TEAM RESPONSE TO FDA BIOMARKER RFI

DOCKET NO: FDA-2014-N-2187

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Introduction

As per **Federal Register** / Vol. 80, No. 30, posted on Friday, February 13, 2015 in Docket No. FDA–2014–N–2187, the FDA is seeking public feedback to identify promising biomarker candidates in areas important to drug development, and to identify considerations for evidence needed to qualify various types of biomarkers for specific contexts of use (COU). FDA requests identification of specific biomarkers with a proposed context of use and of the type of evidence needed to support qualification. FDA intends to facilitate identification of the most promising biomarkers and the areas important to drug development and to promote efforts that will aid in the qualification and regulatory adoption of the drug development framework. After reviewing the information provided, FDA will post the collated information on its Web site.

A. Information Requirements

The FDA has requested the following information for each biomarker nominated, as well as any other relevant information.

- **Areas that have a critical need for biomarkers to assist drug development:**

Traumatic brain injury (TBI) is a complex neurologic condition that affects the entire demographic spectrum of patients. More than 2.5 million people in the United States annually seek medical care for a range of acute and sustained neurological and neuropsychiatric symptoms that are markedly heterogeneous; an estimated 2% of the U.S. population lives with TBI-caused disabilities, at a yearly cost of \$77 billion. As of 2015, no drug or device has been approved by FDA to treat TBI. Decades of well-designed clinical trials have failed. This disappointing progress stems, in part, from our inability to precisely diagnose this multi-factorial 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. Blunt, symptom-based TBI classification approaches divide patients into crude categories of mild, moderate, and severe, using the Glasgow Coma Scale; outcomes are measured using the equally rudimentary Glasgow Outcome Scale-Extended. These do not permit mechanistic targeting for clinical trials.

There is a critical need for simple, biofluid-based biomarkers capable of measuring injury severity and injury mechanism and selecting patients for trials of targeted therapeutic drug development, because:

(1) TBI is a heterogeneous condition characterized by variable mechanisms of injury and presentation (e.g., penetrating, focal vs. diffused impact), location of impact, as well as severity of impact. Sequelae and complications may evolve unpredictably over time. This presents a major population-selection challenge for clinical drug trials.

(2) The variable severity of TBI is neither readily nor definitively defined by a simple set of clinical tools. Current tools are the symptom-based Glasgow Coma Scale (GCS) and cranial computed tomography (CT) abnormality – each of which has significant deficits that could potentially be mitigated with the addition of prognostic and predictive TBI biomarkers.

(3) There are no FDA-approved therapies to treat any forms of TBI, despite over 200 significant clinical trials sponsored by the pharmaceutical industry and university and biotechnology entities, supported in full or in part by federal funding

agencies (e.g., NIH, DOD).

(4) TBI therapy development remains actively pursued– a search of *clinicaltrials.gov* performed on 3-18-2015 with these criteria (traumatic brain injury | Recruiting | Interventional Studies) identified 200 entries.

- **The name of the biomarker:**

We propose that **TBI protein biomarkers** may be useful in assisting drug development for use as **predictive, pharmacodynamic, or surrogate biomarkers** and that such TBI protein biomarker(s) ideally should have the following attributes (**Table 1**).

Table 1. Attributes of an ideal TBI protein biomarker to support TBI drug development.	
1	The protein biomarker levels can be readily measured in accessible biofluid such as cerebrospinal fluid, serum, plasma and/or whole blood in TBI patients. [For severe TBI (i.e. those TBI patients in neurointensive care unit), the biofluid type where the biomarker can be detected should be cerebrospinal fluid (CSF), serum, plasma and/or whole blood, while for moderate and mild TBI (e.g. those patients managed at Emergency Medicine Department or by general hospitalization), the biofluid type should be serum, plasma and/or whole blood.]
2	The protein biomarker levels are either elevated or decreased in biofluid samples from TBI subjects when compared to normal control counterparts
3	The protein biomarker has Low background or basal biofluid levels in >95% of general non-injured healthy control population.
4	The Protein biomarker detected in biofluid after TBI is derived from or originated from the injured brain as the major source.
5	The biomarker protein levels in the above-stated biofluids can be readily determined and quantified using sandwich ELISA or similar immunoassays with at least two assay formats or platforms
6	There are one or more publicly accessible assays for such biomarker with test-retest reliability and reproducibility assay that meet assay analytical performance requirements acceptable to FDA
7	The protein biomarker are elevated in various forms and/or severity of human TBI in the acute phase (3 h to 24 h post-injury) based on published evidence from multiple laboratories of institution
8	The protein biomarker is translational in nature with demonstrated evidence that there are parallel biofluid profile of the same biomarker in at least two different animal models of TBI (e.g. rodent control cortical impact, fluid percussion injury, close head injury, penetrating brain injury or blast overpressure-wave brain injury) - This will further facilitate the translational utilities of such biomarker in drug development.
9	The TBI protein biomarker should be sensitive to severity of TBI as defined by GCS, CT abnormality, and other measurements.
10	The TBI protein biomarker should allow for repeated detections in one of the above mentioned biofluid with a 48 h window following brain injury.
11	The TBI protein biomarker should have initial acute levels (within first 48 h postinjury) that correlates with currently available and commonly accepted of TBI patient outcome indices (such as Glasgow outcome scale-extended (GOS-E).
12	The TBI protein biomarker should have its post-TBI biofluid levels responsive to drug treatments.

We include a list of candidate CSF and/or blood-based TBI protein biomarkers that could be used as predictive, pharmacodynamic or efficacy-surrogate biomarkers to assist drug development (**Table 2**) [1], [2].

Table 2. Examples of potential TBI protein biomarkers that could have drug development-guiding utilities.					
TBI protein Biomarker	Full protein name	Origin	Animal TBI data	Human severe TBI data	Human mild TBI/Concussion data
GFAP (& BDPs)	Glial fibrillary acidic protein (and its breakdown products)	Glial injury	yes	yes	yes
UCH-L1	Ubiquitin C-terminal hydrolase-L1	Neural injury	yes	yes	yes
Tau (P-Tau)	Microtubule associated Tau protein (Phosphorylated Tau protein)	Axonal injury	yes	yes	yes
S100b	S100b protein	Glia /BBB	yes	yes	yes
SBDPs (SBDP150, SBDP145, SBDP120, SNTF)	α II-spectrin breakdown products of 150, 145 and 120 kDa and N-terminal spectrin fragment (~140kDa)	Axonal injury; Brain cell Necrosis-Apoptosis	yes	yes	yes (SNTF)
MBP	Myelin basic protein	De-myelination	yes	yes	-
NSE	Neuron specific enolase	Neural	yes	yes	-
NF-L, NF-H	Neurofilament protein-light Neurofilament-heavy (including phospho-neurofilament-H)	axonal	?	yes	yes (NFL- in CSF)
Footnote: The above list of markers is not exhaustive but reflects the current state-of the art. Other possible markers include neurofilament proteins MAP2 (microtubule associated protein 2A, 2B), H-FABP (heart-type fatty acid binding protein) and BDNF (brain derived neurotrophic factor) . But further studies are required for further clinical utility verification and biomarker characterization.					

Glial Fibrillary Acidic protein (GFAP)

As an example, we highlight the TBI biomarker **Glial Fibrillary Acidic protein (GFAP)**, which we believe fulfills most of the above listed attributes of a predictive, pharmacodynamic and/or efficacy-surrogate biomarker for TBI drug development **because:**

1. GFAP biomarker levels are elevated in biofluid such as cerebrospinal fluid and serum/plasma following severe TBI [3]-[6] and in serum and plasma samples after moderate to mild TBI [7], [8].
2. GFAP biomarker has low background or basal biofluid levels in >95% of general non-injured healthy controls [7], [9], [10].
3. GFAP biomarker, in the form of either the GFAP intact protein (50 kDa) or as a breakdown product (GFAP-BDPs; 44-38 kDa) is predominantly released from injured brain tissue into biofluid such as cerebrospinal fluid and serum/plasma shortly following TBI [3], [6].

4. GFAP biomarker protein levels in CSF can be readily determined and quantified using sandwich ELISA or similar immunoassays with at least two assay formats or platforms (human GFAP chemiluminescence assay (version SOP=5053, Banyan Biomarkers), human GFAP (Biovendor; Cat. #RD192072200R) or academic laboratory-made ELISA) [6], [7], [11], [12].
5. The above publicly accessible assays for GFAP have been through some levels of testing-retesting in terms of assay performance and clinical TBI utility reproducibility verification, but more formal analytic performance testing and standardization is needed for regulatory acceptance.
6. GFAP protein biomarker levels are elevated in various forms and/or severities of human TBI in the acute phase (3 h to 24 h post-injury) based on published evidence from multiple laboratories or institutions [6]-[8], [11]
7. In parallel with human TBI studies, GFAP elevations in CSF have been identified in several rat models of severe TBI (control cortical impact, penetrating brain injury blast overpressure wave brain injury) [13]-[15] (**Attachment A- OBTT** manuscripts) and as well as in serum /plasma samples in mild TBI models [14], [16]-[19]. There is additional evidence that the post-TBI elevation of GFAP is severity-dependent [15].
8. GFAP protein biomarker levels in CSF serum and/or plasma are sensitive to severity of TBI as defined by GCS, CT abnormality, MRI pathological alterations and outcomes [7]-[9], [20], [21] .
9. GFAP protein biomarker can be repeatedly measured in CSF and/or serum/plasma biofluid with a 48 h or longer window following brain injury [4], [7] (**Note: some additional human GFAP data in this area exist but are not yet published or in the public domain.**
10. The TBI protein biomarker should have initial acute levels (within first 48 h post-injury) that correlate with currently available and commonly accepted of TBI clinical outcome indices (e.g., Glasgow Outcome Scale-Extended [GOS-E]).
11. GFAP levels post-TBI should appear responsive to drug treatments.
12. In addition, there is rich preclinical and clinical data from observational studies as well as mounting evidence from interventional studies in which GFAP is being measured as a predictive, pharmacodynamic and/or efficacy-surrogate biomarker tool.

The following are a list of TBI therapeutic clinical and preclinical studies with incorporated protein biomarkers in the experimental design (**Table 3**):

(1) INTREPID-2566 study ClinicalTrials.gov Identifier: NCT00805818), DOD-sponsored (**Table 3**).

The purpose of this randomized, double-blind, placebo-controlled, dose-escalation study of NNZ-2566 is to assess the effect of an experimental drug, NNZ-2566 that is being developed as a treatment to decrease neuronal damage/death to the brain following moderate to severe TBI. Among the secondary outcomes is examination of the modification of the acute physiological processes in TBI by evaluating electroencephalographic (EEG) determinants in patients with moderate to severe TBI (defined as GCS 4-12), and biomarker levels.

- Biomarkers: GFAP, UCH-L1

(2) Blood Biomarkers of Injury and Outcome in Traumatic Brain Injury (BIO-ProTECT) (ClinicalTrials.gov Identifier: NCT01730443) and ProTECT III (ClinicalTrials.gov Identifier: NCT00822900), NIH-sponsored (**Table 3**).

This study examined serum biomarkers of structural brain injury in subjects with severe TBI (S100B, glial fibrillary acid protein, ubiquitin carboxyl-terminal esterase L1, SBDP150) and progesterone levels.

- Biomarkers: S100b, GFAP, UCH-L1 and SBDP150

-(3) **Operation Brain Trauma Therapy (OBTT)** is a DOD-sponsored multi-center consortium study (PI Dr. Pat Kochanek, Univ Pittsburgh) using three rat models: controlled cortical impact (Dr. Ed Dixon, Univ. Pittsburgh), penetrating brain injury (Dr. F. Tortella, WRAIR) and fluid percussion injury (Dr. Dietrich/Bramlett, Univ. Miami) (**Table 3**).

Screening of 5 drugs have been completed with at least one drug showing promising therapeutic efficacy in reducing brain lesion size and improving functional outcome in two of three models, which are correlated with reduction of serum GFAP levels at 24 h and/or reduction delta-GFAP levels (from 4- 24 h). (See **Attachment A** - OBTT manuscripts titles and abstracts, to be submitted to *Neurotrauma* for peer-reviewed publication).

- Biomarkers: GFAP, UCH-L1

Table 3. Clinical and preclinical TBI Intervention studies with protein biomarkers as secondary outcome or a component of score matrix

Study name	Study identifier	Sponsor / Funding agency	Summary of study	Outcome Measures	Biomarkers used:	Number of subjects	Duration	Meeting proceeding/ Publication
Study of NNZ-2566 in Patients With Traumatic Brain Injury (INTREPID2566)	ClinicalTrials.gov Identifier: NCT00805818	: Neuren Pharmaceuticals (industry self-funded)	A Phase 2 study Examining neuroprotective effects of peptidic drug (NNZ-2556) in severe non-penetrating TBI patients (moderate-severe, GCS 4-12)	<u>Primary</u> : Reduce adverse events (AEs) and serious adverse events (SAEs); <u>Secondary</u> : modifying global outcome; improvement in cognitive and neuropsychological functioning; modification of acute physiological processes (by EEG) and biomarker levels.	GFAP, UCH-L1 (study is still on-going)	~260	April 2010 -Aug. 2015 (projected)	Kochanek 2010?; first biomarker data poster from this study presented by Mondello et al. at Int. Neurotrauma Symposium (Budapest, HU, 2013).
Blood Biomarkers of Injury and Outcome in Traumatic Brain Injury (BIO-ProTECT); Progesterone for the Treatment of Traumatic Brain Injury III (ProTECT)	BIO-ProTECT ClinicalTrials.gov Identifier NCT01730443 Parent study ProTECT III ClinicalTrials.gov Identifier NCT00822900	BIO-ProTECT study: Emory Univ. (PI Dr. Michael Frankel) ProTECT III) study: Emory Univ. (PI Dr. David Wright	Observational study measuring protein biomarker levels correlation of progesterone treatment effects in a subset of severe TBI patients (ProTECT III) Examine Progesterone as Treatment of severe Traumatic Brain Injury In human	BIO-ProTECT <u>Primary</u> : S100B, GFAP, UCH-L1, SBDP150) and progesterone levels will be measured. [Time Frame: Baseline, 24 hours, 48 hours] ProTECT III <u>Primary</u> : Favorable outcome (by GOSE); <u>Secondary</u> : Mortality, DRS, 9 potentially associated adverse events	S100B, GFAP, UCH-L1, SBDP150 (Biomarker data completed but data not yet published)	BIO-ProTECT 576 ProTECT III 882	July 2011 – July 2014 (terminated) March 2010 – July 2014 (terminated)	Wright et al., N Engl J Med. 2014 Dec 25;371(26):2457–66.
Operation Brain Trauma Therapy (OBT)	DOD, grant #W81XWH-10-1-0623	Univ. Pittsburgh (PI Kochanek)	Use three rat models of TBI (Controlled cortical impact – CCI, fluid percussion injury- FPI and penetrating brain injury- PBBi) to screen for druggable candidates for neuroprotection	A composite score consisting of tissue preservation score (by histopathology), functional outcome score (by behavioral study endpoints) and biomarker reduction score	GFAP and UCH-L1 (measured at 4 and 24 h post-injury) (Biomarker data completed on five drug studies), more drug studies on going	Total rat number n~40 for FPI, n~40 for CCI and n~55 for PBBi for each drug Total rats with biomarker data, thus far ~ 674	2010 - 2015	Kochanek et al. ; J Trauma. 2011 ed. 2011 Jul;71(1 Suppl):S15–S24. A series of 8 manuscripts to be submitted in mid-2015 to Journal of Neurotrauma special suppl. Issue (for peer reviewed publication)- see ATTACHMENT A

- **The proposed context of use for the biomarker (if known):**

Proposed CONTEXT OF USE (COU) for TBI protein biomarkers (e.g. GFAP)

We propose three potential COUs for TBI biomarkers:

(a) Predictive Biomarker: Use of TBI protein biomarker (such as GFAP) as a patient stratification tool to select for TBI patients who are most likely to respond to a specific therapeutic treatment in a clinical trial setting.

(i) Currently, TBI is categorized according to the GCS symptom severity scale: severe (GCS 3-8), moderate (GCS 9-12) or mild (GCS 13-15); healthy control score a GCS of 15. Unfortunately, GCS was originally designed to categorize relatively severe TBI patients, thus its use for mild-moderate TBI is neither sufficiently sensitive nor accurate. As well, GCS sometimes cannot be assessed, e.g., if the patient is intoxicated. Thus, a biofluid-based TBI biomarker test could offer a superior, more objective and more quantitative marker of both injury and injury severity.

Further, based on preclinical studies and studies investigating the specific therapy, we hypothesize that TBI patients within a certain range of severity may be selectively responsive to a particular treatment. If TBI injury severity can be converted quantitatively within a desired range of one or more TBI predictive biomarkers (e.g. within 6-8 h post injury) we could use such a predictive biomarker to enroll targeted patient populations into these trials, as this subset of patients may be most likely to benefit from the treatment.

As noted, to date there are no FDA-approved drugs to treat severe or severe-moderate TBI, despite the fact that there have been more than 200 TBI therapeutic clinical trials in the last two decades [22]. Drug development can be assisted with a robust TBI-predictive biomarker as a guide to inclusion of the most responsive subset of patients [1], [23].

