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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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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 for FDA and other regulatory agencies to accelerate 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, biofluid biomarker, neuroimaging biomarker, clinical outcome assessment (COA), Glial Fibrillary Acidic Protein (GFAP), pathoanatomic lesion, clinical trial, regulatory readiness, brain magnetic resonance imaging (MRI), brain computed tomography (CT), Food and Drug Administration (FDA)

ACCOMPLISHMENTS

What were the major goals of the project?

Technical Objective I (Stage I | Years 1-2): 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.

YEAR 4 PROGRESS TOWARD COMPLETION OF AIMS:
(Ongoing Aims are bolded)

AIM 1.1. Organize and host a multi-stakeholder consensus conference (CC1) in Year 1 to assess the current landscape of COAs and biomarkers for potential qualification as DDTs. COMPLETED YEAR 1

AIM 1.2. 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. COMPLETED AND ONGOING

AIM 1.3. Curate and harmonize data on candidate clinical outcome assessments and biomarkers from existing military, civilian, and sports mTBI and modTBI databases with well-characterized samples (The TED Metadataset). COMPLETED AND ONGOING

AIM 1.4. Establish Expert Working Groups (EWGs) to organize the analyses of individual studies and the TED Metadataset, and review existing TBI COA and biomarker literatures. COMPLETED AND ONGOING

AIM 1.5. 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. COMPLETED YEAR 1

AIM 1.6. Solicit, evaluate, and collaboratively develop “Seed Projects” to further the TED goals of identification and validation of endpoints for diagnostic and therapeutic trials. COMPLETED YEAR 3

AIM 1.7. Organize and host Consensus Conference 2 (CC2). COMPLETED YEAR 3

New AIM Continued into Stage II

- **Develop and implement TED Friend Control Study**
    - **Develop protocol, obtain IRB and HRPO approval. COMPLETED and ONGOING**
    - **Enroll 300 friend controls utilizing existing TRACK-TBI infrastructure. ONGOING**

New Subtasks Continued Into Stage II

- Initiate Letter of Support Pathway with FDA CDER for Neuroimaging Biomarkers. COMPLETED
- Collaborate with FDA CDER to obtain Letter of Support for Neuroimaging Biomarkers. COMPLETED
- Initiate Letter of Support Pathway with FDA CDER for Biofluid Biomarkers. COMPLETED
- Collaborate with FDA CDER to obtain Letter of Support for Biofluid Biomarkers. COMPLETED

Technical Objective II (Stage II | Years 3-5): 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.

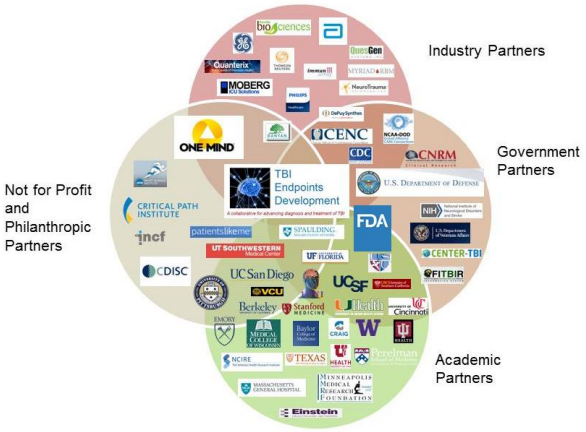
AIM 2.1 Validate COA endpoints. ONGOING

AIM 2.2 Validate biomarkers with diagnostic, prognostic, predictive, and pharmacodynamic endpoints. ONGOING

<u>Development of a Unique Collaborative to Accelerate TBI Regulatory and Clinical Research</u>

No drug or device has been approved by the U.S. Food and Drug Administration (FDA) to treat acute TBI, with decades of well-designed clinical trials failing. 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.

Fig. 1. The Collaborative – A Precompetitive Ecosystem



Expertise from across domains is evidenced by Co-Investigators representing over 30 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. Investigators have also engaged early and often with FDA representatives as described elsewhere in this report. Over the course of the grant, 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. A significant monetary contribution has been made by an industry partner that has supported Stage II imaging curation of the TED Metadataset, and will be further outlined later in this report. This type of cross-cutting collaboration is essential to overcome the myriad challenges of TBI research.

In the past funding year, TED investigators also entered into an exciting collaboration with data scientists and neuroscientists from the Department of Energy National Laboratories. This collaboration has already proved fruitful and is further described in the *New Initiatives* section of this report.