(ii) Cranial CT is the most commonly used tool to distinguish “moderate” from “mild” TBI; moderate TBI presents with CT abnormality while mild TBI does not (by definition). CT has been used for TBI patient stratification in therapeutic trials. Although about 85% of mild TBI patients recover spontaneously and fully from initial injury and transient post-concussive symptoms (PCS), the remaining 15% can develop a range of sustained neurological, neuropsychiatric symptoms. To date there are no predictive markers or indicators that can predict which individuals will develop sustained PCS. We hypothesize that this is the subset of patients most likely to be responsive to therapeutic treatment and thus should be the target population for new drug trials. The current lack of such a tool has also contributed to a relatively few clinical therapeutic trials targeting mild TBI.

If a TBI predictive biomarker exists that can help enrich the patient population in clinical trials to the more probable responders, it will be highly useful for addressing these unmet medical needs.

(b) Pharmacodynamic biomarker: Use of TBI protein biomarker (such as GFAP) as a response-indicator biomarker.

Biomarker test(s) could be performed on archived samples post-therapeutic intervention. The test(s) can be done with stand-alone biosamples or as pre-post therapeutic intervention samples from the same patients for pair-wise comparisons.

Our supposition is that if the therapy is designed to suppress pharmacodynamic biomarker signals, a failure to achieve such a biomarker reduction with treatment could indicate: (i) possible under-dosage, (ii) technical failure to deliver the targeted drug dose to the patient, or (iii) the patient’s unresponsiveness to this therapy. The use of the TBI pharmacodynamic biomarker in conjunction with primary outcome data could provide more detailed insights as to why clinical efficacy was not demonstrated in particular subjects and help shed light on future improvement of drug trials of the same or related compounds.

(c) Efficacy-surrogate biomarker: Use of a TBI protein biomarker to track efficacy of TBI therapies

We understand that establishing a protein biomarker as a TBI efficacy-surrogate endpoint will be a long and intense process requiring a wealth of supportive data, especially if such a marker can serve as a therapy-independent surrogate biomarker. However we want to initiate this dialogue with FDA stakeholders.

Using a TBI-derived protein biomarker as an efficacy-surrogate endpoint would permit us to track the efficacy or beneficial effects of a TBI therapy in a clinical trial setting. This could uncover additional pathways and provide feedback to facilitate the next therapeutic development. For example, about 15% of mild TBI cases develop a range of sustained neurological, neuropsychiatric symptoms that are markedly heterogeneous. GOS, GOS-E, the Disability Rating Scale (DRS), and various quality of life outcome measures have been established and used as mild TBI endpoints. However, most of these tools were originally developed for more severe forms of TBI, thus they are only variably sensitive to detect the diverse neurobehavioral deficits that could result from mild TBI. In addition, currently almost all severe TBI therapeutic trials use long term (3-6 mo.) outcome measures (e.g. GOS-E, DRS) as the sole primary outcome of drug efficacy. It might be desirable to have a biomarker measurement (reduction) as a secondary outcome measure. In addition, there are no good, fully developed consensus outcome measures to confirm clinical drug efficacy for TBI. We submit that a TBI efficacy-surrogate biomarker (such as GFAP) could help enhance and improve these aspects of TBI clinical trials.

As a general note, we envision that measurement / quantification of TBI biomarker (e.g. GFAP) levels in CSF, serum, plasma or whole blood samples will be assessed before and after therapeutic treatment to assist in drug development of clinical trials for TBI therapies.

- **The reason why the biomarker should be considered, taking into account its usefulness as a drug development tool**

- GFAP is now shown to be robustly and rapidly elevated in blood (serum, plasma) in a range of human TBI severities (from severe, moderate to mild) [4], [6]-[9], [11].

- For two biomarkers (GFAP and UCH-L1), at least one form of such assay (chemiluminescence) has been extensively characterized by Banyan Biomarkers, Inc. since this company intends to seek FDA *in vitro* diagnostic (IVD) approval of the tests as diagnostic tools. Therefore, reliability and reproducibility, limitation of quantification data of these two tests exists.

- GFAP (and UCH-L1) are also the subjects of observational TBI biomarker clinical trials (Evaluation of Biomarkers of Traumatic Brain Injury (ALERT-TBI) Sponsor: Biomarkers, Inc.; 2,000 mild-moderate TBI patients, ClinicalTrials.gov Identifier NCT01426919

- GFAP blood levels have been shown to be associated with poor outcome in TBI patients (*see above references*).

- A DOD-funded multi-year model drug screening study: OBTT (Operation Brain Trauma Therapy) (PI Dr. P. Kochanek, grant #W81XWH-10-1-0623) is the first paper published outlining this strategy [24] . Today more than 6 drugs have been screened with GFAP and UCH-L1 measured at 4 h and 24 h post-injury in three animal models of TBI (i.e., controlled cortical impact, fluid percussion injury and penetrating brain injury). The data thus strongly indicate that GFAP shows robust elevation in serum after all three types of TBI at both 4 h and 24 h post injury. GFAP levels appear to differ between drug-treated versus vehicle-treated animals with TBI. Several neurotrauma-scientific conference posters containing results of the biomarker profile and its responsiveness to drug treatments and correlation of neuropathology outcome have been reported in the last three years. The OBTT is now preparing a series of full manuscripts on these data. Dr. K. Wang, of the OBTT team has secured a set of manuscript titles and abstracts from OBTT to share with the NINDS-funded TRACK-TBI trial (see **Attachment A**). If desired, further confirmation and preprint of the above-stated manuscripts could potentially be obtained from OBTT study, PI Dr. Kochanek.

- Based on these attributes, we propose that certain TBI biomarkers (such as GFAP) can be used as a potential predictive biomarker, pharmacodynamic biomarker, and as an efficacy surrogate biomarker in guiding drug development and/or companion biomarker development.

- **Any evidence that should be established to support qualification of the biomarker?**

Current state-of-the-art:

- For the NNZ-2556, Progesterone PROTECT-III/ BioPROTECT clinical studies and OBTT (rat) studies, sandwich ELISA assay formats of GFAP and UCH-L1 have been performed on archived frozen serum/plasma sample aliquots (**Table 3**).
- GFAP (and UCH-L1) are also the subject of an observational TBI biomarker clinical trial (“Evaluation of Biomarkers of Traumatic Brain Injury (ALERT-TBI)” Sponsor: Banyan Biomarkers, Inc.; 2,000 mild-moderate TBI patients, ClinicalTrials.gov Identifier NCT01426919.) This trial recently concluded patient recruitment (June, 2014) using sandwich ELISA assay format (chemiluminescent readout) (**Table 3**).

Recommended evidence to be established to support biomarker qualification:

To address the regulatory readiness of TBI biomarker qualification we propose that the following types of evidence should be collected:

- Standardized assays format and qualified protein antigen standard and reference materials for the top TBI protein biomarkers candidates (e.g., GFAP assay) should be established. Assays may also undergo further analytical validation in accordance with GMP and GLP guidance or CLSI guidelines.
- Possible CSF, serum, plasma (e.g., EDTA-K3, heparin plasma) and whole blood cutoff -values for the potential TBI protein biomarker candidates identified in Table 2 (e.g., GFAP) under the defined three TBI-related biomarker utilities should be established.
- Correlation of blood-based (serum, plasma, whole blood) levels with central levels (CSF) after injury for the top TBI protein biomarkers candidates (e.g., GFAP) should be established.
- Baseline CSF, serum, plasma and whole blood values of top TBI protein biomarker candidates (e.g., GFAP) in different gender, race and ethnic groups should be established (optional).
- Potential adult age effects (age range 18- 80y) for baseline CSF, serum, plasma and whole blood values for top TBI protein biomarker candidates (e.g., GFAP) should be established

B. Questions and Requests

The FDA has requested response to the specific questions and requests below:

1. Are there specific aspects of drug development that could be enhanced through the development of biomarkers?

a. Please list the specific applications of biomarkers that address areas important to drug development.

- Use of TBI predictive biomarkers for patient stratification in therapeutic trials; to identify the TBI severity of injury that might be most responsive to treatment will enhance and improve TBI therapeutic trials.
- Use TBI predictive biomarkers for patient stratification to identify mild TBI patients that are likely to develop one or more post-concussive symptoms will enhance and improve TBI Tx trials.
- Currently there is no pharmacodynamic biomarker 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 will provide more detailed insights as to why clinical efficacy is not demonstrated in subsets of subjects

and help shed light on future improvement of drug trials of the same or related compounds.

- TBI-derived biomarkers could serve as potential efficacy-surrogate biomarkers. Currently, almost all severe TBI therapeutic trials use incidents of adverse events e.g., mortality as a short-term outcome measure, and GOS, GOS-E, DRS and quality of life as long-term (3-6 mo.) outcome measures for the primary endpoints of drug efficacy. However, 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 TBI. It might be desirable to have a biomarker measurement (reduction) as secondary outcome. A TBI efficacy-surrogate biomarker (such as GFAP) could help enhance and improve these aspects of TBI clinical trials.

b. Please list the specific areas (for example, a specific disease area or an organ toxicity) needed for development of biomarkers important to drug development.

-Biomarkers for Traumatic Brain Injury therapeutic development (see Section 1)

c. Is there information or efforts which could be leveraged to advance these areas? If yes, please describe.

- See Section 1, Tables 2, 3 and 4.

d1. Are there areas that appear to be promising for the development of new biomarkers and for which collaborative engagement from stakeholders offers a path forward? If so, please explain.

We propose that the DOD-funded TBI Endpoint Development (TED) Program (grant #W81XWH-13-PHTBI-TED), an innovative public-private initiative that includes the NIH-funded multi-site TRACK-TBI project studying civilian TBI (Grant #1U01 NS086090-01) (PI Geoffrey T. Manley, UCSF), the Concussion Research Consortium (PI Michael McCrea Medical College of Wisconsin), a large, well-characterized sport TBI cohort, and CENC (W81XWH-12-PHTBI-CENC) (PI, David Cifu, VCU/Co-PI Ramon Diaz-Arrastia, USUHS) an extensive military/veteran TBI cohort, and a committed cadre of pharmaceutical, imaging, and emerging technology industry members, philanthropies, and patient advocacy organizations is uniquely positioned to assist FDA and other TBI public and private stakeholders in the development of utilities and guidelines on the use of biomarkers for TBI drug development.

d2. Are there groups positioned to accomplish this? If yes, please describe.

See response to d1.

e. Are there barriers that preclude engagement or investment in biomarkers for these priority areas? If yes, please explain.

- Lack of success thus far in TBI drug trials has resulted in fewer new TBI drug trials in which to test biomarkers.

- Additional costs for incorporating GFAP or other biomarker into clinical drug trials

- Lack of both information dissimulation and endorsement by FDA limits current adaptation of blood-based biomarker in TBI drug trials.

2. In each of these priority areas that are important to drug development, please provide the following information:

a. Biomarker: What specific biomarkers do you believe represent the greatest near-term opportunity to establish utility in drug development (i.e., that could be substantially advanced by facilitating discussion and consensus building)?

- All evidence considered, protein biomarkers such as GFAP as **predictive and pharmacodynamic biomarkers** for TBI represent the strongest near-term opportunities.

Thus seeking **FDA letter of support** to use certain TBI biomarkers (such as GFAP) as predictive and pharmacodynamic biomarkers is considered a possible near-term opportunity to establish utility in drug development for TBI.

-As an intermediate to longer-term goal, assay qualification for the one or more top TBI protein biomarkers that can aid drug development as predictive and pharmacodynamic biomarkers should be pursued.

-As a long-term goal, protein biomarkers such as GFAP could also be considered as candidate efficacy-surrogate biomarkers for TBI therapeutic development. This represents a future opportunity.

b. Rationale: Why should the biomarker(s) be included on the list, taking into account its usefulness in regulatory decision making as a drug development tool?

Selected biomarkers such as GFAP represent a near-term opportunity based on the following:

-Existing clinical TBI biomarkers data thus far are encouraging that TBI biomarkers are sensitive enough to distinguish different severities of TBI (see above) in acute and longitudinal, observational TBI clinical studies.

-In the US, ongoing TRACK-TBI (NIH, Grant #1U01 NS086090-01) (2,700 TBI patients), GFAP will be one of the biomarkers assayed (ClinicalTrials.gov Identifier: NCT02119182). Two GFAP biomarker papers based on the preceding TRACK-TBI Pilot study (ClinicalTrials.gov Identifier: NCT01565551) have been published [8], [10] (see **Table 4**).

- In Europe, ongoing CENTER-TBI study (Collaborative European NeuroTrauma Effectiveness Research in TBI) (5,400 patients) funded by European Commission (FP7-HEALTH-2013-INNOVATION-1 Consortium grant, ## 602150-2) GFAP will be one of the biomarkers assayed (ClinicalTrials.gov Identifier: NCT02210221) [25] (see **Table 4**).

-Extensive GFAP data on drug effects in three rat models of TBI therapeutic study (OBTT) (see **Table 4** and **Attachment A**).

Table 4. Current observational TBI clinical studies with a major protein biomarker component							
Location	Project Name	Project Abbrev.	Funding agency	Target Population	Clinical sites	Main aims	Study period
Europe	Collaborative Research on Acute Traumatic brain injury in intensive care medicine in Europe	CENTER-TBI	European Commission	5,400 adult TBI – all levels of severity	60 hospitals; 6 analysis sites	Biomarkers, CER, Classification Outcome & prognosis	2013 - 2020
USA	Transforming Research and Clinical Knowledge in Traumatic Brain Injury	TRACK-TBI + TED	NIH (U01) + DOD (TED)	2,700 adult TBI, all levels of severity, 300 controls	11 hospitals; 5 analysis sites	Biomarkers, CER, Classification, Outcome & prognosis	2013- 2018 2014 - 2019
*CER: comparative effectiveness research; NIH – National Institute of Health; DOD – US Department of Defense; TED – TBI Endpoint Development							

c. Context of use: Can you please describe/propose a specific context of use for the biomarker(s)?

- Biomarkers will be used to enhance patient stratification in therapeutic trials; the ability to identify the TBI severity of

injury that might be most responsive to treatment will enhance and improve TBI therapeutic trials.

- TBI predictive biomarkers can be used for patient stratification to identify mild TBI patients that are likely to develop one or more post-concussive symptoms; this will enhance and improve TBI therapeutic trials.

- Currently there is no pharmacodynamic biomarker 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 will provide more detailed insights as to why clinical efficacy is not demonstrated in subsets of subjects and help shed light on future improvement of drug trials of the same or related compounds.

d. Evidentiary gaps: To support the proposed context of use, what do you see as the largest evidentiary gaps that need to be addressed to permit “fit for purpose” qualification?

- There are at least two current clinical trials of Tx for TBI that employed TBI biomarkers as secondary endpoint measures (**Table 3** and above). Both trials include the use of GFAP and UCH-L1 protein biomarkers. To complement current biomarker-supported trials, we identify the following **gaps** that need to be filled:

- Better understanding of GFAP biomarker properties in normal populations

- Most current TBI biomarker studies have used fit-for-purpose research-use only (RUO) assays on different platforms and with different antibody and antigen reagents. Thus there is a lack of standardized antibody reagents, antigen standards and GFAP assay format. In addition, publically available test-retest reliability and general analytical performance data on GFAP assay and/or other top TBI biomarker assays are also lacking.

- Formal clinical therapeutic trials supporting GFAP biomarker has predictive, pharmacodynamic and/or efficacy surrogate biomarker property in assisting TBI therapeutic development.

e. How can these evidentiary gaps be addressed?

- Additional federal funding, private-public funding partnership

- CDISC (Clinical Data Interchange Standards Consortium) standards for TBI Tx trials to include biomarkers

- Leverage existing funding (e.g., TED study)

- In conjunction with TED, implementation of a new TBI therapeutic clinical trial with an embedded, clearly defined or qualified GFAP assay and predefined endpoints regarding the biomarker utilities in such studies

- FDA to incentivize data standardization implementation and data sharing (e.g., Letter of Support)

- Working with NIST, academic biomarker assay leaders and commercial antigen and antibody and ELISA suppliers to establish standardized/approved GFAP assay format and reagents for GFAP and other top markers.

- Establishing test-retest reliability and general analytical performance requirements of top biomarker assays (e.g., GFAP) that are deemed suitable for reliability/reproducibility in multiple sites/labs.

- Leverage and expand partnerships with relevant stakeholders (industry, non-profit organization, such as Critical Path Institute [C-Path])

f. Collaborative data sharing: Can any of these gaps be addressed by collaborative data sharing of existing data versus prospective studies specifically dedicated to addressing the gap?

- Yes, collaborative data sharing can enhance private-public partnerships

3. Please indicate your affiliation from the following list:

Academia, pharmaceutical sector, biotechnology sector, government, professional organization, non-profit organization, clinician, patient advocacy group, patient, or other (please provide specifics, if you choose other).

- TBI Endpoint Development (TED) Investigators Team

Kevin K.W. Wang, (Academia: Univ. Florida)

Diane Stephenson (Not-for-profit: C-Path)

Ann Robbins (Not-for-profit: C-Path)

Amy Markowitz (Academia: UCSF)

Ramon Diaz Arrastia (Academia: USUHS)

Andreas Jeromin (Industry: Quanterix Corporation)

Geoffrey Manley (Academia: UCSF)

- National Neurotrauma Association

- International Brain Injury Association

- The Academy for Multidisciplinary Neurotraumatology (AMN)

- American Association of Neurological Surgeons

- Journal of Neurotrauma

- DOD

- NINDS/ NIH

- Veterans Affairs administration

- Banyan Biomarkers, Inc. (Industry)

- ABBOTT Diagnostics (Industry)

- Quanterix Corporation (industry)

- CENTER-TBI project (Academia: Andrew Maas; David Menon; Project manager: Annina Sorgner)

- TRACK-TBI project (Academia: Geoff Manley and colleagues)

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APPENDIX A

Titles and Authors¹ for *Journal of Neurotrauma* – Special Issue on OBTT Study

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7. Mondello, S., Shear, D.A., Bramlett, H.M., Dixon, C.E., Schmid, K.W., Dietrich, D.W., Wang, K.K.W., Hayes, R.L., Povlishock, J., Tortella, F.C., and Kochanek, P.M. (2015). Insight into Preclinical Models of Traumatic Brain Injury Using Circulating Brain Damage Biomarkers: Findings of Operations Brain Trauma Therapy. *J. Neurotrauma*, in preparation.
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¹Preliminary listing of authors and titles.

¹**Note, these represent preliminary drafts.**

Operation Brain Trauma Therapy: Approach to modeling, therapy evaluation, drug selection, and biomarker assessments, for a multi-center pre-clinical drug screening consortium for acute therapies in severe traumatic brain injury.

Patrick M. Kochanek, Helen M. Bramlett, C. Edward Dixon, Deborah Shear, W. Dalton Dietrich, Kara E. Schmid, Stefania Mondello, Kevin Wang, Ronald L. Hayes, John Povlishock, Frank C. Tortella

Abstract:

Traumatic brain injury (TBI) represented the signature injury in both the Iraq and Afghan wars, and the magnitude of its importance in the civilian setting is also finally being recognized. Given the scope of the problem, new therapies are needed across the continuum of care. Few therapies have been shown to be successful. In severe TBI, current guidelines-based acute therapies are focused on the reduction of intracranial hypertension and optimization cerebral perfusion. One factor considered important to the failure of drug development and translation in TBI relates to the recognition that TBI is extremely heterogeneous and presents with multiple phenotypes even within the category of severe injury. To address this possibility and attempt to bring the most promising therapies to clinical trials, we developed Operation brain trauma therapy (OBTT), a multi-center, pre-clinical drug screening consortium for acute therapies in severe TBI. OBTT was developed to include a spectrum of established TBI models at experienced centers and assess the effect of promising therapies on both conventional outcomes and circulating biomarker levels. In this review, we outline the approach to TBI modeling, evaluation of therapies, drug selection, and biomarker assessments for OBTT, and provide a framework for reports in this issue on the first five therapies evaluated by the Consortium.

Operation Brain Trauma Therapy: Nicotinamide Treatment in Traumatic Brain Injury

Deborah A. Shear, C. Edward Dixon, Helen M. Bramlett, Stefania Mondello, W. Dalton Dietrich, Ying Deng-Bryant, Kara E. Schmid, Kevin K.W. Wang, Ronald L. Hayes, John T. Povlishock, Patrick M. Kochanek and Frank C. Tortella

ABSTRACT

Nicotinamide (Vitamin B₃) was the first drug selected for cross-model testing by the Operation Brain Trauma Therapy (OBTT) consortium based on a compelling record of positive results in preclinical models of traumatic brain injury (TBI). Adult male Sprague-Dawley rats were exposed to either moderate fluid percussion injury (FPI), controlled cortical impact injury (CCI) or penetrating ballistic-like brain injury (PBBI). Nicotinamide (50 or 500 mg/kg) was delivered intravenously (IV) at 15m and 24h after injury with subsequent behavioral, biomarker and histopathological outcome assessments. There was an intermediate beneficial effect on balance beam performance with the high (500 mg/kg) dose in the CCI model, but no significant therapeutic benefit was detected on any other motor task across the OBTT TBI models. There was an intermediate benefit on working memory with the high dose in the FPI model. However, a negative effect of the low (50 mg/kg) dose was observed on cognitive outcome in the CCI model and no cognitive improvement was observed in the PBBI model. Lesion volume analysis showed no treatment effects after either FPI or PBBI, but the high dose of nicotinamide resulted in significant hemispheric tissue sparing in the CCI model. Biomarker assessments included measurements of GFAP and UCH-LI in blood at 4 or 24 h after injury. Negative effects (both doses) were detected on biomarker levels of GFAP following FPI and on biomarker levels of UCH-L1 following PBBI. However, the high dose of nicotinamide reduced GFAP levels following both PBBI and CCI. Overall, our results showed a surprising lack of benefit from low dose nicotinamide. In contrast, and partly in keeping with the literature, some benefit was achieved with the high dose. However, the marginal benefits achieved with nicotinamide, which appeared sporadically across the TBI models, failed to meet expectations established by the literature and reduced enthusiasm for further investigation by the OBTT Consortium.

Operation Brain Trauma Therapy: Erythropoietin Treatment in Traumatic Brain Injury

Helen M. Bramlett, W. Dalton Dietrich, C. Edward Dixon, Deborah A. Shear, Kara E. Schmid, Stefania Mondello, Kevin K.W. Wang, Ronald L. Hayes, John T. Povlishock, Frank C. Tortella, and Patrick M. Kochanek

ABSTRACT

Experimental studies targeting traumatic brain injury (TBI) have reported that erythropoietin (EPO) is an endogenous mediator of neuroprotection in multiple models. In addition to its neuroprotective effects, EPO treatment has also been shown to enhance reparative processes including angiogenesis and neurogenesis. Based on compelling preclinical data, EPO was tested by the Operation Brain Trauma Therapy (OBTT) consortium to evaluate therapeutic potential in multiple TBI models in parallel to biomarker assessments. Based on the pre-clinical TBI literature, two doses of EPO (5,000 and 10,000 IU/kg) were tested given at 15 min after moderate fluid percussion brain injury (FPI), controlled cortical impact (CCI) or penetrating ballistic like brain injury (PBBi) with subsequent behavioral, biomarker and histopathological outcome assessments. There was a significant benefit on beamwalk testing with the 5,000 IU dose in the CCI model, but no benefit on any other motor task across models in the OBTT consortium. Also, no benefit of EPO treatment across the three TBI models was noted using the Morris water maze to assess cognitive deficits. Biomarker assessments included measurements of GFAP and UCH-L1 in blood at 4 or 24 h after injury. No treatment effects were seen on biomarker levels after FPI or PBBi whereas significant treatment alterations in UCH-L1 were seen with EPO at 4 and 24 h after CCI. Lesion volume analysis showed no treatment effects after either FPI or CCI, however, with the 5,000 IU/kg dose of EPO, a paradoxical increase in lesion volume and percent hemispheric tissue loss were seen after PBBi. Our data indicate a surprising lack of efficiency of EPO across three established TBI models in terms of behavioral, histopathological and biomarker assessments. Although we cannot rule out the possibility that other doses or more prolonged treatment could have shown different effects, the general lack of efficacy of EPO reduced enthusiasm for its further investigation by the OBTT consortium.

Operation Brain Trauma Therapy: Cyclosporine A Treatment in Traumatic Brain Injury

C. Edward Dixon, Helen M. Bramlett, W. Dalton Dietrich, , Deborah A. Shear, Ying Deng-Bryant, Stefania Mondello, Kevin K.W. Wang, Ronald L. Hayes, John T. Povlishock, Frank C. Tortella, and Patrick M. Kochanek

ABSTRACT

OBTT is a consortium of investigators using multiple pre-clinical TBI models to bring acute therapies to clinical trials. To screen therapies we use three rat models (parasagittal fluid percussion injury [FPI], controlled cortical impact [CCI], and penetrating ballistic-like brain injury [PBBI]). We report results of the 3rd therapy (cyclosporin-A; Cyclosporine; [CsA]) tested by OBTT. At each site, rats were randomized to treatment with an identical regimen (TBI+vehicle, TBI+CsA [10 mg/kg] or TBI+CsA [20mg/kg] given IV at 15min and 24h after injury, and sham). We assessed motor and Morris water maze (MWM) tasks over 3 wks after TBI and lesion volume and hemispheric tissue loss at 21d. In FPI, CsA (10mg/kg) produced histological protection but 20mg/kg worsened working memory. In CCI, CsA (20 mg/kg) impaired MWM performance; surprisingly neither dose showed benefit on any outcome. After PBBI neither dose produced benefit on any outcome and mortality was increased (20mg/kg) partly caused by the vehicle. In OBTT, CsA produced complex effects with histological protection at the lowest dose in the least severe model (FPI), but only deleterious effects as model severity increased (CCI and PBBI). Biomarker assessments included measurements of GFAP and UCH-LI in blood at 4 or 24h after injury. No positive treatment effects were seen on biomarker levels in any of the models whereas significant increase in 24h UCH-L1 levels were seen with CsA (20mg/kg) after CCI and 24h GFAP levels in both CsA treated groups in the PBBI model. Lack of behavioral protection in any model, indicators of toxicity, and a narrow therapeutic index reduce enthusiasm for clinical translation.

Operation Brain Trauma Therapy: Cross-Model Comparison of Chronic Oral Administration of Simvastatin following Traumatic Brain Injury

Andrea Mountney, Helen M. Bramlett, C. Edward Dixon, Stefania Mondello, Dalton Dietrich, Kevin K.W. Wang, Kara E. Schmid, Ronald L. Hayes, John T. Povlishock, Frank Tortella, Patrick M. Kochanek and Deborah A. Shear

ABSTRACT

Simvastatin, the 4th drug selected for testing by OBTT, is a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor used clinically to reduce serum cholesterol. Additionally, Simvastatin has been reported to demonstrate potent anti-neuroinflammatory and brain edema reducing effects and has shown promise in promoting functional recovery in preclinical models of traumatic brain injury (TBI). The purpose of this study was to assess the potential neuroprotective effects of oral administration of Simvastatin on neurobehavioral, histopathological and biomarker outcome measures compared across three pre-clinical TBI animal models. Adult male Sprague-Dawley rats were exposed to either parasagittal fluid percussion injury (FPI), controlled cortical impact injury (CCI) or penetrating ballistic-like brain injury (PBBI). Simvastatin (1 or 5 mg/kg) was delivered via oral gavage at 3 h post-injury and continued once daily out to 14 days post-injury. Results indicated an intermediate effect of Simvastatin across models on motor performance on the gridwalk (FPI), balance beam (CCI) and rotarod tasks (PBBI). However no significant therapeutic benefit was detected on cognitive outcome across the OBTT TBI models. In fact, MWM performance was actually worsened by treatment in the FPI model and scored full negative points for low dose in the MWM latency and swim distance to locate the hidden platform. There was no benefit across models on histology. Simvastatin also produced negative effects on GFAP biomarker outcomes that were evident in the FPI and PBBI models. Overall, the current findings support only modest motor benefit of Simvastatin using a literature based oral treatment regimen and as such, will not be further pursued by OBTT.

Operation Brain Trauma Therapy: Early Levetiracetam Treatment in Traumatic Brain Injury

Megan Browning, Deborah Shear, Helen M. Bramlett, C. Edward Dixon, Stefania Mondello, Kara E. Schmid, Samuel M. Poloyac, W. Dalton Dietrich, Ronald L. Hayes, Kevin Wang, John Povlishock, Michael Catania, Olena Glushakova, Frank C. Tortella, Patrick M. Kochanek

ABSTRACT

Levetiracetam (LEV) is a second generation anti-epileptic drug that targets seizures via novel pathways. There is a growing understanding of its neuroprotective properties. Coupled with a favorable safety profile and increasing empiric use in post-traumatic patients, it was the fifth drug selected for testing by Operation Brain Trauma Therapy (OBT) in multiple TBI models in tandem with biomarker assessments. We assessed the efficacy of a single 15 min post-injury IV dose (54 or 170 mg/kg) on behavioral, histo-pathological, and biomarker outcomes over 21d after parasagittal fluid percussion brain injury (FPI), controlled cortical impact (CCI), and penetrating ballistic like brain injury (PBLI) in rats. In FPI, there was no benefit on motor function but on Morris water maze (MWM) testing both LEV treated groups showed improved latencies and path lengths vs vehicle ($p<0.05$). On probe trial, the vehicle group was impaired vs sham, but both LEV treated groups did not differ vs sham, and the 54mg/kg group was improved vs vehicle ($p<0.05$). No benefit on histology was seen. In CCI, there was a motor benefit on beam balance at 170mg/kg ($p<0.05$ vs vehicle). On MWM the 54 mg/kg dose was improved and not different from sham but probe trail did not differ between groups for either dose. There was a reduction in hemispheric tissue loss ($p<0.05$ vs vehicle) with 170mg/kg. In PBLI there was no motor or cognitive benefit from either dose and no benefit on histology. Biomarker assessments included measurements of GFAP and UCH-L1 in blood at 4 and 24h after TBI. In CCI, 24h GFAP blood levels were lower in the 170mg/kg group vs vehicle ($p<0.05$). In PBLI, GFAP blood levels were increased in vehicle and 170mg/kg groups vs sham ($p<0.05$) but not in the 54mg/kg group. No treatment effects were seen for UCH-L1 levels across models. Early single IV LEV produced multiple benefits in CCI and FPI and an effect on GFAP levels in PBLI. LEV achieved 10 points each in the low and high doses in the OBT scoring matrix, is the most promising drug tested thus far by OBT, and the only drug to improve cognitive outcome in any model. Our data suggest that further pre-clinical studies are warranted including dose optimization, therapeutic window, and also potential for clinical translation. Our data also suggest theranostic potential for GFAP as a biomarker in pre-clinical therapy screening in TBI.

Operation Brain Trauma Therapy: Insight into Preclinical Models of Traumatic Brain Injury Using Circulating Brain Damage Biomarkers

Stefania Mondello, Deborah A. Shear, Helen M. Bramlett, C. Edward Dixon, Kara Schmid, W. Dalton Dietrich, Kevin K. Wang, Ronald L. Hayes, John Povlishock, Frank C. Tortella, Patrick M. Kochanek

ABSTRACT

Operation Brain Trauma Therapy (OBTT) is a multi-center pre-clinical drug screening consortium testing promising therapies for traumatic brain injury (TBI) in 3 well-established TBI models, namely parasagittal fluid percussion injury (FPI), controlled cortical impact (CCI), and penetrating ballistic-like brain injury (PBBI). The present work presents unique characterization of these models using conventional histological and behavioral outcomes and novel candidate biomarkers from the first three treatment trials of OBTT. Adult rats were subjected to CCI, FPI, or PBBI and treated with vehicle. Sham rats underwent all manipulations except trauma. The glial marker glial fibrillary acidic protein (GFAP) and the neuronal marker ubiquitin C-terminal hydrolase (UCH-L1) were measured by ELISA in blood at 4, 24 h and their delta 24-4 h was calculated for each marker. Comparing sham groups across experiments no differences were found in the same model. Similarly, comparing TBI+vehicle groups across experiments no differences were found in the same model. Acute increases in GFAP were evident in injured rats in each model, with significant differences in terms of levels and temporal patterns that were mirrored by significant differences in delta 24-4h GFAP levels as well as neuropathological and behavioral outcomes. UCH-L1 showed similar tendencies albeit with less robust differences between sham and injury groups. Significant differences were also found comparing shams across the models. Our findings (1) demonstrate that experimental TBI models display specific biomarker profiles, functional deficits and pathological consequence in brain tissue, (2) support the concept that there are fundamentally different cellular, molecular and pathophysiological responses triggered by TBI in distinct rat TBI models, and (3) help advance our neurobiological understanding of TBI providing opportunities for a successful translational research and holding promise for targeted theranostic applications.

Operation Brain Trauma Therapy: Synthesis of Findings, Current Investigations, and Future Directions

Patrick M. Kochanek, MD, Helen M. Bramlett, Deborah Shear, C. Edward Dixon, Stefania Mondello, John T. Povlishock, Ronald L. Hayes, Kevin K. Wang, W. Dalton Dietrich, Samuel M. Poloyac, Philip E. Empey, Michael Catania, John Anagli, Olena Glushakova, Frank C. Tortella

ABSTRACT

Operation Brain Trauma Therapy (OBTT) is a fully operational, rigorous, and productive multi-center, pre-clinical drug and circulating biomarker screening consortium for the field of traumatic brain injury (TBI). In this manuscript, we synthesize the findings from the first five therapies tested by OBTT, and discuss both the current work that is ongoing and potential future directions. Based on the results generated from the first five therapies tested within the exacting approach used by OBTT, four (nicotinamide, erythropoietin, cyclosporine A, and simvastatin) performed below or well below what was expected based on the published literature. However, OBTT has identified the early post-TBI administration of levetiracetam as a promising agent and has advanced it up the phylogenic scale to a FPI model in micropigs. The 6th and 7th therapies have just completed testing (glibenclamide and Kollidon VA 64) and an 8th drug (AER 271) is in testing. Incorporation of circulating brain injury biomarker assessments into these pre-clinical studies suggests considerable potential for diagnostic and theranostic utility of glial fibrillary acidic protein (GFAP) in pre-clinical studies. Given the concerns related to what has been described as a reproducibility crisis in basic and pre-clinical research, and the failures in clinical translation of therapies in TBI, rigorous multi-center, pre-clinical approaches to therapeutic screening such as OBTT may be important for the ultimate translation of therapies to the human condition.