1. Engagement with FDA; Advances in Regulatory Efforts toward Endpoint Validation

Early and consistent communication and collaboration with the FDA has been an integral goal of the TED Initiative. The TED Initiative has demonstrated its commitment to regulatory science since the first Consensus Conference with active participation from key members from multiple FDA divisions.

C. Center for Devices and Radiological Health (CDRH). Members of the TED Neuroimaging Core initiated contact with representatives from CDRH in March 2016. Close collaboration has continued with CDRH over the past two years. This ongoing collaboration has resulted in tangible progress as the TED's Medical Device Development Tools proposal has passed through multiple stages in the process culminating in submission of a Qualification Package.

The proposed MDDT consists of a software module that facilitates identification and measurement of the number of brain contusions, in conjunction with validation of the prognostic utility of this biomarker for the purpose of identifying patients at higher risk for poor outcome for participation in clinical trials of therapies for mild TBI. The FDA Context of Use is articulated as: *Contusions, as assessed by an expert rater from MRI using this MDDT, may be used for prognostic enrichment of clinical trials for therapeutic medical devices intended to improve outcomes at 3-months for patients aged 18-65 years with acute nonpenetrating head trauma and GCS 13-15 that have undergone acute head CT (e.g., as part of standard clinical care) at a U.S. Level 1 trauma center.*

C.1. CDRH Medical Device Development Tool (MDDT) Qualification Stage. As noted, TED leadership has been formally engaged with FDA CDRH via the MDDT program for more than two years. During the Year 4 reporting period, Dr. Esther Yuh's team made significant progress with the MDDT proposal. Dating back to September 2016, Dr. Yuh's team progressed through multiple stages of the Qualification process. These teleconferences and pre-qualification submissions are detailed in previous annual and quarterly reports. In April 2017, the team received formal approval from Dr. Ochs, FDA Office of In Vitro Diagnostics Radiological Health Deputy Director, to submit a Qualification Package. Following FDA-directed analysis, on July 26, 2018 Dr. Yuh and team submitted a Qualification Package to FDA. (Appendix 1)

In this Qualification Package, the prognostic significance of an MRI biomarker, brain contusion, was validated for 3-month outcome after mild traumatic brain injury. The impact of this is significant. An estimated 2.8 million patients in the U.S. alone are treated in emergency departments annually for mild TBI, and no prognostic imaging biomarker has been validated to identify patients at risk for persistent impairment. Physicians and other medical professionals, other than those engaged in TBI research, are generally unaware of the prognostic significance of imaging findings in mild TBI, including findings on both CT and MRI. This study shows that a specific imaging biomarker can be reliably measured and can identify at- risk patients, an important step in finding ways to treat mild TBI and reduce its social and economic costs. In Dr. Yuh's study, brain contusion on MRI was prognostic not only for 3-month GOS-E, the primary outcome measure, but remained prognostic out to 6 months, and was also prognostic at 2 weeks. These results were based on a carefully curated data set from 10 TRACK-TBI sites, all U.S. Level 1 trauma centers.

A second biomarker, diffuse axonal injury (DAI) on MRI was also studied. Like contusion, DAI was prognostic for 2-week outcome, but was no longer prognostic at 3 or 6 months. This suggests a possible differential recovery rate for these two different pathologies, and supports the hypothesis that identification of specific pathoanatomic lesions is important to understanding prognosis after mild TBI and for attempts to find effective treatments.

The team validated the utility of these imaging biomarkers as a means to enrich cohorts for clinical trials of therapies for mild TBI. We anticipate that medical product developers will enroll patients at greater risk for poor outcome, in order to study the therapeutic efficacy of devices. Developers should have a greater chance of demonstrating a statistically significant improvement in outcomes for this carefully selected and enriched study population. Use of the tool will be highly beneficial for TBI clinical trials, whose 100% failure rate has been attributed to heterogeneous pathology not accounted for by grading CT scans as "positive" or "negative."

The FDA CDRH review team reached out recently for clarification on a few minor points of the Qualification Package. Dr. Yuh's team followed a scheduled teleconference with a response to the CDRH review team's queries. This response included a revised context of use statement, a clarification on the 'intent to diagnose' population, addition of Wilcoxon rank sum test statistics, and recalculation of PPA and NNA confidence intervals. This response was submitted on 10/06/2018. (Appendix 2)

Follow up discussions with the review team was favorable and we are optimistic that a decision on qualification will come in Q1 of Year 5 of the grant.