Appendix 4

Metadataset Table of Contents

Metadataset Baseline Assessments Table

Metadataset Clinical Data Domains Table

TED Metadataset Table of Contents
(10/29/2015)

Study Name	Timepoints	Sample Size	Sample Size Mild Moderate Severe	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	ED, Hospital, Rehab, 3 Month, 6 Month, 12 month	586	Mild: 480 Mod: 28 Severe: 42 Unk: 5	Adults/Children with TBI	Observational	12 months	GCS 3-15	No	Yes (plasma, whole blood)	Yes	Yes
TRACK-TBI	ED, 2 week, 3 Month, 6 month, 12 month	1200 as of 10/29/15	TBD	Adults/Children with TBI	Observational	12 months	GCS 3-15	No	Yes (serum, plasma, DNA, RNA)	Yes	Yes
TBicare	ED, day 1, 2, 3, 7, 6 months, 12 months.	203	Mild: 103 Mod: 35 Severe: 64	Adult patients, age ≥ 18 years, with clinically diagnosed mild, moderate or severe brain trauma	Observational	12 months	Very mild to severe	Yes	Yes (blood)	Yes	Yes
Concussion Research Consortium (CRC)	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, posttraumatic amnesia, retrograde amnesia	Yes	No	TBD	Yes - in select sub-studies
ProTECT III	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)	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	daily timepoints after injury (day 1-7), 3 follow up timepoints at 30 day, 90 day, 180 day	1207	Mild: 651 Moderate: 116 Severe: 440	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)	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)	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

METADATASET BASELINE DATA DOMAINS
(Use TRACK, TRACK-Pilot as reference studies)

BASIC DEMOGRAPHICS	TRACK (n=1,146)**	TRACK- Pilot (n=586)	COBRIT (n=1,207)	MISSION CONNECT (330; 200 for obs)	Mukherjee R01* (n=234)	ProTECT (n=882)	CNRM (n=450)	CRC (~200)	Dilantin (n=404)	Valproate	Mag. Sulfare (n=499)
Number of controls in the study				65 (inter)	115						
Name	x	x					x		x	x	x
Gender (Sex)	x	x	x	x	x	x	x		x	x	x
Race (either single variable or checkbox)	x	x	x	x	x	x	x		x	x	x
White	x	x	x	x	x	x	x		x	x	x
Black	x	x	x	x	x	x	x		x	x	x
Asian	x	x	x	x	x	x	x		x	x	
Indian (Native American?)	x	x			x		x		x	x	x
Alaskan Native/Inuit	x	x			x	x	x				
Native Hawaiian/Pacific Islander	x	x	x	x	x	x	x				
Ethnicity	x	x	x	x	x	x	x		x	x	x
Hispanic or Latino	x	x	x	x	x		x				
Non-Hispanic or Latino	x	x	x	x	x		x				
Unknown	x	x	x		x		x				
Birthplace	x	x					x				
Country of Residence	x	x									
Age	x	x	x	x	x	x	x	x	x	x	x
Primary Language	x	x	x	x	x						
Handedness	x	x	x	x	x		x				
Height	?	?		x				x			
Weight	?	?	x	x				x		x	x
Consent - Participant*	x	x	x		x		x		x	x	x
SOCIODEMOGRAPHICS (SES MEASURES)	TRACK	TRACK- Pilot	COBRIT	MISSION CONNECT	Mukherjee R01*	ProTECT	CNRM	CRC	Dilantin	Valproate	Mag. Sulfare
Employment Status	x	x	x		x	x	x				x
Total years	x	x									
Type of Employment (Field/Nature of job)	x	x					x				
Education (highest level)	x	x	x	x	x	x	x				x
Total years	x	x	x		x						
Annual Income			x	?							
Marital Status	x	x	x	x			x		x	x	x
Student Status (or currently in school)	x	x		x	x		x				
Living Situation (includes with WHOM)	x	x	x				x			x	x
Military Experience	x	x									
PRE-ED and EMERGENCY DEPARTMENT (ED) VARIABLES	TRACK	TRACK- Pilot	COBRIT	MISSION CONNECT	Mukherjee R01*	ProTECT	CNRM	CRC	Dilantin	Valproate	Mag. Sulfare
Time and date of visit	x	x	x	x	x	x	x		x	x	x
Method of Arrival (i.e. Ambulance)	x	x	x			x	x		x		x
Referral Information	x	x	x	x			x		x		

METADATASET BASELINE and Acute Injury DATA DOMAINS - CLINICAL MEASURES ONLY
(Use TRACK, TRACK-Pilot as reference studies)

BASIC MEASURES	TRACK (n=1,146)**	TRACK-Pilot (n=586)	COBRIT (n=1,207)	MISSION CONNECT (330; 200 for obs)	Mukherjee R01* (n=234)	ProTECT (n=882)	CNRM (n=450)	CRC (n~200)	Dilantin (n=404)	Valproate	Mag. Sulfare (n=499)
Systolic blood pressure (SBP)	mmHg	mmHg	mmHg		NS				mmHg		mmHg
Diastolic blood pressure (DBP)	mmHg	mmHg	mmHg		NS				mmHg		
Heart rate (HR)	not specified (NS)	NS	beats/min		NS				categorical		
Method (Cuff, arterial)			both								
Respiratory rate (RR)	NS	NS	breath/min		NS				NS		breath/min
Ventilation	X	X			X						
SpO2 (Oxygenation)	%	%	%		%						
PaO2 (measure of hypoxia)	mmHg	mmHg	mmHg								NS
O2	mmHg	mmHg	mmHg								
PCO2	mmHg	mmHg	mmHg								
FiO2	NS	NS	%								
Temperature	C	C	C		C						
Hematocrit	% (mMol/L)	%	%		%						
Hemoglobin	mMol/L	mMol/L	g/dL		NS						
Bicarbonate	mMol/L (mEq/L)	mMol/L									
WBC Count	10 ⁹ /L, 10 ³ /microm	10 ⁹ /L	10 ⁹ /L, 10 ³ /mm ³		NS						
Osmolality	Osm/L	Osm/L			NS						
INR	X	X	X		NS						
aPTT	sec	sec	sec		NS						
PT	sec	sec	sec		NS						
Sodium	mMol/L (mEq/L)	mMol/L	mMol/L		NS						
Potassium	mMol/L (mEq/L)	mMol/L	mMol/L		NS						
Chloride	mMol/L (mEq/L)	mMol/L			NS						
CO2	mMol/L (mEq/L)	mmol/L			NS						
Glucose	mg/dL (mMol/L)	mmol/L	mg/dL		NS						
Creatinine	mg/dL (microMol/L)	μmol/L	mg/dL		NS						
Bun (Blood urea nitrogen)	mg/dL (mMol/L)	mg/dL			NS						
Lactate	mg/dL (mMol/L)	mmol/L	mEq/L		NS						
pH (Blood)	scale	scale	scale								
BIOSPECIMENS	TRACK	TRACK-Pilot	COBRIT	MISSION CONNECT	Mukherjee R01*	ProTECT	CNRM	CRC	Dilantin	Valproate	Mag. Sulfare
Whole Blood	X	X	X	X							
Packed RBC (PRBC)			X								
Plasma	X	X	X	X							
Serum	X		X								
DNA	X				X						
RNA	X										
Saliva				X							
Platelets			X		X						

METADATASET BASELINE and Acute Injury DATA DOMAINS - CLINICAL MEASURES ONLY
(Use TRACK, TRACK-Pilot as reference studies)

IMAGING	TRACK	TRACK-Pilot	COBRIT	MISSION CONNECT	Mukherjee R01*	ProTECT	CNRM	CRC	Dilantin	Valproate	Mag. Sulfare
CT Scan Completed		x	x	x	x	x	x		x	x	x
Midline Shift		x	x	x	x	x	x				
Subdural hematoma			?	x	x	x	x	These are all recorded			x
Epidural hematoma			?	x	x	x	x	as part of inclusion			x
Sub. Hemorrhage			x		x	x	x		criteria		x
Intraventricular Hemorrhage			x	x	x		x				
Lesions		x	x			x					
Hydrocephalus		x	x								
Edema		x	x	x	x	x					x
Skull Fracture		x		x	x	x	x		x		x
Contusion(s)		x		x	x	x	x				x
Reported as positive or negative				x		x	x				
MRI Scan Completed				x	fMRI	x	x				
Reported as positive or negative						x	x				
MEDICAL HISTORY	TRACK	TRACK-Pilot	COBRIT	MISSION CONNECT	Mukherjee R01*	ProTECT	CNRM	CRC	Dilantin	Valproate	Mag. Sulfare
Medical history obtained	x	x		x			x				x
Cardiovascular	x	x	x	x			x				
Endocrine	x	x		x	x						
Eye, ear, nose and throat	x	x	x	x							
Gastrointestinal	x	x		x							
Neurologic	x	x		x	x						x
Oncologic	x	x	x	x			x				
Hematologic	x	x		x	x		x				
Pulmonary	x	x	x	x							
Hepatic	x	x	x								
Renal	x	x	x								
Muscoskeletal	x	x		x	x						
Developmental	x	x	x	x	x						
Spinal	x										x
Psychiatric	x	x	x	x	x		x	x			x
Depression and/or anxiety	x	x		x			x				
Post-traumatic stress disorder	x										
Bi-polar disorder	x			x							
Schizophrenia	x	x		x			x				
Sleep disorders	x	x					x				
Other/unknown	x	x		x				x			
INJURY	TRACK	TRACK-Pilot	COBRIT	MISSION CONNECT	Mukherjee R01*	ProTECT	CNRM	CRC	Dilantin	Valproate	Mag. Sulfare
Injury History	x	x	x		x		x	x			x
History of one or more TBI	x	x	x	x	x		x	x			x
Prior TBI treatment or hospital admittance	x	x		x	x		x				

METADATASET BASELINE and Acute Injury DATA DOMAINS - CLINICAL MEASURES ONLY

(Use TRACK, TRACK-Pilot as reference studies)

LOC recorded or reported	X	X			X						
PTA recorded or reported					X						
Injury Cause	X	X	X	X	X	X	X		X	X	X
Motor Vehicle	X	X	X	X	X	X	X		X	X	X
Suicide Attempt	X	X			X		X				
Assault	X	X	X	X	X	X	X		X	X	X
Mass violence	X	X									
Falls	X	X	X	X	X	X	X		X	X	X
Striking	X		X	X		X				X	X
Cutting	X									X	
Organized sports									X	X	X
Firearms, explosives		X								X	
Other (Unintentional)	X	X	X		X	X	X		X	X	X
Injury Mechanism	X				X	X	X		X		
Blast	X				X	X	X				
Falls (from > 1 meter)	X				X		X				
Acceration/Deceleration	X				X		X		X		
Direct impact	X				X		X				
Gunshot wound	X				X		X		Missile		
Crush	X				X		X				
Fragment/penetrating	X				X				X		
Safety Measures	X	X		X	X		X		X	X	X
Helmet/hat	X	X		X	X		X		X	X	X
Seat belt	X	X		X	X		X			X	X
Airbag	X	X		X	X		X				X
Non-Head Injury	X	X	X	X					X	X	X
Injury Severity Score (ISS)	X	X	X	X						X	X
For head injury	X	X	X							X	X
For all injuries	X	X	X							X	X
AIS	X	X	X	X		X				X	X
For head injury	X	X	X	X		X				X	X
For all injuries	X	X	X	X		X				X	X
PHYSICAL ASSESSMENTS AND COMPLICATIONS	TRACK	TRACK-Pilot	COBRIT	MISSION CONNECT	Mukherjee R01*	ProTECT	CNRM**	CRC	Dilantin	Valproate	Mag. Sulfare
Pre Arrival (to ED) GCS Assessment	X	X	X			?	X	X		X	X
Eye Opening	X		X				X			X	X
Best Verbal	X		X				X			X	X
Best Motor	X		X				X			X	X
Pupil Size			X							X	X
Pupil Reactivity			X							X	X
Pre ED - LOC (at injury)				X		X	X	X	X		
Pre ED - PTA (at injury)				X		X	X	X	Coma?		
Pre ED - AOC (at injury)								X			

METADATASET BASELINE and Acute Injury DATA DOMAINS - CLINICAL MEASURES ONLY
(Use TRACK, TRACK-Pilot as reference studies)

<i>Pre-Arrival GCS Score</i>	X	X	X		X		X	X			X
Medicated/Paralysis during Pre- GCS?			X				"Untestable"				
Pre-ED Complications	X	X									
<i>Hypoxia</i>	X	X									X
<i>Hypotension</i>	X	X									
<i>Intubation in field</i>	X	X				X				X	X
Pre-ED Medication Administered			X			X					
Arrival ED GCS Assessment	X	X	X	X	X	X	X		X	X	X
<i>Eye Opening</i>	X	X	X	X	X	X	X		X	X	X
<i>Best Verbal</i>	X	X	X	X	X	X	X		X	X	X
<i>Best Motor</i>	X	X	X	X	X	X	X		X	X	X
<i>Pupil Size</i>	X	X	X		X	X			?	X	X
<i>Pupil Reactivity</i>	X	X	X		X	X			X	X	X
<i>LOC</i>	X	X		X	X				X	?	
<i>PTA</i>	X	X		X	X				X		
<i>AOC</i>											
<i>GCS Score</i>	X	X	X	X	X		X		X		X
Medicated/Paralysis during GCS?	X	X	X	X		X					
In-hospital/ED complications	X	X	X			X			X	X	X
<i>Seizure</i>	X	X	X								?
<i>Aspiration</i>	X	X									
<i>Heart (Cardiac Arrest)</i>	X	X								X	X
<i>Hypoxia</i>	X	X			X					X	
<i>Hypotension</i>	X	X			X					X	
Discharge GCS Assessment	X	X					X				
<i>Eye Opening</i>	X	X					X				
<i>Best Verbal</i>	X	X					X				
<i>Best Motor</i>	X	X					X				
<i>Pupil Size</i>	X	X									
<i>Pupil Reactivity</i>	X	X									
<i>Discharge GCS Score</i>	X	X					X				
TOXICOLOGY	TRACK	TRACK-Pilot	COBRIT	MISSION CONNECT	Mukherjee R01*	ProTECT	CNRM		Dilantin	Valproate	Mag. Sulfare
Drug Screen (done?)	X	X	X		X		X				X
<i>Opioids (As positive, negative, or unknown)</i>	X	X	X		X		X				
<i>Benzodiazepines</i>	X	X	X		X		X				
<i>Cannabis</i>	X	X	X		X		X				
<i>Amphetamines</i>	X	X	X		X						
<i>Cocaine</i>	X	X	X		X		X				
<i>PCP</i>	X	X	X		X		X				
<i>Barbituates</i>	X	X	X		X		X				
<i>Methadone</i>	X	X	X				X				
<i>Methamphetamines</i>			X								

METADATASET BASELINE and Acute Injury DATA DOMAINS - CLINICAL MEASURES ONLY

(Use TRACK, TRACK-Pilot as reference studies)

<i>Other/Unknown</i>	x	x	x		x						
Alcohol Screen	x	x	x	x	x		x		x	x	x
<i>Intoxicated?</i>				x							
<i>BAC</i>	x	x	x	x			x		x	x	x
TREATMENTS/MEDICATIONS	TRACK	TRACK-Pilot	COBRIT	MISSION CONNECT	Mukherjee R01*	ProTECT	CNRM		Dilantin	Valproate	Mag. Sulfate
Anticoagulants in the ED (See Notes page)											
Hospital Medications	x	x	x						x		x
<i>Saline</i>			x								
<i>Anticoagulants (See notes page)</i>											
<i>Other</i>			x								
Study Medication			x			x			x		x
<i>Dose</i>			x			x			x		
<i>Time and date of administration</i>			x			x			x		x

Some of these measures (including Biospecimens) were taken from the earlier metadataset forms describing what the studies collected

For ProTECT, it is difficult to ascertain WHEN the GCS was completed (pre or post ED)

***LOC and PTA were collected during injury interview (thus Pre-ED classification)*

For CRC, the GCS is done at the time of injury (baseline)

METADATASET BASELINE DATA DOMAINS
(Use TRACK, TRACK-Pilot as reference studies)

GCS Pre ED Assessment	X	X	X		X	?	X	X		X	X
Medical History	X	X	X	X	X	X	X				X
Imaging and Specimen Records	X	X	X	X	X	X	X		X	X	X
Biospecimen	X	X	X	X	X						
CT	X	X	X	X	X	X	X		X	X	X
MRI	X	X		X	X	X	X				
Medication (s) history	X	X	X	X	X		X				
Behavioral history	X	X		X			X				
Drug use	X	X		X			X				
Alcohol use	X	X		X			X				
Tobacco Use	X	X		X			X				
Drug Screen	X	X	X	Self report?	X	X	X		X	X	X
Alcohol Screen	X	X	X	X	X		X				
Pregnancy Test	X	X	X	X	X	X					
Laboratory Values											
CBC Panel		X									
Metabolic Panel	X	X	X		X	X					X
Blood gas	X	X									
ED Vitals	X	X	X		X	X			X		X
GCS Arrival Assessment	X	X	X	X	X	?	X		X	X	X
Intubated in the ED	X	X			X						
Treatment	X	X	X	X	X						
Fluids	X	X	X		X						
Pressors	X	X			X						
Other	X	X			X						
Discharge GCS	X	X			X						
Disposition	X	X	X	X	X	X	X		X	X	
HOSPITAL VARIABLES	TRACK	TRACK-Pilot	COBRIT	MISSION CONNECT	Mukherjee R01*	ProTECT	CNRM	CRC	Dilantin	Valproate	Mag. Sulfare
Time and date of visit	X	X	X		X						
Hospital labs	X	X									
Hospital vitals	X	X	X								
Hospital Procedures	X	X	X		X					baseline?	X
Surgeries	X	X	X		X						X
Other (ICP monitoring, probing)	X	X									X
Complications	X	X									
Medication(s) Administered	X	X	X								X
INJURY VARIABLES	TRACK	TRACK-Pilot	COBRIT	MISSION CONNECT (OBS)	Mukherjee R01*	ProTECT	CNRM	CRC	Dilantin	Valproate	Mag. Sulfare
Time and date of Injury	X	X	X	X		X	X		X	X	X
Injury Intent	X	X	X		X	X			X	X	X
Injury Type (Closed, penetrating, blast, crush)	X	X			X						
Injury Mechanism	X	X	X	X	X	X	X		X		X

METADATASET BASELINE DATA DOMAINS
(Use TRACK, TRACK-Pilot as reference studies)

Injury Cause	X				X			Sport type		X	
Place of Injury	X	X		X	X		X		X		
Other injury (non-head injury)	X	X	X	X	X				X	X	X
Injury history, including TBI	X	X	X				X	X			X
Safety measures used	X	X		X	X				X	X	X
INCLUSION CRITERIA	TRACK	TRACK-Pilot	COBRIT	MISSION CONNECT	Mukherjee R01*	ProTECT	CNRM	CRC	Dilantin	Valproate	Mag. Sulfare
Age 0-100	X	X									
Documented/verified TBI	X	X	X	X		Suspect	Suspect		X	X	
Acute injury (< 24 hours)	X	X		X							
Head CT scan or imaging completed	X	X			X				?	?	?
<i>Negative</i>	X	X									
<i>Positive</i>	X	X									
Acuity for testing (hearing/eye)	X	X	X	X							
Speak English or Spanish	X	X	X	X			X				
Informed consent	X	X	X		X		X				
EXCLUSION CRITERIA	TRACK	TRACK-Pilot	COBRIT	MISSION CONNECT	Mukherjee R01*	ProTECT	CNRM		Dilantin	Valproate	Mag. Sulfare
Significant polytrauma that would interfere with follow-up and outcome assessment	X	X		X		X			X		
Prisoners or patients in custody	X	X	X		X	X					
Pregnancy in female subjects	X	X	X	X	X	X			X	X	X
Patients on psychiatric hold (e.g. 5150, 5250)	X	X			X				?		
Major debilitating baseline mental health disorders (e.g. schizophrenia or bipolar disorder) that would interfere with follow-up and the validity of outcome assessment	X	X	X			?	X		X		
Major debilitating neurological disease (e.g. stroke, CVA, dementia, tumor) impairing baseline awareness, cognition, or validity of follow-up and outcome assessment	X	X	X			?					
Significant history of pre-existing conditions that would interfere with follow-up and outcome assessment (e.g. substance abuse, alcoholism, HIV/AIDS, major transmittable diseases that may interfere with consent, end-stage cancers, learning disabilities, developmental disorders)	X	X	X			?			X	X	
Contraindications to MRI (for CA+MRI cohort)	X	X		X	X		X				
Low likelihood of follow-up (e.g. participant or family indicating low interest, residence in another state or country, homelessness or lack of reliable contacts)	X	X							X	X	X
Current participant in an interventional trial (e.g drug, device, behavioral)	X	X	X							X	
Penetrating TBI	X	X			X						
Spinal cord injury with ASIA score of C or worse	X	X			X	X					

Mission Connect info came from medical records according to forms

** English language only*

***As of 9/22/2015*



TBI Endpoints Development Initiative

A collaborative for advancing diagnosis and treatment of TBI

TBI ENDPOINTS DEVELOPMENT (TED) INITIATIVE METADATASET DATA USE AGREEMENT AND HUMAN MATERIAL TRANSFER AGREEMENT

This Data Use Agreement and Human Material Transfer Agreement (“DUA/HMTA”) is between The Regents of the University of California, on behalf of its San Francisco campus (“UCSF”) and [INSERT NAME OF INSTITUTION on behalf of Principal Investigator and PI] (“Data User”) and is effective as of the date of last signature “Effective Date.”

UCSF and Data User are hereinafter also referred to individually as “Party” and collectively as “Parties.”

Preamble:

1. The Parties wish to collaborate and share data with the ultimate goal of furthering progress in research on traumatic brain injury related to the specific aims of the TBI Endpoints Development Study (TED) initiative and any adjunct research activities generated by the TED initiative; and
2. Under this Agreement’s terms and conditions, Data User will be provided access to original and/or derivative clinical data file(s) (“Clinical Data”), and/or human materials (hereafter “Biospecimens”), and/or neuroimaging studies (“Imaging Studies”), provided that TED Executive Committee (“Executive Committee”) has approved the transfer of Biospecimens, Imaging Studies, and/or Data.
3. The Parties acknowledge the Clinical Data, Biospecimens, and/or Imaging Studies have come in through related Data Contribution and Use Agreements (“DCUAs”) from collaborators in the field of traumatic brain injury (“Data Contributors”) with the undertaking to provide UCSF as the administrative custodian (“Custodian”), information that is integrated and stored as part of the TBI Endpoints Initiative’s “TED Metadataset,” on a data integration platform or repository, as relevant (“Repository” or “Repositories”); and
4. The TED Executive Committee (“Executive Committee”) controls decisions surrounding the storage and use of such data in the Repository; and
5. The Parties acknowledge that any publications or presentations generated from investigation and analysis of the TED Metadataset are governed by policies set forth in the TED Publication and Authorship Guideline incorporated herein by reference, subject to future amendment by TED Executive Committee as needed, along with recognition and disclosure of the source grant(s) for the utilized dataset(s).
- 6 Data User will also have the opportunity to explore the TED Metadatset pursuant to the TED Research Collaboration Policy, incorporated here by reference, subject to future amendment by the TED Executive Committee as needed.
7. Notification shall be in writing either electronic or by mail:

UCSF Principal Investigator (“PI”) facilitating this Agreement for Custodian:

Geoffrey T. Manley, MD, PhD

Study Title: TED

Address: University of California, San Francisco
Department of Neurological Surgery
Brain and Spinal Injury Center
1001 Potrero Avenue, Bldg. 1, Room 101
San Francisco, California, USA

Contact: Email: manleyg@neurosurg.ucsf.edu Tel: 415-206-8300 Fax: 415-206-3948

Administrative Contact for Custodian:**The Regents of the University of California, on behalf its San Francisco Campus****Address:** UCSF - Office of Innovation, Technology, & Alliances
3333 California St., S-11
San Francisco, CA 94143-1209**Contact:** industrycontracts@ucsf.edu**Data User Agreements and Obligations**

8. Except as otherwise specified herein, the Data User may make all uses and disclosures of the sample of the de-identified Clinical Data, Biospecimens, and/or Imaging Studies to conduct the Research Project as described in Data User's Research Proposal (Exhibit A) and this section. For the purposes of the Agreement, derivative data file(s) are any and all data file(s) created using the original data in any way. This Agreement addresses the terms and conditions pursuant to which the Data User is permitted to obtain, use, reuse, and disclose the Clinical Data, Biospecimens, and/or Imaging Studies, or derivatives of any. Data Contributor retains all applicable rights to the Clinical Data, Biospecimens, and/or Imaging Studies referred to in this Agreement, and the Data User does not obtain any intellectual property rights related to, or any other right, title, or interest in any of the Clinical Data, Biospecimens, and/or Imaging Studies or derivatives other than those which are expressly granted in this Agreement. Data User understands and acknowledges that the Clinical Data, Biospecimens, and/or Imaging Studies may be protected by copyright and other intellectual property rights, and that duplication, except as reasonably necessary to carry out the Research Proposal, or sale of all or part of the Clinical Data, Biospecimens, and/or Imaging Studies is not permitted.

- a) The following original Clinical Data are being made available pursuant to this Agreement for research purposes:

Name of Study Providing the Biospecimens, Imaging Studies, and/or De-Identified Data**[insert list]**

- b) The following Biospecimens are being made available pursuant to this Agreement for research purposes:

Name of Study Providing the Biospecimens, Imaging Studies, and/or De-Identified Data**[insert list]**

- c) The following original Imaging Study Files are being made available pursuant to this Agreement for research purposes:

Name of Study Providing the Biospecimens, Imaging Studies, and/or De-Identified Data**[insert list]**

9. The TED Metadataset access and/or access to Clinical Data, Biospecimens, and/or Imaging Studies is provided to Data User for the purpose of ongoing collaboration in TBI research and will be used only as described in Research Proposal.

10. Data User will provide to UCSF a Research Completion Report on a form to be provided by UCSF PI, upon completion of the agreed project. The Research Completion Report shall include a recitation of the findings of the project, and a copy of all derivative data that Data User develops in the course of the project. The Report will contain a completed form (the "Minimal Dataset Form") that describes the "minimal dataset" – that is, the dataset used to reach the conclusions reached in the report and any manuscript produced, with related metadata and methods, and any additional data required to replicate

the reported study findings in their entirety. Core descriptive data, methods, and study results should be included within the report, regardless of data deposition.

11. The facts and statements made by Data User in the Research Proposal are complete and accurate;

12. The requested Clinical Data, Biospecimens, and/or Imaging Studies are the minimum necessary to achieve the purposes set forth in the Research Proposal;

13. Data User has obtained Institutional Review Board approval to use the Clinical Data, Biospecimens, and/or Imaging Studies;

14. Data User has sufficient resources to and intends to complete the research project as set forth in User's Research Proposal; and

15. Data User agrees to use the Clinical Data, Biospecimens, and/or Imaging Studies strictly in accordance with applicable local and federal laws, including but not limited to the following related to confidentiality, privacy, and security regulation:

- i. The Privacy Act of 1974, as most currently amended
- ii. California's Confidentiality of Medical Information Act (CMIA)
- iii. "HIPAA": the Health Insurance Portability and Accountability Act of 1996, Public Law 104-191. The data provided to UCSF is de-identified in accordance with the de-identification standards set forth under the Health Insurance Portability and Accountability Act (HIPAA) and all implementing regulations, including, but not limited to 45 CFR § 164.514(a)-(c) and § 164.502(d) as well as applicable human subjects regulations and guidance, 45 C.F.R. Part 46, 21 C.F.R. Parts 50 and 56

16. Data User will receive access to de-identified data and will not attempt to establish the identity of, or attempt to contact any of the individuals, whose data are contained in the TED Metadataset.

17. Data User and members of their research team that are under the direct supervision of the Data User shall be entitled to use Clinical Data, Biospecimens, and/or Imaging Studies from the TED Metadataset, and agree to do so in a secure manner using appropriate administrative, physical storage and technical safeguards to prevent use or disclosure of such in ways other than are permitted under this Agreement.

All personnel certify that they have completed a Collaborative Institutional Training Initiative (CITI Program) module, with specific certification in Human Subjects Protection Training.

18. Except as otherwise required by law, any transfer to or from third parties of Clinical Data, Biospecimens, and/or Imaging Studies is prohibited without authorization from the TED Executive Committee with the exception that Data User may transfer to, and permit the use of such by the subcontractors or collaborators listed in Research Proposal to aid in the performance of the Research Project under a data use and human materials transfer agreement with terms that are no less strict than the terms of this Agreement. It is incumbent on the Data User to seek out and engage in separate agreements with non-UCSF third parties such as other repositories or collaborators providing Clinical Data, Biospecimens, and/or Imaging Studies. These separate agreements shall not contain terms that conflict with the rights and obligations under this Agreement of UCSF, the TED Executive Committee, or the Data User or Data Contributor, and shall have no less stringent obligations than are imposed under this Agreement. Under these separate agreements, the terms of this agreement shall be incorporated through reference, including but not limited to those contained in the TED Research Collaboration Policy and the TED Publication and Authorship Guideline.

19. If Data User moves to another institution or company, Data User will notify the UCSF Principal Investigator in writing within 30 days regarding disposition of the TED Metadataset as well as the Clinical Data, Biospecimens, and/or Imaging Studies in possession or control by Data User.

20. Data User and Other Users entitled to use the Data from the TED Metadataset agree to notify the UCSF Principal Investigator within 2 days of becoming aware of any use or disclosure of the Data in violation of the law or this Agreement.

21. The TED Metadataset as a whole, and any of its constituent data, are experimental in nature and are provided without any warranties, express or implied, including any warranty of merchantability, accuracy,

or fitness for a particular purpose. UCSF makes no representation and provides no warranty that the use of the Data Contributors' Data or the TED Metadataset will not infringe any patent or other proprietary rights.

22. To the extent allowable under applicable laws, Data User agrees to indemnify, defend and hold harmless UCSF and its trustees, officers, staff, representatives and agents against all damages, expenses (including without limitation legal expenses), claims, demands, suits or other actions arising from Data User's negligence or intentional misconduct in its acceptance, storage, use and disposal of the Data Contributors' Data and TED Metadataset, as well as all other information provided to Data User under this Agreement or arising in connection with this Agreement.

23. This Agreement is not assignable by Data User.

24. Neither party will use the name of the other party or its employees in any advertisement, press release, or other publicity without prior written approval of the other party.

25. The term of this Agreement shall commence on the Effective Date (indicated above) and shall continue for a period of two (2) years, unless terminated sooner as set forth in this Agreement. This Agreement may be renewed for additional one (1) year terms by written amendment signed by authorized officials of both parties.

26. Upon termination or expiration of this Agreement, the Data User agrees to promptly provide UCSF with a summary of the results of the research conducted using the TED Metadataset in accordance with the Research Proposal ("Research Summary"), as well as all materials and data provided by Data Contributors and UCSF under this Agreement, without limitation. The Data User further agrees to promptly provide UCSF with a Research Summary prior to the execution of a written amendment to extend the term of this Agreement.

27. The Data User may terminate this Agreement at any time by notifying the UCSF Principal Investigator in writing, and promptly returning all Data provided to Data User under this Agreement.

28. UCSF or the TED Executive Committee may terminate this Agreement at any time by denying the Data User's access to additional data and other study materials. UCSF may terminate with or without cause, for any reason, and shall indicate so in writing to Data User. In the event that UCSF terminates this Agreement, Data User shall at UCSF's option, return or destroy (and confirm in writing such destruction), the Clinical Data, Biospecimens, and/or Imaging Studies and all copies, including all documents created by Data User where portions of the TED Metadataset, Biospecimens, and/or Imaging Studies are reproduced. Use of the Clinical Data, Biospecimens, and/or Imaging Studies for a new purpose or project will require a new application to and subsequent approval by Executive Committee.

29. This Agreement may be executed in one or more counterparts. Delivery of an executed counterpart of this Agreement by facsimile or a .pdf data file or other scanned executed counterpart by email shall be equally as effective as delivery of a manually executed counterpart of this Agreement.

Signatures

If Data User and Data User principal investigator acknowledge and agree to the above terms and conditions for transfer of the TED Metadataset Clinical Data, Biospecimens, and/or Imaging Studies, please so indicate by returning one copy of this Agreement signed and dated by Data User principal investigator and by a duly authorized representative of Data User. Upon receipt of signed Agreement by UCSF Principal Investigator and UCSF authorized representative, and confirmation that CITI Human Subjects Protection Training certification has been completed, the Data described in Paragraphs 8 (a)-(c) will be provided to Data User for the purposes set forth in Research Proposal. **All members of Data User's Research Team who will access or analyze data must individually sign this Agreement.**

READ AND ACKNOWLEDGED

DATA USER or PRINCIPAL INVESTIGATOR

Signature: _____

Printed Name: _____

Title: _____

Date: _____

AUTHORIZED SIGNATORY FOR DATA USER INSTITUTION

Signature: _____

Printed Name: _____

Title: _____

Date: _____

AUTHORIZED SIGNATORY FOR UCSF

Signature: _____

Printed Name: _____

Title: _____

Date: _____

READ AND ACKNOWLEDGED BY UCSF PRINCIPAL INVESTIGATOR

Signature: _____

Printed Name: _____

Title: _____

Date: _____

EXHIBIT A

Research Proposal



Department of Neurological Surgery
Brain and Spinal Injury Center

DATA USE AGREEMENT

This Data Use Agreement ("Agreement") is entered into by and between The Regents of the University of California, on behalf of its San Francisco campus ("UCSF" or "Data User"), and [full legal name of entity] _____ having a principal place of business located at [address] _____ ("Data Contributor" or "Covered Entity") and shall be effective as of _____ (the "Agreement Effective Date")

UCSF and Data Contributor are hereinafter also referred to individually as "Party" and collectively as "Parties".

Preamble:

1. The Parties wish to collaborate and share data with the ultimate goal of furthering progress in research on traumatic brain injury; and
2. Data Contributor undertakes to provide to UCSF as the custodian, certain data to be integrated and stored as part of the TED MetaDataset, on a data integration platform (the "Repository"); and
3. The Parties acknowledge this Data Use Agreement relates to the separate DUA between UCSF and such Repository; and
4. The TED Executive and Steering Committees control decisions surrounding the storage and use of such data in the Repository; and
5. The Parties acknowledge that any publications generated from the TED MetaDataset using the Data Contributor's Data will include Data Contributor and other investigators Data Contributor identifies in Data Contributor Information below in the author block for such publications, along with recognition and disclosure of the source grant(s) for Data Contributor's dataset, as set forth in the TED Publication and Authorship Guidelines incorporated here by reference, subject to future amendment by the TED Executive Committee as needed; and
6. Data Contributor will also have the opportunity to explore the TED MetaDataset pursuant to the TED Research Collaboration Policy, incorporated here by reference, subject to future amendment by the TED Executive Committee as needed;

NOW THEREFORE, in consideration of the premises and mutual covenants herein contained, the Parties agree to the following:

Data Contributor Information

List information for Organization Principal Investigator ("Data Contributor" or "You") and include any co-investigators, subcontractors, students, fellows or staff.