D. Center for Drug Evaluation and Research (CDER) Letter of Support for Biofluid Biomarkers

Using the strategy developed by the Neuroimaging EWG that resulted in the first ever CDER Letter of Support focusing on TBI, the Biofluid EWG developed and submitted an evidentiary dossier in support of an LOS to encourage the further study of blood levels of glial fibrillary acidic protein (GFAP), a biomarker of astrocytic injury and ubiquitin carboxyl-terminal hydrolase-L1 (UCH-L1), a biomarker of neuronal injury as exploratory prognostic enrichment biomarkers to identify patients who are at risk for having poor functional outcome during the course of traumatic brain injury clinical trials. On January 10, 2018, The TED Initiative, collaboratively with TRACK-TBI, received this Letter of Support signed by Dr. Billy Dunn, Director, Office of New Drugs, Division of Neurology Products, and Dr. Christopher Leptak, Director, CDER Biomarker Qualification Program. (Appendix 3) As important as the support for the particular prognostic biomarkers nominated, is that the LOS calls out specifically FDA's endorsement of the TED Initiative's approach to leveraging data across studies, paying particular attention to use of data standards, data sharing, and analytic processes. This Letter of Support complements the letter received last year to explore neuroimaging prognostic biomarkers. To date, these are the only two Letters of Support issued by FDA related to TBI.

These two Letters of Support for TBI biomarkers can be publically accessed on the FDA's website: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm602478.htm#FDA_issued_Letters_of_Support

2. Progress by Expert Working Groups (EWGs)

Expert Working Groups in the domains of Clinical Outcome Assessments, Blood-Based Biomarkers, and Neuroimaging Biomarkers have developed and are continuously refining work streams to move our research forward. During the course of Year 4, the EWGs (previously merged with their corresponding Core Teams from the NIH-funded TRACK-TBI study) have held bi-monthly conference calls and have met in-person at two joint TED Initiate/TRACK-TBI Investigator Meetings (UCSF: January 31 – February 1, 2018 (Appendix 4) and in conjunction with the National Neurotrauma Society annual meeting in Toronto, ON, August 11-12, 2018 (Appendix 5), and at numerous other professional events, including the annual MHSRS convening in Florida in August 2018. The Toronto meeting corresponded with The 3rd Joint Symposium of the International and National Neurotrauma Societies, thus reducing travel costs as many TED investigators combined the two meetings. The cross pollination of TED EWGs and TRACK-TBI Cores leverages the intellectual effort and synergistic workflows of these groups.

All three works groups have been extremely productive over the course of the past year. This is evidenced by the strong showing at the recently convened 2018 Military Health System Research Symposium where 14 abstracts were accepted. Four of these abstracts were selected for oral presentation.