Organization	
Name of Principal Investigator	
Title	
Institution/Department	
Address 1	
Address 2	

Department of Neurological Surgery
Brain and Spinal Injury Center

City, State, Zip			
Phone		Fax	
Email			
Title of Project			
List of any Co-investigators, Subcontractors, Students, Fellows or Staff			
Description of Data Contributor			
Data			

Name of UCSF Principal Investigator facilitating this Agreement and data sharing:

Geoffrey T. Manley, MD, PhD
Professor and Vice Chairman of Neurological Surgery
University of California, San Francisco
Chief of Neurosurgery, San Francisco General Hospital
Co-Director, Brain and Spinal Injury Center (BASIC)
1001 Potrero Avenue, Building 1, Room 101
San Francisco, CA 94110
Phone: (415) 206-8300
Fax: (415) 206-3948
E-mail: manleyg@neurosurg.ucsf.edu

- 1. Definitions.** The parties agree that the following terms when used in this Agreement shall have the following meanings and that the terms set forth below shall be deemed to be modified to reflect any changes made hereafter to such terms by law or regulation.
 - a. *"HIPAA"* means the Health Insurance Portability and Accountability Act of 1996, Public Law 104-191.
 - b. *"HIPAA Regulations"* means the regulations promulgated under HIPAA by the United States Department of Health and Human Services, including, but not limited to, 45 C.F.R. Part 160 and 45 C.F.R. Part 164.
 - c. *"Covered Entity"* means a health plan, a health care clearinghouse, or a health care provider (each as defined by HIPAA and the HIPAA Regulations) that transmits any health information in electronic form in connection with a transaction covered by the HIPAA Regulations.
 - d. *"Protected Health Information"* or *"PHI"* means individually identifiable health information, except that Protected Health Information excludes individually identifiable health information in education records covered by the Family Educational Right and Privacy Act, as amended, 20 U.S.C. §1232g, records described at 20 U.S.C. §1232g(a)(4)(B)(iv), and employment records held by a covered entity in its role as employer.
- 2. Obligations of Covered Entity.**
 - a. *Data Set.* Covered Entity agrees to share the following data with Data User: [insert description, or include as an attachment]_____ (the **"Data Set"**).

Department of Neurological Surgery
Brain and Spinal Injury Center

Such Data Set shall not contain any of the following identifiers of the individual(s) who is(are) the subject(s) of the Protected Health Information, or of relatives, employers or household members of the individual(s): names; postal address information, other than town or city, state and zip code; telephone numbers; fax numbers; electronic mail addresses; social security numbers; medical record numbers; health plan beneficiary numbers; account numbers; certificate/license numbers; vehicle identifiers and serial numbers, including license plate numbers; device identifiers and serial numbers; Web Universal Resource Locators (URLs); Internet Protocol (IP) address numbers; biometric identifiers, including finger and voice prints; and full face photographic images and any comparable images.

3. Obligations of Data User.

- a. *Performance of Activities.* Data User may use and disclose the Data Set received from Covered Entity only in connection with the performance of the following research activities: Completion of the Specific Aims of the TED initiative and any adjunct research activities generated by the TED initiative.
- b. *Assurances of Data User's Non-Employee Agents.* Data User shall not disclose the Data Set to any non-employee agent, or subcontractor of Data User except with the express prior written consent of Covered Entity. Data User shall ensure that any agents, including subcontractors, to whom it provides the Data Set agree in writing to be bound by the same restrictions and conditions that apply to Data User with respect to such Data Set.
- c. *Nondisclosure Except As Provided In Agreement.* Data User shall not use or further disclose the Data Set except as permitted or required by this Agreement or as otherwise required by law.
- d. *Safeguards.* Data User shall use appropriate safeguards to prevent use or disclosure of the Data Set other than as provided by this Agreement.
- e. *Reporting.* Data User shall report to Covered Entity within twenty-four (24) hours of Data User becoming aware of any use or disclosure of the Data Set in violation of this Agreement or applicable law.
- f. *Identification and Contacting of Individuals.* Data User shall not identify the information or contact the individuals included in the Data Set.

4. Material Breach, Enforcement and Termination.

- a. *Term.* This Agreement shall be effective as of the Agreement Effective Date and shall continue until the Agreement is terminated by the parties or in accordance with the provisions of this Section 4. All of Data User's confidentiality obligations herein shall survive the expiration or termination of this Agreement indefinitely.
- b. *Covered Entity's Rights of Access and Inspection.* From time to time upon reasonable notice, or upon a reasonable determination by Covered Entity that Data User has breached this Agreement, Covered Entity may inspect the facilities, systems, books and records of Data User to monitor compliance with this Agreement. The fact that Covered Entity inspects, or fails to inspect, or has the right to inspect, Data User's facilities, systems and procedures does not relieve Data User of its responsibility to comply with this Agreement, nor does Covered Entity's (1) failure to detect or (2) detection of, but failure to notify Data User or require Data User's remediation of, any unsatisfactory practices constitute acceptance of such practice or a waiver of Covered Entity's

Department of Neurological Surgery
Brain and Spinal Injury Center

enforcement or termination rights under this Agreement. The parties' respective rights and obligations under this Section 4.b. shall survive termination of the Agreement.

- c. **Indemnification.** Data User shall indemnify, hold harmless and defend Covered Entity from and against any and all claims, losses, liabilities, costs and other expenses resulting from, or relating to, the acts or omissions of Data User in connection with the representations, duties and obligations of Data User under this Agreement. Covered Entity shall likewise indemnify, hold harmless and defend Data User from any and all claims, losses, liabilities, costs and other expenses resulting from, or relating to, the acts or omissions in connection with the representations, duties and obligations of any party including but not limited to the Repository. UCSF will not be liable for any claims, losses, liabilities, costs and other expenses or damages, including but not limited to data breaches not caused by the gross negligence of UCSF. The parties' respective rights and obligations under this Section 4.f. shall survive termination of the Agreement.

5. Miscellaneous Terms.

- a. **Governing Law.** Parties agree to remain silent on choice of law.
- b. **Amendment.** Covered Entity and Data User agree that amendment of this Agreement may be required to ensure that Covered Entity and Data User comply with changes in state and federal laws and regulations relating to the privacy, security, and confidentiality of PHI or the Limited Data Set.
- c. **No Third-Party Beneficiaries.** Nothing express or implied in this Agreement is intended or shall be deemed to confer upon any person other than Covered Entity and Data User, and their respective successors and assigns, any rights, obligations, remedies or liabilities.
- d. **Order of Precedence.** To the extent that any provisions of this Agreement conflict with the provisions of any other agreement or understanding between the parties with respect to use of the Data Set provided hereunder, this Agreement shall control.

IN WITNESS WHEREOF, the parties hereto have duly executed this Agreement as of the dates set forth below.

**THE REGENTS OF THE UNIVERSITY OF
CALIFORNIA, ON BEHALF OF ITS
SAN FRANCISCO CAMPUS**

[DATA CONTRIBUTOR]

Signature: _____

Signature: _____

Printed Name: _____

Printed Name: _____

Title: _____

Title: _____

Date: _____

Date: _____



TBI Endpoints Development Initiative

A collaborative for advancing diagnosis and treatment of TBI

Research Collaboration Policy

September 4, 2015

Table of Contents

1. Objectives	3
1.1. TED Study Description	3
1.2. TED Executive and Steering Committees	4
2. Process for Research Collaboration Requests	4
2.1. Research Collaboration Requests	4
2.2. Data Use Agreements	4
3. Intellectual Property	5
4. Authorship and Publications	5
5. Conflict of Interest	5
6. Budget	5
7. Termination of Research Collaboration Agreements	6

Appendix 1: Research Collaboration Proposal Form

Appendix 2: Data Use Agreement/Human Materials Transfer Agreement

Appendix 3: Publication and Authorship Guidelines

TED Research Collaboration Policy

1. OBJECTIVES

The objective of the TBI Endpoints Development (*TED*) *Research Collaboration Policy* is to establish a framework to support the conduct of collaborative research projects involving the TED Investigators, the TED Metadataset, and external parties.

1.1 TED STUDY DESCRIPTION

The TED study will directly impact public health by creating a Metadataset of integrated clinical, imaging, proteomic, genomic, and outcome biomarkers, contributed by numerous individual studies across civilian, military, and sports cohorts, which will permit more precise TBI diagnosis, prognosis, and treatment, and which will accelerate the validation and regulatory readiness of candidate clinical outcome assessments (COAs), biomarkers, and devices for use in the U.S. Food and Drug Administration (FDA) Qualification Process for Drug and Medical Device Development Tools and other regulatory processes. Creating a range of validated COAs, biomarkers, and devices will: 1) permit more accurate disease/condition diagnosis, 2) identify patient subpopulations likely to benefit from therapy/intervention, and 3) provide refined outcome assessments to confirm efficacy. With the support of the Department of Defense, and the unique private-public partnership model of the TED Initiative, over the 5-year duration of the TED Initiative, we will create the TED Metadataset, and identify (Stage I) and validate (Stage II) candidate COAs and biomarkers that could enter the regulatory pipeline, and/or be qualified by FDA as DDTs or MDDTs for future TBI trials to benefit military and civilian populations.

Detailed data from numerous clinical studies enrolling subjects across the TBI injury spectrum, along with CT/MRI imaging, blood biospecimens, and outcomes measures, will be curated and analyzed, permitting the identification/validation of COAs and biomarkers, and identification of structural abnormalities that may be predictive of outcomes, making strides toward a new taxonomy for TBI. The infrastructure of integrated databases and imaging and biospecimen repositories will create a high quality, legacy database for current and future generations of international researchers.

1.2 TED LEADERSHIP (EXECUTIVE and STEERING COMMITTEES)

TED is a large and complex project. Its institutional and public-private partnership is comprised of numerous study sites, managed through 7 Cores (Administrative, Clinical/Rehabilitation, Emerging Technologies, Informatics, Neuroimaging, Outcomes, Biostatistics), totaling nearly 50 collaborating institutions, corporations, and philanthropies. Governance is implemented by the Executive Committee, consisting of leaders of the Cores. The Executive Committee receives input from a Steering Committee, consultants, and participating organizations as to strategic research participation and planning, and dissemination of TED scientific findings, as well as oversight from its Government Steering Committee.

Oversight of Research Collaborations will be performed by the TED Executive Committee, which meets bi-weekly with few exceptions, and the Steering Committee. Submitted Research Collaboration Request forms will be screened by the Executive Committee, and reviewed, and approved/rejected by the Steering Committee.

TED Executive Committee		
Name	Role	Institution
Geoffrey Manley, MD, PhD	Contact PI, Admin Core Leader	UCSF
Harvey Levin, PhD	PI, Outcomes Core Leader	Baylor Institute of Medicine
Joseph Giacino, PhD	PI, Clinical/Rehab Core Leader	Spaulding Rehabilitation Center
Michael McCrea, PhD	PI, Outcomes Core Leader	Medical College of Wisconsin
Murray Stein, MD MPH	PI, Outcomes Core Leader	University of California, San Diego
Nancy Temkin, PhD	PI, Biostatistics Core Leader	University of Washington
Ramon Diaz-Arrastia, MD	PI, Emerging Tech Core Leader	Center for Neuroscience and
Steven Wisniewski, PhD	PI, Biostatistics Core Leader	University of Pittsburgh
Sureyya Dikmen, PhD	PI, Outcomes Core Leader	University of Washington

TED Steering Committee		
Name	Role	Institution
Geoffrey Manley, MD PhD	Contact PI, Admin Core Leader	UCSF
Arthur Toga, PhD	Informatics Core	University of Southern California
Claudia Robertson, MD	Clinical & Rehabilitation Core	Baylor College of Medicine
David Cifu, MD	Clinical & Rehabilitation Core	Virginia Commonwealth University
David Okonkwo, MD PhD	Clinical & Rehabilitation Core	University of Pittsburgh
David W. Wright, MD	Clinical & Rehabilitation Core	Emory University
Harvey Levin, MD	Outcomes Core	Baylor College of Medicine
James Kelly, MD	Outcomes Core	National Intrepid Center of Excellence
John Whyte, MD PhD	Clinical & Rehabilitation Core	Moss Rehabilitation Research Inst.
Joseph Giacino, PhD	Clinical & Rehabilitation Core	Spaulding Rehabilitation Center
Kevin Guskiewicz, PhD	Outcomes Core	University of North Carolina
Michael McCrea, PhD	Outcomes Core	Medical College of Wisconsin
Michael Weiner, MD	Neuroimaging Core	UCSF
Murray Stein, MD MPH	Outcomes Core	University of California, San Diego
Nancy Temkin, PhD	Biostatistics Core	University of Washington
Pratik Mukherjee, MD PhD	Neuroimaging Core	UCSF
Ramon Diaz-Arrastia, MD PhD	Emerging Technologies Core	Uniformed Services University of the Health Sciences
Rick Williams, PhD	Biostatistics Core	RTI International
Robert Knight, MD	Emerging Technologies Core	University of California, Berkeley
Stephen Wisniewski, PhD	Biostatistics Core	University of Pittsburgh
Sureyya Dikmen, PhD	Outcomes Core	University of Washington
William Jagust, MD	Emerging Technologies Core	University of California, Berkeley

2. PROCESS FOR RESEARCH COLLABORATION REQUESTS

Access to study data, materials sharing, and mutual collaboration among research teams in order to accelerate research in TBI are fundamental tenets of the TED project and are core beliefs of its investigators. The TED Metadataset and repositories can only serve their intended purposes as a current and legacy resource for further research with a robust, transparent, and open-access collaboration policy. To ensure optimal use and to limit possible misuse of the data and materials derived from an effort of this magnitude, the TED Executive Committee will monitor all ongoing Research Collaborations.

The TED Executive and Steering Committees will not entertain unfunded collaborations that increase cost to the TED study. Furthermore, all potential collaborations must not interfere with or otherwise compromise the specific aims, outcomes, follow-up rates, or integrity of the parent TED study objectives and mandates.

2.1 Research Collaboration Requests

All Research Collaborations with TED will begin with a written request submitted to the TED Executive Committee. The Research Collaboration Proposal form is attached here as Appendix 1. Completed Research Collaboration Proposal forms are to be submitted to Dr. Geoffrey Manley, Contact PI for TED, in care of Brian Fabian (Brian.Fabian@ucsf.edu).

Research Collaboration Requests will include notation of the TED PI who will serve as a sponsor of the proposal, a table of authors and their affiliations, as well as the study aims and sub-aims, and a description of the methodologies and approaches to be used to address the scientific questions involved.

The Research Collaboration Request will also provide a proposed budget (see Section 6 below).

Research Collaboration Requests will be screened by the TED Executive Committee, and sent for review, and approval/rejection/request for revision by the TED Steering Committee.

2.2 Data Use Agreements

The Data Use Agreement/Human Materials Transfer Agreement for TED Research Collaborations is attached as Appendix 2. This Agreement is for the use of clinical and experimental data collected by the TED investigators.

The Data Use Agreement must be endorsed by the Organization Principal Investigator for the collaborating entity, and UCSF via the TED Contact PI (Dr. Manley).

3. INTELLECTUAL PROPERTY

Management of intellectual property rights, including copyright, will be handled by the Office of Technology Management at the University of California, San Francisco, in accordance with applicable University of California policies governing intellectual property rights.

4. AUTHORSHIP AND PUBLICATIONS

Any publications that emerge from use of TED data and material are subject to the review and authorship acknowledgments set forth in the TED Data Use Agreement (Appendix 2) and Publication and Authorship Guideline (Appendix 3).

In the spirit of collaboration, all publications will be joint publications with Data Contributors, Collaborators, and TED Investigators.

All efforts will be made to protect proprietary information or intellectual property that might be disclosed by the manuscript or abstract.

Failure to comply with authorship and publication expectations will result in termination of the Research Collaboration Agreement(s).

5. CONFLICT OF INTEREST

Researchers involved in collaborative research projects must disclose and manage any actual or apparent conflicts of interest relating to any aspect of the research collaboration with the TED study in accordance with the Conflict of Interest Policy of the University of California, San Francisco.

6. BUDGET

The goal of research collaboration with TED is to build intellectual synergism that will enhance the objectives of the TED study and serve public health. TED on its own, does not have adequate funding, resources, or intellectual capacity to maximize its potential impact on traumatic brain injury and public health. Forming strategic collaborations can be an effective and economical way of accessing resources and may lead to longer-term partnerships.

Nevertheless, the scope of work for any and all collaborations with external parties must be accounted for with appropriate resources. The budget must be an accurate reflection of the amount and the timing of the resources required for the collaborative project, as included in the Research Collaboration Request Form.

There must be enough funding to undertake the proposed collaboration without detracting from other efforts and core deliverables already underway. Staff time in managing and executing the collaboration must be reflected in the budget. In-kind contributions from corporate collaborators will be taken into consideration in the overall budget assessment.

The budget provided in the Research Collaboration Request must specify when payments will be made and clearly indicate when the contributed in-kind resources, if any, will be provided. Failure to adhere to the specified, agreed-upon budget will result in termination of the Research Collaboration Agreement and any and all attendant Data Use or Material Transfer Agreements.

7. TERMINATION OF RESEARCH COLLABORATION AGREEMENTS

All Research Collaboration Agreements with TED will have a specified date upon which the research collaboration project must end. The end date may be extended through the amendment process, if both parties agree.

The TED Leadership reserves the right to terminate a Research Collaboration Agreement or Data Use Agreement before the end date at the discretion of the Executive Committee with a 30-day written notice.

Appendix 1: Research Collaboration Proposal Request Form

Instructions: A completed and approved Research Collaboration Proposal Request is required to be submitted to the TED Executive Committee (care of brian.fabian@ucsf.edu) and should be no more than 2 pages long. Authors are encouraged to contact the Biostatistics Core to receive assistance with the statistical analysis plan. Clinical site statisticians are also encouraged to participate in these consultations. Proposals will be reviewed by the TED Executive Committee. All aspects of manuscript development will be governed by this Guideline. Proposals should contain the following elements:

Date:

Investigator's Name:

Investigator's Title:

Organization or Clinical Center:

E-mail:

Telephone:

TED Sponsor (if not a TED investigator):

Other investigators who will be working on this analysis:

Analysis Plan Title:

TED Dataset files to be used: Pilot Study ☐ Currently Enrolling Study ☐

Purpose of Data Request (check all that apply)		TED Core (check all that apply)	
☐	Exploratory	☐	Clinical Core
☐	Data analysis for manuscript	☐	Biospecimens Core
☐	Preliminary data for grant proposal	☐	Neuroimaging Core
☐	Inputs for simulation model	☐	Biostatistics/CER Core
☐	Development of statistical methods	☐	Outcomes Core
☐	Other (describe)		

Please attach a 2-page description of your analysis plan including:

- 1) Short background/rationale for addressing the research question
- 2) Primary variables to be used in the analysis (please provide mock tables)
- 3) Brief description of methods and statistical analysis plan
- 4) What is the impact if successful?

For exploratory requests, complete item 1 now and submit items 2 through 4 within 60-days of accessing the dataset(s).

Research Collaboration Request Tracking Log			
☐	Received by Executive Committee Member	By:	Date:
☐	Reviewed by Executive Committee		Date:
☐	Decision communicated to Requestor	By:	Date:
Decision: ☐ Accept ☐ Decline ☐ Return for revision			

Appendix 2: Data Use Agreement/Human Materials Transfer Agreement

TED METADATASET DATA USE AGREEMENT AND HUMAN MATERIAL TRANSFER AGREEMENT

This Data Use Agreement and Human Material Transfer Agreement (“DUA/HMTA”) is between The Regents of the University of California, on behalf of its San Francisco campus (“UCSF”) and [INSERT NAME OF INSTITUTION and PI] (“Data User”) and is effective as of the “Effective Date.”

UCSF and Data User are hereinafter also referred to individually as “Party” and collectively as “Parties.”

Preamble:

1. The Parties wish to collaborate and share data with the ultimate goal of furthering progress in research on traumatic brain injury related to the specific aims of the TBI Endpoints Development Study (TED) initiative and any adjunct research activities generated by the TED initiative; and
2. Under this Agreement’s terms and conditions, Data User will be provided access to original and/or derivative clinical data file(s) (“Clinical Data”), and/or human materials (hereafter “Biospecimens”), and/or neuroimaging studies (“Imaging Studies”), provided that TED Executive Committee (“Executive Committee”) has approved the transfer of Biospecimens, Imaging Studies, and/or Data.
3. The Parties acknowledge the Clinical Data, Biospecimens, and/or Imaging Studies have come in through related Data Contribution and Use Agreements (“DCUAs”) from collaborators in the field of traumatic brain injury (“Data Contributors”) with the undertaking to provide UCSF as the administrative custodian (“Custodian”), information that is integrated and stored as part of the TBI Endpoints Initiative’s “TED Metadataset,” on a data integration platform or repository, as relevant (“Repository or “Repositories”); and
4. The TED Executive Committee (“Executive Committee”) controls decisions surrounding the storage and use of such data in the Repository; and
5. The Parties acknowledge that any publications or presentations generated from investigation and analysis of the TED Metadataset are governed by policies set forth in the TED Publication and Authorship Guideline incorporated herein by reference, subject to future amendment by TED Executive Committee as needed, along with recognition and disclosure of the source grant(s) for the utilized dataset(s).
6. Data User will also have the opportunity to explore the TED Metadataset pursuant to the TED Research Collaboration Policy, incorporated here by reference, subject to future amendment by the TED Executive Committee as needed.
7. Notification shall be in writing either electronic or by mail:

UCSF Principal Investigator facilitating this Agreement for Custodian:

Geoffrey T. Manley, MD, PhD

Study Title: TED

Address: University of California, San Francisco
Department of Neurological Surgery
Brain and Spinal Injury Center
1001 Potrero Avenue, Bldg. 1, Room 101
San Francisco, California, USA

Contact: Email: manleyg@ucsf.edu Tel: 415-206-8300 Fax: 415-206-3948

Administrative Contact for Custodian:**The Regents of the University of California, on behalf its San Francisco Campus****Address:** UCSF - Office of Innovation, Technology, & Alliances

3333 California St., S-11

San Francisco, CA 94143-1209

Contact: industrycontracts@ucsf.edu**Data User Agreements and Obligations**

8. Except as otherwise specified herein, the Data User may make all uses and disclosures of the sample of the de-identified Clinical Data, Biospecimens, and/or Imaging Studies to conduct the Research Project as described in Data User's Research Proposal (Exhibit A) and this section. For the purposes of the Agreement, derivative data file(s) are any and all data file(s) created using the original data in any way. This Agreement addresses the terms and conditions pursuant to which the Data User is permitted to obtain, use, reuse, and disclose the Clinical Data, Biospecimens, and/or Imaging Studies, or derivatives of any. Data Contributor retains all applicable rights to the Clinical Data, Biospecimens, and/or Imaging Studies referred to in this Agreement, and the Data User does not obtain any intellectual property rights related to, or any other right, title, or interest in any of the Clinical Data, Biospecimens, and/or Imaging Studies or derivatives other than those which are expressly granted in this Agreement. Data User understands and acknowledges that the Clinical Data, Biospecimens, and/or Imaging Studies may be protected by copyright and other intellectual property rights, and that duplication, except as reasonably necessary to carry out the Research Proposal, or sale of all or part of the Clinical Data, Biospecimens, and/or Imaging Studies is not permitted.

- a) The following original Clinical Data are being made available pursuant to this Agreement for research purposes:

Name of Study Providing the Biospecimens, Imaging Studies, and/or De-Identified Data**[insert list]**

- b) The following Biospecimens are being made available pursuant to this Agreement for research purposes:

Name of Study Providing the Biospecimens, Imaging Studies, and/or De-Identified Data**[insert list]**

- c) The following original Imaging Study Files are being made available pursuant to this Agreement for research purposes:

Name of Study Providing the Biospecimens, Imaging Studies, and/or De-Identified Data**[insert list]**

9. The TED Metadataset access and/or access to Clinical Data, Biospecimens, and/or Imaging Studies is provided to Data User for the purpose of ongoing collaboration in TBI research and will be used only as described in Research Proposal.

10. Data User will provide to UCSF a Research Completion Report on a form to be provided by UCSF PI, upon completion of the agreed project. The Research Completion Report shall include a recitation of the findings of the project, and a copy of all derivative data that Data User develops in the course of the project. The Report will contain a completed form (the "Minimal Dataset Form") that describes the "minimal dataset" – that is, the dataset used to reach the conclusions reached in the report and any manuscript produced, with related metadata and methods, and any additional data required to replicate the reported study findings in their entirety. Core descriptive data, methods, and study results should be included within the report, regardless of data deposition.

11. The facts and statements made by Data User in the Research Proposal are complete and accurate;

12. The requested Clinical Data, Biospecimens, and/or Imaging Studies are the minimum necessary to achieve the purposes set forth in the Research Proposal;

TED Research Collaboration Policy

Page 7

13. Data User has obtained Institutional Review Board approval to use the Clinical Data, Biospecimens, and/or Imaging Studies;

14. Data User has sufficient resources to and intends to complete the research project as set forth in User's Research Proposal; and

15. Data User agrees to use the Clinical Data, Biospecimens, and/or Imaging Studies strictly in accordance with applicable local and federal laws, including but not limited to the following related to confidentiality, privacy, and security regulation:

- i. The Privacy Act of 1974, as most currently amended
- ii. California's Confidentiality of Medical Information Act (CMIA)
- iii. "HIPAA": the Health Insurance Portability and Accountability Act of 1996, Public Law 104-191. The data provided to UCSF is de-identified in accordance with the de-identification standards set forth under the Health Insurance Portability and Accountability Act (HIPAA) and all implementing regulations, including, but not limited to 45 CFR § 164.514(a)-(c) and § 164.502(d) as well as applicable human subjects regulations and guidance, 45 C.F.R. Part 46, 21 C.F.R. Parts 50 and 56.

16. Data User will receive access to de-identified data and will not attempt to establish the identity of, or attempt to contact any of the individuals, whose data are contained in the TED Metadataset.

17. Data User and members of their research team that are under the direct supervision of the Data User shall be entitled to use Clinical Data, Biospecimens, and/or Imaging Studies from the TED Metadataset, and agree to do so in a secure manner using appropriate administrative, physical storage and technical safeguards to prevent use or disclosure of such in ways other than are permitted under this Agreement. **All personnel certify that they have completed a Collaborative Institutional Training Initiative (CITI Program) module, with specific certification in Human Subjects Protection Training.**

18. Except as otherwise required by law, any transfer to or from third parties of Clinical Data, Biospecimens, and/or Imaging Studies is prohibited without authorization from the TED Executive Committee with the exception that User may transfer to, and permit the use of such by the subcontractors or collaborators listed in Research Proposal to aid in the performance of the Research Project under a data use and human materials transfer agreement with terms that are no less strict than the terms of this Agreement. It is incumbent on the Data User to seek out and engage in separate agreements with non-UCSF third parties such as other repositories or collaborators providing Clinical Data, Biospecimens, and/or Imaging Studies. These separate agreements shall not contain terms that conflict with the rights and obligations under this Agreement of UCSF, the TED Executive Committee, or the Data User or Data Contributor, and shall have no less stringent obligations than are imposed under this Agreement. Under these separate agreements, the terms of this agreement shall be incorporated through reference, including but not limited to those contained in the TED Research Collaboration Policy and the TED Publication and Authorship Guideline.

19. If Data User moves to another institution or company, Data User will notify the UCSF Principal Investigator in writing within 30 days regarding disposition of the TED Metadataset as well as the Clinical Data, Biospecimens, and/or Imaging Studies in possession or control by Data User.

20. Data User and Other Users entitled to use the Data from the TED Metadataset agree to notify the UCSF Principal Investigator within 2 days of becoming aware of any use or disclosure of the Data in violation of this Agreement.

21. The TED Metadataset as a whole, and any of its constituent data, are experimental in nature and are provided without any warranties, express or implied, including any warranty of merchantability, accuracy, or fitness for a particular purpose. UCSF makes no representation and provides no warranty that the use of the Data Contributors' Data or the TED Metadataset will not infringe any patent or other proprietary rights.

22. To the extent allowable under applicable laws, Data User agrees to indemnify, defend and hold harmless UCSF and its trustees, officers, staff, representatives and agents against all damages, expenses (including without limitation legal expenses), claims, demands, suits or other actions arising from Data User's negligence or intentional misconduct in its acceptance, storage, use and disposal of the Data Contributors' Data and TED

Metadataset, as well as all other information provided to Data User under this Agreement or arising in connection with this Agreement.

23. This Agreement is not assignable by Data User.

24. Neither party will use the name of the other party or its employees in any advertisement, press release, or other publicity without prior written approval of the other party.

25. The term of this Agreement shall commence on the Effective Date (indicated above) and shall continue for a period of two (2) years, unless terminated sooner as set forth in this Agreement. This Agreement may be renewed for additional one (1) year terms by written amendment signed by authorized officials of both parties.

26. Upon termination or expiration of this Agreement, the Data User agrees to promptly provide UCSF with a summary of the results of the research conducted using the TED Metadataset in accordance with the Research Proposal ("Research Summary"), as well as all materials and data provided by Data Contributors and UCSF under this Agreement, without limitation. The Data User further agrees to promptly provide UCSF with a Research Summary prior to the execution of a written amendment to extend the term of this Agreement.

27. The Data User may terminate this Agreement at any time by notifying the UCSF Principal Investigator in writing, and promptly returning all Data provided to Data User under this Agreement.

28. UCSF or the TED Executive Committee may terminate this Agreement at any time by denying the Data User's access to additional data and other study materials. UCSF may terminate with or without cause, for any reason, and shall indicate so in writing to Data User. In the event that UCSF terminates this Agreement, Data User shall at UCSF's option, return or destroy (and confirm in writing such destruction), the Clinical Data, Biospecimens, and/or Imaging Studies and all copies, including all documents created by Data User where portions of the TED Metadataset, Biospecimens, and/or Imaging Studies are reproduced. Use of the Clinical Data, Biospecimens, and/or Imaging Studies for a new purpose or project will require a new application to and subsequent approval by Executive Committee.

29. This Agreement may be executed in one or more counterparts. Delivery of an executed counterpart of this Agreement by facsimile or a .pdf data file or other scanned executed counterpart by email shall be equally as effective as delivery of a manually executed counterpart of this Agreement.

Signatures

If Data User and Data User principal investigator acknowledge and agree to the above terms and conditions for transfer of the TED Metadataset Clinical Data, Biospecimens, and/or Imaging Studies, please so indicate by returning one copy of this Agreement signed and dated by Data User principal investigator and by a duly authorized representative of Data User. Upon receipt of signed Agreement by UCSF Principal Investigator and UCSF authorized representative, and confirmation that CITI Human Subjects Protection Training certification has been completed, the Data described in Paragraphs 8 (a)-(c) will be provided to Data User for the purposes set forth in Research Proposal. **All members of Data User's Research Team who will access or analyze data must individually sign this Agreement.**

READ AND ACKNOWLEDGED – PRINCIPAL INVESTIGATOR

Signature: _____

Printed Name: _____

Title: _____

Date: _____

DATA USER:

Signature: _____

Printed Name: _____

Title: _____

Date: _____

SIGNATURE OF DATA USER INSTITUTION

Signature: _____

Printed Name: _____

Title: _____

Date: _____

AUTHORIZED SIGNATURE FOR UCSF

Signature: _____

Printed Name: _____

Title: _____

Date: _____

READ AND ACKNOWLEDGED BY UCSF PRINCIPAL INVESTIGATOR

Signature: _____

Printed Name: _____

Title: _____

Date: _____

Appendix 3: TED Publication and Authorship Guideline

This **Publication and Authorship Guideline** has been established by the TED Executive Committee for the publication of data collected under the protocol entitled: Traumatic Brain Injury Endpoints Development Initiative (TED). TED is governed by data use guidelines, as described in the TED Data Contribution and Use Agreement, the Data Use Agreement, and the TED Research Collaboration Policy. This Publication and Authorship Guideline will be in effect until such time as the data may become publically accessible, and is subject to amendment by the TED Executive Committee.

This guideline addresses three major types of manuscripts. **Primary manuscripts** are those that report the conduct and outcome of the major objectives of the trial (i.e., the major results of the collaboration). **Secondary manuscripts** refer to secondary hypotheses and ancillary analyses that come from data that were collected for this study. **Tertiary manuscripts** are those in which data collected are used as an illustrative example of a proposed preferred methodology or studies for which ancillary data, unrelated to the primary study hypotheses, are collected, sometimes on only a subset of study sites. All data presentations, including abstracts, oral presentations, and posters, are encompassed by the term “manuscript.”

General Principles

1. This guideline may be subject to ongoing interpretation by the Executive Committee. Experience and new insights from this trial may necessitate periodic modification by consensus of the Executive Committee.
2. No TED data shall be presented, submitted or published in any way without the express prior written approval of the Executive Committee.
3. Primary Authorship, denoted as those on the first line(s) of the authorship attribution in a journal and in indexing services, should be based on appropriate effort as defined in the guidelines published by the International Committee of Medical Journal Editors (ICMJE, http://www.icmje.org/roles_a.html). Primary authors should meet all four of the following criteria:
 - 1) Substantial contributions to the conception or design of the work; or the acquisition, analysis or interpretation of data for the work; AND
 - 2) Drafting the work or revising it critically for important intellectual content; AND
 - 3) Final approval of the version to be published; AND
 - 4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
4. Authorship credit will be granted to the primary authors *with the TED Study Investigators as an author*. Following the list of primary authors, all publications using TED data will bear the following attribution: “and the TED Study Investigators” listed in alphabetic order. Including the TED Study Investigators allows for all members to be indexed as authors (not contributors) in PubMed.
5. Responsibilities and tasks for production of primary manuscripts will be determined by the Executive Committee and the Biostatistical Core. The results to be included in the primary manuscript will be presented to the Executive and Steering Committees for review and response. Twenty-one days prior to submission, a complete draft will be circulated to the Executive Committee for review and comment.
6. Secondary and tertiary manuscripts are strongly encouraged and may be initiated by any participating TED investigator. Two-page proposals for secondary and tertiary manuscripts must include a tentative title, primary author(s), background/rationale, and statistical analysis plan (NOTE: see Appendix 1 to Research Collaboration Agreement) and must be submitted to the Executive Committee in care of Contact Principal Investigator, Geoffrey T. Manley, MD PhD via the Project Administrator (brian.fabian@ucsf.edu). Consultations with the Biostatistical Core are essential to developing adequate statistical plans prior to final submission to the Executive Committee. Clinical site statisticians and epidemiologists are encouraged to participate in these consultations, which should take place after

proposal submission to the Executive Committee and acceptance by the TED Steering Committee, and before posting on the One Mind Portal. All submitted and finalized proposals will be posted on the One Mind Portal for review and comment by all TED PIs and co-Is. All eligible proposals will be presented, discussed, reviewed, and voted on either during Steering Committee meetings, or via email ballot within 14 days following the meeting. Approval will be determined by simple majority.