Table 1. MHSRS Abstracts and Oral Presentations

Biofluid Biomarker EWG	
Title	**Authors**
Point-of-Care GFAP versus core lab S100B Biomarker Testing for CT Abnormalities in Traumatic Brain Injury: a prospective TRACK-TBI study ***Selected for Oral Presentation***	Okonkwo D, Puffer R, Puccio A, Yue J, Diaz-Arrastia R, Korley F, Wang K, Mukherjee P, Yuh E, Temkin N, Robertson C, Manley G and the TRACK-TBI Investigators
Acute blood levels of two neuronal biomarkers (UCH-L and NSE): Correlation to injury cranial CT abnormality – a TRACK-TBI Phase 1 study ***Selected for Oral Presentation***	Wang K, Lautenslager L, Munoz-Pareja J, Diaz-Arrastia R, Korley F, Puccio A, Yue J, Mukherjee P, Yuh E, Temkin N, Robertson C, Sun X, Jain S, Manley G and the TRACK-TBI Investigators and TED Investigators
Diagnostic utility of plasma glial fibrillary acidic protein (GFAP) for identification of traumatic brain injury patients with MRI abnormalities despite a normal head CT: A TRACK-TBI study	Yue, Korley, Choy W, Puffer R, Winkler E, Deng H, Taylor S, Ferguson A, Huie J, Sun X, Jain S, Yuh E, Mukherjee P, Puccio A, Wang K, Diaz-Arrastia R, Okonkwo D, Manley G, and the TRACK-TBI Investigators
Imaging Biomarker EWG	
CT and MRI prognostic biomarkers for 3-month outcome in mild traumatic brain injury	Yuh E, Levin H, Taylor S, Sun X, Mac Donald C, Temkin N, Giacino J, Markowitz A, Mukherjee P, Dikmen S, Jain S, Manley G, and the TRACK-TBI Investigators
Clinical Outcome Assessment EWG	
Characteristics and Course of Clinical Recovery in Civilian Patients with Mild Traumatic Brain Injury (GCS 13-15) ***Selected for Oral Presentation***	Nelson L, Temkin N, Dikmen S, Manley G, and the TRACK-TBI Investigators
Glasgow Outcome Scale Extended—Differences counting disability from only brain injury versus including peripheral injuries in those with Glasgow Coma Scale 13-15: A TRACK-TBI study ***Selected for Oral Presentation***	Temkin N, Zahniser E, Morrissey M, Barber J, Machamer J, Manley G, Dikmen S
Glasgow Outcome Scale Extended—Differences Counting Disability from Only Brain Injury versus Including Peripheral Injuries in those with GCS Scale 3-12	Temkin N, Satris G, Machamer J, Manley G, Dikmen S
The Functional Status Examination as a Measure of Functional Status Following Mild Traumatic Brain Injury	Zahniser E, Temkin N, Machamer J, Manley G, Nelson L, Dikmen S
Functional Status Examination in Patients With Moderate-to-Severe Traumatic Brain Injuries	Machamer J, Temkin N, Manley G, Dikmen S
Prevalence and predictors of suicidality following mild TBI	Fisher L, Agtarap S, Jain S, Sun X, Manley G, Giacino J, Stein M
An Evidentiary Review of the Glasgow Outcome Scale – Extended: Is it Appropriate for Use in TBI Clinical Trials	Christoforou A, Bergin M, Armstrong M, Robbins A, Merillat S, Erwin P, Getchius T, McCrea M, Giacino J
The Validity of the Rivermead Post-Concussion Questionnaire in Detection and Monitoring of Post-Concussive Symptoms	Christoforou A, Agtarap S, Merillat S, Erwin P, Stein M, Giacino J
Feasibility assessment of a Flexible Outcome Assessment Battery for use in longitudinal TBI Research	Bodien Y, Sherer M, Taylor S, Dikemen S, Yue J, Murray S, Corrigan J, Levin H, Temkin N, Machamer J, Boase K, Vasser M, McCrea M, McAllister T, Whyte J, Kramer J, Ngwnenya L, Manley G, Giacino J, and the TRACK-TBI Investigators
Location of Brain Contusions and Outcome of GCS 9- TBI Patients in the TRACK-TBI Pilot Study	Levin H, Robertson C, Mukherjee P, Yuh E, Giacino J, Temkin N, Yan F, Manley G and the TRACK-TBI Pilot Investigators

Complete abstracts can be found in Appendix 6.

A. Clinical Outcome Assessments (COAs) EWG.

The COA EWG is charged with identifying a multidimensional set of clinical outcome assessments to be validated for use in applied therapeutic clinical trials for TBI. The ultimate goal of this EWG is the development of a complex, multi-dimensional modeling of TBI outcome measurement that moves us closer to a neurobiopsychosocial understanding of TBI effects and recovery. Now merged with the TRACK-TBI Outcomes Core, these two groups continue to meet bi-monthly to develop workstreams developed to reach research goals stipulated in the grant. This group has diligently worked over the past year to refine protocols for the TED Friend Control Study, described in more detail later in the report. The COA EWG leads have also mapped out key COA deliverables with corresponding priorities and approach described the Table 2.

Table 2. COA EWG Deliverables

TED COA EWG Deliverable	COA EWG Priorities & Approach (leads)
Application of EB-COP to selected COAs	• EB-COP Pilot project complete, EB-COP manuscript, in process (Giacino) • Submit Trail Making Test and PTSD Checklist to EB-COP process (akin to GOS-E pilot project) (funding approval pending) (Giacino) • Application of EB-COP to Rivermead Post-concussion Questionnaire using multiple validation approaches – **In Process** (Stein, Giacino)
Longitudinal performance of multidimensional COAs in TBI over time	• Main focus of analysis and manuscript by TED COA EWG members (Nelson); leverages TRACK pilot dataset and TED Meta dataset (MDS) • Manuscript published: ***Validating Multi-Dimensional Outcome Assessment: Using the Traumatic Brain Injury Common Data Elements: An Analysis of the TRACK-TBI Pilot Study Sample.*** Nelson et al. *J Neurotrauma*. 2017 Nov 34:3158–3172
Utility of multidimensional COAs to stratify TBI patients into clinical phenotypes for targeted intervention trials	• Primary aim of the TRACK Outcomes Core, with TED COA EWG, pending completion TRACK-TBI data curation (Giacino, McCrea) • Analysis of TRACK and CARE dataset using SEM and factor models in deriving distinct clinical phenotypes in TBI (Nelson, NIH R03)
COAs as predictors of recovery and outcome after TBI	• Focused analysis of TRACK and TED MDS on COA predictors of (acute, subacute) outcome (McCrea, Nelson) • Leverages TRACK and TED MDS
Compare performance of COA's measuring same COI (e.g., memory)	• Focused analysis of BTACT to legacy COA measures • Comparison of legacy COA measures to NIH Toolbox (Temkin, Ranson)
Influence of injury and non-injury factors on COA performance	• Focus of analysis from UW mag-sulfate study on effects of TBI vs. Other injuries on performance of GOSE (Temkin) • Analysis of TRACK and TED MDS examining effects of premorbid, comorbid factors on COA performance (Levin)

The COA EWG has also worked extensively with collaborators from the Department of Energy National Labs (Lawrence Livermore, Berkeley, and Argonne) to create novel exploratory analyses of our COA data. This collaboration began with bi-monthly conference calls that have now increased in frequency to weekly calls as the high computing capabilities of the Labs are being exploited to create an Outcomes landscape analysis. Expertise of the COA EWG has been essential to provide DOE data scientists with guidance on domain specific variables in the dataset, as well as expected results (directionality, magnitude, trend) for core outcome variables. These weekly conference calls built the foundation for a highly productive, face-to-face data blitz meeting on the UCSF campus that was attended by TED and TRACK-TBI key personnel and 27 members of the National Labs. (Appendix 7)

At this meeting, the COA EWG and DoE collaborators developed three main priorities for analysis:

1. Co-Linearity and Redundancy Analysis: conduct analysis of TRACK PILOT outcome measures to determine the degree of co-linearity/redundancy across the measure set, and determine each measure's contribution to overall variance in outcome with core functional domains.

2. Cluster/Subtype Analysis: apply multiple approaches (cluster analysis, LCM, etc.) to determine subtypes/clusters of TBI outcomes at 6 months; first conduct analysis on all TBI patients (GCS 3-15), followed by focused analysis of mTBI cohort (GCS 13-15).

3. Outcome Prediction Analysis: apply multiple approaches to determine predictors of outcome at 6 months; include pre-injury, acute injury and post injury variables in prediction models. The dependent (outcome) variable in these analyses may be, depending on the results of Analysis #2, cluster or subtype group membership.

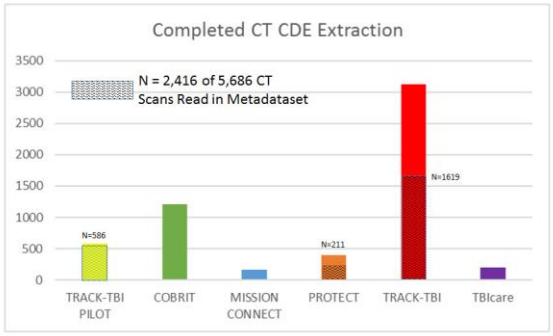
More detail on this collaboration is found in the *New Initiatives* section of this report.

B. Neuroimaging EWG. 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 TBI imaging methodologies and make recommendations as to further validation that may be required and/or if new imaging modalities are needed.

The Neuroimaging EWG has been instrumental in advancing two different regulatory pathways. Having already been successful in securing the first FDA CDER Letter of Support focusing on TBI, more recently the EWG has supported work by Dr. Esther Yuh, a TED Seed Project recipient, who is driving ongoing collaboration with FDA via submission of a proposed tool to validate neuroimaging biomarkers. Dr. Yuh's team has now submitted a Qualification Package that is currently under review. (See, *Engagement with FDA section, above)*

Members of the Neuroimaging EWG have also been working over the past year to complete Common Data Element Interpretation and recording of CT scans collected as part of the TED Metadataset. To date, the EWG has catalogued nearly 2,500 of the approximately 5,700 CT scans in the TED Metadataset. Quantitative interpretation has been completed on at least 200 of these scans. (Fig. 2.)

Fig. 2. Metadataset CT CDE Extraction



Finally, the team has multiple manuscripts that are in advanced stages of production. These manuscripts are listed in the *Next Reporting Period* section of this report.