7. Each secondary and tertiary manuscript proposal will identify a primary author/writing group leader, who will be responsible for assigning tasks to members of the writing group. To uphold the authorship criteria presented in General Principle 3, it is expected that primary authors will delegate writing responsibilities early enough so that all members of the writing group are given the opportunity to contribute substantively. The primary author will have sole responsibility for ensuring that authorship order has been discussed and confirmed by co-authors. There is no prescribed limit of authors from each institution; however, each named author must have contributed significantly to the manuscript as described above. If there is a disagreement among the potential co-authors, the Executive Committee will determine inclusion of an author and/or order. If agreement cannot be reached by the Executive Committee, Michael Weiner, MD PhD, of the TED Scientific Advisory Board will be the tie-breaker and serve as mediator. For secondary (and possibly tertiary) manuscripts, the author list will include the named authors followed by “and the TED Study Investigators.”
8. Before submission of an abstract to a scientific meeting, it is expected that the associated data analyses and interpretation will be completed. The abstract, data tables, and text of the interpretation will be submitted to the Executive Committee and posted on the One Mind Portal for comment and the designated author(s) will present their data and interpretation (10-minute presentation) to the Executive Committee for discussion and review during an Executive Committee telephone meeting. The Executive Committee will discuss the presentation and approve submission by simple majority vote. It is expected that the resultant manuscript will be submitted to a journal by or before 3 months following presentation of the abstract at the scientific meeting. The same process is required before submitting a manuscript to a journal if no associated abstract has been previously approved.
9. If preparation and submission of manuscripts is not accomplished in a timely manner (within six months following the receipt of data), the Executive Committee reserves the right to delegate manuscript-writing responsibility to another investigator. These requirements are in place to ensure the timely publication and dissemination of study results to the public and the scientific community.
10. Using TED data as preliminary data for grant submission by investigators at participating institutions is encouraged. However, any data tables included in a grant proposal must be approved by the Steering Committee before submission.
11. Proposals for single-site analyses of TED data will be handled the same way as multi-site analyses.
12. The Steering Committee will consider requests from unrelated third parties for access to study data for research and publication purposes *prior* to the data becoming available publically. All parties obtaining access to the data will agree to abide by the obligations of the TED Data Use Agreement and as set forth in this Guideline.
13. All authors are responsible for notifying the Executive Committee (via email to Brian Fabian brian.fabian@ucsf.edu) of all accepted manuscripts, abstracts, and oral and poster presentations, as well as the journal, date of publication, page number(s) and other information necessary to reference the publication/presentation. The TED Administrative Core will maintain a central list of all accepted abstracts, presentations and publications relating to TED, which will be posted on the TED Web site.

Acknowledgements

1. As this study was sponsored by external sources an acknowledgement is required on all publications.

“Sponsored by the U.S. Department of Defense (Grant #W81XWH-14-2-0176), and our public and private partners. The opinions or assertions contained here are the private views of the authors and are not to be construed as official or as reflecting the views of any sponsor.”

2. Contributions from other collaborators, including laboratory, economists, scientists, consultants or other individuals providing expertise during the trial design, conduct and manuscript processes but not members of the official TED Study Investigators and not meeting the prescribed authorship criteria should also be listed in the acknowledgments.

TED Executive Committee		
Name	Role	Institution
Geoffrey Manley, MD, PhD	Contact PI, Admin Core Leader	UCSF
Harvey Levin, PhD	PI, Outcomes Core Leader	Baylor Institute of Medicine
Joseph Giacino, PhD	PI, Clinical/Rehab Core Leader	Spaulding Rehabilitation Center
Michael McCrea, PhD	PI, Outcomes Core Leader	Medical College of Wisconsin
Murray Stein, MD MPH	PI, Outcomes Core Leader	University of California, San Diego
Nancy Temkin, PhD	PI, Biostatistics Core Leader	University of Washington
Ramon Diaz-Arrastia, MD	PI, Emerging Tech Core Leader	Center for Neuroscience and
Steven Wisniewski, PhD	PI, Biostatistics Core Leader	University of Pittsburgh
Sureyya Dikmen, PhD	PI, Outcomes Core Leader	University of Washington

TED Steering Committee		
Name	Role	Institution
Geoffrey Manley, MD PhD	Contact PI, Admin Core Leader	UCSF
Arthur Toga, PhD	Informatics Core	University of Southern California
Claudia Robertson, MD	Clinical & Rehabilitation Core	Baylor College of Medicine
David Cifu, MD	Clinical & Rehabilitation Core	Virginia Commonwealth University
David Okonkwo, MD PhD	Clinical & Rehabilitation Core	University of Pittsburgh
David W. Wright, MD	Clinical & Rehabilitation Core	Emory University
Harvey Levin, MD	Outcomes Core	Baylor College of Medicine
James Kelly, MD	Outcomes Core	National Intrepid Center of Excellence
John Whyte, MD PhD	Clinical & Rehabilitation Core	Moss Rehabilitation Research Inst.
Joseph Giacino, PhD	Clinical & Rehabilitation Core	Spaulding Rehabilitation Center
Kevin Guskiewicz, PhD	Outcomes Core	University of North Carolina
Michael McCrea, PhD	Outcomes Core	Medical College of Wisconsin
Michael Weiner, MD	Neuroimaging Core	UCSF
Murray Stein, MD MPH	Outcomes Core	University of California, San Diego
Nancy Temkin, PhD	Biostatistics Core	University of Washington
Pratik Mukherjee, MD PhD	Neuroimaging Core	UCSF
Ramon Diaz-Arrastia, MD PhD	Emerging Technologies Core	Uniformed Services University of the Health Sciences
Rick Williams, PhD	Biostatistics Core	RTI International
Robert Knight, MD	Emerging Technologies Core	University of California, Berkeley
Stephen Wisniewski, PhD	Biostatistics Core	University of Pittsburgh
Sureyya Dikmen, PhD	Outcomes Core	University of Washington
William Jagust, MD	Emerging Technologies Core	University of California, Berkeley

EXHIBIT A

Research Proposal



TBI Endpoints Development Initiative

A collaborative for advancing diagnosis and treatment of TBI

Publication and Authorship Guidelines

This **Publication and Authorship Guideline** has been established by the TED Executive Committee for the publication of data collected under the protocol entitled: Traumatic Brain Injury Endpoints Development Initiative (TED). TED is governed by data use guidelines, as described in the TED Data Contribution and Use Agreement, the Data Use Agreement, and the TED Research Collaboration Policy. This Publication and Authorship Guideline will be in effect until such time as the data may become publically accessible, and is subject to amendment by the TED Executive Committee.

This guideline addresses three major types of manuscripts. **Primary manuscripts** are those that report the conduct and outcome of the major objectives of the trial (i.e., the major results of the collaboration). **Secondary manuscripts** refer to secondary hypotheses and ancillary analyses that come from data that were collected for this study. **Tertiary manuscripts** are those in which data collected are used as an illustrative example of a proposed preferred methodology or studies for which ancillary data, unrelated to the primary study hypotheses, are collected, sometimes on only a subset of study sites. All data presentations, including abstracts, oral presentations, and posters, are encompassed by the term “manuscript.”

General Principles

1. This guideline may be subject to ongoing interpretation by the Executive Committee. Experience and new insights from this trial may necessitate periodic modification by consensus of the Executive Committee.
2. No TED data shall be presented, submitted or published in any way without the express prior written approval of the Executive Committee.
3. Primary Authorship, denoted as those on the first line(s) of the authorship attribution in a journal and in indexing services, should be based on appropriate effort as defined in the guidelines published by the International Committee of Medical Journal Editors (ICMJE, http://www.icmje.org/roles_a.html). Primary authors should meet all four of the following criteria:
 - 1) Substantial contributions to the conception or design of the work; or the acquisition, analysis or interpretation of data for the work; AND
 - 2) Drafting the work or revising it critically for important intellectual content; AND
 - 3) Final approval of the version to be published; AND
 - 4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
4. Authorship credit will be granted to the primary authors *with the TED Study Investigators as an author*. Following the list of primary authors, all publications using TED data will bear the following attribution: “and the TED Study Investigators” listed in alphabetic order. Including the TED Study Investigators allows for all members to be indexed as authors (not contributors) in PubMed.
5. Responsibilities and tasks for production of primary manuscripts will be determined by the Executive Committee and the Biostatistical Core. The results to be included in the primary manuscript will be presented to the Executive and Steering Committees for review and response. Twenty-one days prior to

submission, a complete draft will be circulated to the Executive Committee for review and comment.

6. Secondary and tertiary manuscripts are strongly encouraged and may be initiated by any participating TED investigator. Two-page proposals for secondary and tertiary manuscripts must include a tentative title, primary author(s), background/rationale, and statistical analysis plan (see template in Appendix 1) and must be submitted to the Executive Committee in care of Contact Principal Investigator, Geoffrey T. Manley, MD PhD via the Project Administrator (brian.fabian@ucsf.edu). Consultations with the Biostatistical Core are essential to developing adequate statistical plans prior to final submission to the Executive Committee. Clinical site statisticians and epidemiologists are encouraged to participate in these consultations, which should take place after proposal submission to the Executive Committee and acceptance by the TED Steering Committee, and before posting on the One Mind Portal. All submitted and finalized proposals will be posted on the One Mind Portal for review and comment by all TED PIs and co-Is. All eligible proposals will be presented, discussed, reviewed, and voted on either during Steering Committee meetings, or via email ballot within 14 days following the meeting. Approval will be determined by simple majority.
7. Each secondary and tertiary manuscript proposal will identify a primary author/writing group leader, who will be responsible for assigning tasks to members of the writing group. To uphold the authorship criteria presented in General Principle 3, it is expected that primary authors will delegate writing responsibilities early enough so that all members of the writing group are given the opportunity to contribute substantively. The primary author will have sole responsibility for ensuring that authorship order has been discussed and confirmed by co-authors. There is no prescribed limit of authors from each institution; however, each named author must have contributed significantly to the manuscript as described above. If there is a disagreement among the potential co-authors, the Executive Committee will determine inclusion of an author and/or order. If agreement cannot be reached by the Executive Committee, Michael Weiner, MD PhD, of the TED Scientific Advisory Board will be the tie-breaker and serve as mediator. For secondary (and possibly tertiary) manuscripts, the author list will include the named authors followed by “and the TED Study Investigators.”
8. Before submission of an abstract to a scientific meeting, it is expected that the associated data analyses and interpretation will be completed. The abstract, data tables, and text of the interpretation will be submitted to the Executive Committee and posted on the One Mind Portal for comment and the designated author(s) will present their data and interpretation (10-minute presentation) to the Executive Committee for discussion and review during an Executive Committee telephone meeting. The Executive Committee will discuss the presentation and approve submission by simple majority vote. It is expected that the resultant manuscript will be submitted to a journal by or before 3 months following presentation of the abstract at the scientific meeting. The same process is required before submitting a manuscript to a journal if no associated abstract has been previously approved.
9. If preparation and submission of manuscripts is not accomplished in a timely manner (within six months following the receipt of data), the Executive Committee reserves the right to delegate manuscript-writing responsibility to another investigator. These requirements are in place to ensure the timely publication and dissemination of study results to the public and the scientific community.
10. Using TED data as preliminary data for grant submission by investigators at participating institutions is encouraged. However, any data tables included in a grant proposal must be approved by the Steering Committee before submission.
11. Proposals for single-site analyses of TED data will be handled the same way as multi-site analyses.
12. The Steering Committee will consider requests from unrelated third parties for access to study data for research and publication purposes *prior* to the data becoming available publically. All parties obtaining

access to the data will agree to abide by the obligations of the TED Data Use Agreement and as set forth in this Guideline.

13. All authors are responsible for notifying the Executive Committee (via email to Brian Fabian brian.fabian@ucsf.edu) of all accepted manuscripts, abstracts, and oral and poster presentations, as well as the journal, date of publication, page number(s) and other information necessary to reference the publication/presentation. The TED Administrative Core will maintain a central list of all accepted abstracts, presentations and publications relating to TED, which will be posted on the TED Web site.

Acknowledgements

1. As this study was sponsored by external sources an acknowledgement is required on all publications.

“Sponsored by the U.S. Department of Defense (Grant #W81XWH-14-2-0176), and our public and private partners. The opinions or assertions contained here are the private views of the authors and are not to be construed as official or as reflecting the views of any sponsor.”

2. Contributions from other collaborators, including laboratory, economists, scientists, consultants or other individuals providing expertise during the trial design, conduct and manuscript processes but not members of the official TED Study Investigators and not meeting the prescribed authorship criteria should also be listed in the acknowledgments.

TED Executive Committee		
Name	Role	Institution
Geoffrey Manley, MD, PhD	Contact PI, Admin Core Leader	UCSF
Harvey Levin, PhD	PI, Outcomes Core Leader	Baylor Institute of Medicine
Joseph Giacino, PhD	PI, Clinical/Rehab Core Leader	Spaulding Rehabilitation Center
Michael McCrea, PhD	PI, Outcomes Core Leader	Medical College of Wisconsin
Murray Stein, MD MPH	PI, Outcomes Core Leader	University of California, San Diego
Nancy Temkin, PhD	PI, Biostatistics Core Leader	University of Washington
Ramon Diaz-Arrastia, MD	PI, Emerging Tech Core Leader	Center for Neuroscience and
Steven Wisniewski, PhD	PI, Biostatistics Core Leader	University of Pittsburgh
Sureyya Dikmen, PhD	PI, Outcomes Core Leader	University of Washington

TED Steering Committee		
Name	Role	Institution
Geoffrey Manley, MD PhD	Contact PI, Admin Core Leader	UCSF
Arthur Toga, PhD	Informatics Core	University of Southern California
Claudia Robertson, MD	Clinical & Rehabilitation Core	Baylor College of Medicine
David Cifu, MD	Clinical & Rehabilitation Core	Virginia Commonwealth University
David Okonkwo, MD PhD	Clinical & Rehabilitation Core	University of Pittsburgh
David W. Wright, MD	Clinical & Rehabilitation Core	Emory University
Harvey Levin, MD	Outcomes Core	Baylor College of Medicine
James Kelly, MD	Outcomes Core	National Intrepid Center of Excellence
John Whyte, MD PhD	Clinical & Rehabilitation Core	Moss Rehabilitation Research Inst.
Joseph Giacino, PhD	Clinical & Rehabilitation Core	Spaulding Rehabilitation Center
Kevin Guskiewicz, PhD	Outcomes Core	University of North Carolina
Michael McCrea, PhD	Outcomes Core	Medical College of Wisconsin
Michael Weiner, MD	Neuroimaging Core	UCSF
Murray Stein, MD MPH	Outcomes Core	University of California, San Diego

Nancy Temkin, PhD	Biostatistics Core	University of Washington
Pratik Mukherjee, MD PhD	Neuroimaging Core	UCSF
Ramon Diaz-Arrastia, MD PhD	Emerging Technologies Core	Uniformed Services University of the Health Sciences
Rick Williams, PhD	Biostatistics Core	RTI International
Robert Knight, MD	Emerging Technologies Core	University of California, Berkeley
Stephen Wisniewski, PhD	Biostatistics Core	University of Pittsburgh
Sureyya Dikmen, PhD	Outcomes Core	University of Washington
William Jagust, MD	Emerging Technologies Core	University of California, Berkeley

Appendix 1: Research Collaboration Proposal Request Form

Instructions: A completed and approved Research Collaboration Proposal Request is required to be submitted to the TED Executive Committee (care of brian.fabian@ucsf.edu) and should be no more than 2 pages long. Authors are encouraged to contact the Biostatistics Core to receive assistance with the statistical analysis plan. Clinical site statisticians are also encouraged to participate in these consultations. Proposals will be reviewed by the TED Executive Committee. All aspects of manuscript development will be governed by this Guideline. Proposals should contain the following elements:

Date:

Investigator's Name:

Investigator's Title:

Organization or Clinical Center:

E-mail:

Telephone:

TED Sponsor (if not a TED investigator):

Other investigators who will be working on this analysis:

Analysis Plan Title:

TED Dataset files to be used: Pilot Study ☐ Currently Enrolling Study ☐

Purpose of Data Request (check all that apply)		TED Core (check all that apply)	
☐	Exploratory	☐	Clinical Core
☐	Data analysis for manuscript	☐	Biospecimens Core
☐	Preliminary data for grant proposal	☐	Neuroimaging Core
☐	Inputs for simulation model	☐	Biostatistics/CER Core
☐	Development of statistical methods	☐	Outcomes Core
☐	Other (describe)		

Please attach a 2-page description of your analysis plan including:

- 1) Short background/rationale for addressing the research question
- 2) Primary variables to be used in the analysis (please provide mock tables)
- 3) Brief description of methods and statistical analysis plan
- 4) What is the impact if successful?

For exploratory requests, complete item 1 now and submit items 2 through 4 within 60-days of accessing the dataset(s).

Research Collaboration Request Tracking Log			
☐ Received by Executive Committee Member	By:		Date:
☐ Reviewed by Executive Committee			Date:
☐ Decision communicated to Requestor	By:		Date:
Decision:	☐ Accept	☐ Decline	☐ Return for revision

Appendix 6

TED Seed Project Request for Applications



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 from the [TED website](#).

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, posttraumatic 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