Table 3. Imaging EWG Deliverables

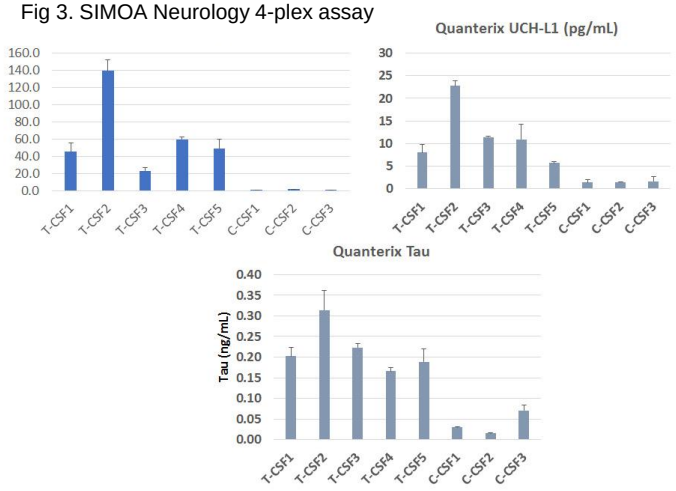
TED Neuroimaging EWG Deliverable	Neuroimaging EWG Priorities & Approach (leads)
MDDT Qualification Submission	• Address comments made by CDRH review team in Pre-Qualification Package • Submit Qualification Package **(Completed)**
Metadataset imaging curation	• Remainder of Metadataset CT scans to be read and imaging features catalogued • Utilize new imaging annotation and management tool designed by Rancho Bioscience

Manuscript preparation and submission	• Interrater reliability of Traumatic Brain Injury CT Common Data Elements (Yuh) • Interrater reliability of Traumatic Brain Injury MRI Common Data Elements (Yuh) • Regulatory Science of Neuroimaging-based TBI Biomarkers as Drug Development Tools (companion piece with Biofluid Biomarker EWG) (Mukjerjee, Mac Donald, Yuh) • DTI vs NODDI manuscript **(Submitted to *BRAIN*)**

C. Biofluid Biomarker EWG. The Blood-Based Biomarker EWG is tasked with 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 proposed submission of one or more blood-based biomarkers to the FDA biomarker qualification program. To facilitate achievement of these goals, the Biofluid Biomarker EWG holds monthly conference calls facilitated by leads Drs. Ramon Diaz-Arrastia and Kevin Wang, with their European counterparts at InTBIR to align strategies of both efforts.

The Blood-Based Biomarker EWG worked collaboratively to build an evidentiary dossier of research findings contained in their Letter of Support submission package that resulted in receipt of an FDA Letter of Support to encourage further study of GFAP and UCHL-1 at biofluid biomarkers of TBI. (See, *Engagement with FDA section, above*).

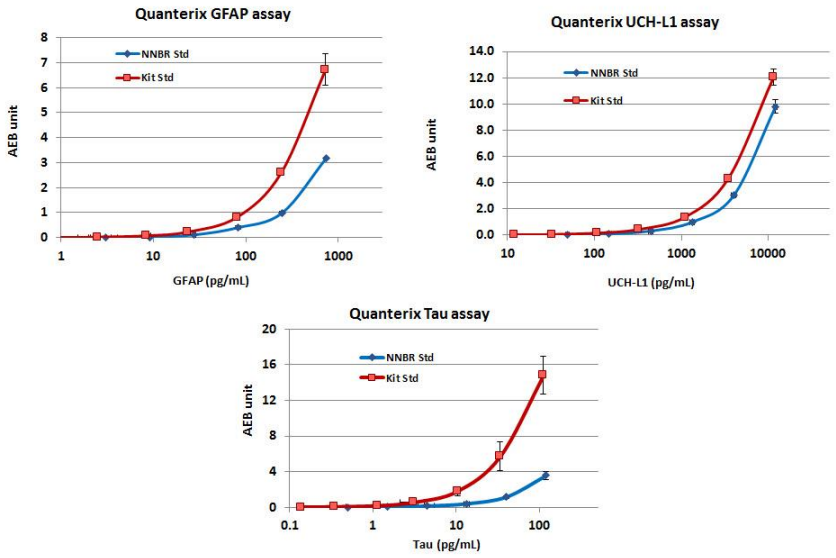
Fig 3. SIMOA Neurology 4-plex assay



Blood-Based Biomarker EWG Co-Lead Dr. Kevin Wang completed the Mesoscale Discovery (MSD) Tau assay, finding that the format can detect a qualified Tau standard protein For the 5 pooled human TBI CSF samples, with loading of 5 uL, signals were marginally detectable over controls. Increasing to 25 uL resulted in good signals for the TBI CSF samples that are clearly above the levels of the 3 control CSF samples.

Dr. Wang also completed installation of the Quanterix SR-X equipment and has run the SIMOA Neurology 4-plex assay (including Tau, GFAP and UCH-L1).
(Fig. 4) This Quanterix format is the highest sensitivity commercial platform for TBI biomarker studies.
Data has been collected on generating standard curves with the vendor's analyte standard as well as University of Florida NNBR gold standard recombinant proteins (UCH_L1, GFAP and Tau). Figure 1 shows analytical performance of Quanterix high sensitivity GFAP, UCH-L1 and Tau assay formats. Using the Quanterix SIMOA Neurology 4-plex assay, Dr. Wang obtained comparative standard curves using vendor's standard as well the UF NNBR qualified analyte gold standards for GFAP, UCH-L1 and Tau.

Fig 4. Quanterix assay



Dr. Wang's team also completed ability tests of the Quanterix high sensitivity GFAP, UCH-L1 and Tau assay formats in detecting native biomarker targets in human TBI CSF versus healthy control CSF. The Quanterix neurology four-plex platform was capable of simultaneously detecting native TBI biomarker targets (GFAP, UCH-L1 and Tau) in 5 pooled TBI CSF samples over three pooled control CSF samples (5 µL loading).

These tests have provided Dr. Wang and his team the requisite data to write his final Seed Project results manuscript, slated for submission to *Clinical Chemistry* in December 2018.

During the last quarter of Year 4, members of the Biofluid Biomarker EWG have continued important biomarker assay work. The EWG has assayed several cytokine and inflammatory biomarkers in samples from the TRACK-TBI Pilot study. The aim was to confirm sensitivity of the assays, and insure that we are likely to obtain valuable data when we run the samples from the TRACK-TBI U01 dataset. IL-10, TNF, and IL-6 were assayed using the Quanterix Cytokine 3-plex A (Quanterix, Lexington MA) on the Simoa Platform. Also assayed was HMGB-1 using commercially available ELISA (IBL International GmbH, Hamburg Germany). The group found that the Quanterix Cytokine 3-plex is sensitive for detecting cytokine elevations in mild TBI patients from the TRACK-TBI Pilot. However, the HMGB1 assays used are not sufficiently sensitive, and over one-third of samples were below the lower limit of detection. The conclusion is that more sensitive assays will have to be developed for measuring HMGB1 in the samples from the TRACK-TBI U01. These results were presented at the 3rd Joint Symposium of the International and National Neurotrauma Societies in Toronto, ON in August 2018 in two separate posters. Dr. Wang's University of Florida team is now working to identify a more robust HMGB1 assay to be test on the TRACK-TBI Pilot samples first.

In addition, Dr. Wang's team at University of Florida identified a MSD V-plex panel of inflammation/vascular injury biomarkers to be first tested on TRACK-TBI Pilot for detection sensitivity and ability to distinguish TBI from healthy controls. They will minimally contain the following top priority markers: GM-CSF, IL-10, IL-17A, IL-1α, IL-1β, IL-6, IL-7, IL-8, MCP-1, TARC, TNF-α, ICAM-1, VCAM-1, IFN-γ, MIP-1α, MIP-1β, and VEGF-A. These will be completed at Dr. Wang's lab.

Using orthopedic controls from the TRACK-TBI cohort and normal 'friend controls' enrolled in the TED Friend Control Study, Dr. Wang compared acute (< 25 h) levels of 4 markers (GFAP, UCH-L1, NSE, S100b) in TBI patients versus healthy controls and orthopedic injury controls. GFAP, UCH-L1, and NSE demonstrated good separation of TBI vs. orthopedic controls. All four markers were able to distinguish TBI from healthy controls. These data were also presented at the International Neurotrauma meeting in Toronto in August 2018.

Table 3. Biofluid Biomarker EWG Deliverables

TED Biofluid Biomarker EWG Deliverable	Biofluid Biomarker Priorities & Approach (leads)
FDA CDER Letter of Support	• Collaborate with FDA CDER on LOS package submitted (Diaz-Arrastia, Wang) • Address feedback from CDER to obtain Letter of Support • Obtain FDA CDER Letter of Support **(COMPLETED)**
Manuscript preparation and submission	• Regulatory Science of Biofluid-based TBI Biomarkers as Drug Development Tools (companion piece with Neuroimaging Biomarker EWG) (Diaz-Arrastia, Wang) • Validation of GFAP as a diagnostic biomarker for TBI (compared to CT as FDA standard for diagnosis) To definitively determine the prognostic accuracy of day-of-injury GFAP and UCHL1 and their combination for identifying TBI patients with a high probability of having delayed functional recovery. (Diaz-Arrastia) • Validation of GFAP as a diagnostic biomarker for TBI in CT-negative subjects (subgroup MRI+ and MRI- TBI subjects) vs Orthopedic Controls and Healthy Volunteer Controls (Manley, Korley)

3. Seed Projects

The TED Initiative awarded four Seed Projects with a period of performance from February 1, 2016 to January 31, 2017. All four were completed, and two, the Giacino and Yuh projects, have continued to progress. Dr. Giacino's *Evidence-Based Clinical Outcome Assessment Platform (EB-COP)* is currently being housed by the American Academy of Neurology. Dr. Yuh's Seed Project had developed into full FDA MDDT Qualification Submission.

3.A. Joseph Giacino, PhD – Harvard Medical School – $218,239

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

Objective

Design, build and pilot test an evidence-based platform for assessment of COAs, placing particular emphasis on the validity of the COA as it pertains to a specific concept of interest within a given context of use.

Recent activities have focused the completion of EB-COP validation of the Rivermead Post-Concussion Questionnaire (RPQ) and preparation for associated dissemination activities. Work also continued on the optimization of the EB-COP Web-Based Data Entry Tool and accompanying Manual of Operating Procedures. Progress toward these objectives and recent dissemination activities are described below:

1) **EB-COP Validation of Rivermead Post-Concussion Questionnaire (RPQ)**: As previously reported, the RPQ was selected to undergo systematic review using the 6-step EB-COP platform, in collaboration with Drs. Murray Stein and Stephanie Agtarap (UCSD). Over the past year, Dr. Giacino's team had completed Steps I-IV-A, including (Step I) formulating the evidence question to investigate the psychometric 'readiness' of the RPQ in measuring post-concussive symptoms in the subacute (<6 month) mild TBI population for 3 independent purposes of use – (1) TBI symptom detection, (2) TBI stratification and (3) sensitivity to natural history changes; (Step II) determining that there is sufficient evidence to support the face validity, the relevance of the item content and the feasibility of administration and scoring of the RPQ relative to the evidence questions; (Step III) performing a systematic literature search which identified a total of 437 abstracts for review; and (Step IV-A) completing the abstract review by two independent reviewers (Drs. Andrea Christoforou and Stephanie Agtarap). The abstract review identified 78 articles that were taken forward for full-text review in Steps IV-B-D. In this last quarter, the final steps of the EB-COP review were completed, including confirmation of the relevance of the articles to the evidence questions (Step IV-B), evaluation of the general (Step IV-C) and QI-specific (Step IV-D) methodological quality of each study, analysis and synthesis (Step V) of the evidence toward a grade and recommendation for the use of the RPQ in the pre-specified contexts of use (Step VI). Please refer to Appendix 8 for the poster for summary of findings that was presented at 2018 MHSRS.

2) EB-COP Web-Based Data Entry Tool: As previously reported, in collaboration with the Guideline Development Office of the American Academy of Neurology, the team continues to refine and test the Qualtrics Web-based Data Entry tool, which was developed to steer and semi-automate the EB-COP Review Process. This past quarter, updates were completed to Step IV-D, including relevant user-friendly introductory pages and clarifying instructions and guidance. The team is now in the process of completing the workflow for Step V (Data Synthesis) and the web-based back-end logic for Step IV (COA Grading and Recommendation), so that the appropriate grade and recommendation for future research is produced on the basis of the evidence that the user identifies and subsequently enters into the Web-based tool.

3) Dissemination Activities: As previously reported, an abstract describing the EB-COP validation of the RPQ and an abstract describing the EB-COP Pilot Run on the Glasgow Outcome Scale – Extended (GOS-E) (Appendix 9) were accepted for poster presentations. This past quarter, both posters were presented at the Military Health Services Research Symposium (MHSRS; Kissimmee, Florida). The RPQ poster was also presented at the 3rd Joint Symposium of the International and National Neurotrauma Societies.

3.B. Esther Yuh, MD PhD – UCSF – $ 236,655

CT and MRI Prognostic Biomarkers for Mild to Moderate Traumatic Brain Injury

Objective:
Demonstrate interrater reliability of TBI imaging Common Data Elements (CDE) and prognostic validity of CT and MRI CDEs

Key Milestones:

- Submission of MDDT Qualification Package to FDA CDRH in Q4 Year 4.

4. Creation and Curation of the TED Metadataset

The TED Metadataset now contains granular data on over 6,000 mild-moderate and severe TBI study participants. The constituent studies include TRACK-TBI, TRACK-TBI Pilot, COBRIT, TBICare, Concussion Research Consortium, ProTECT III, Mission Connect, an NIH-funded neuroimaging study led by TED Neuroimaging EWG Lead Dr. Pratik Mukherjee, the Center for Neuroscience and Regenerative Medicine Neuren study, and the INTREPID study.

Over the past year and a half, The TED data management team at University of Pittsburgh created a methodology to harmonize variables among the disparate datasets that comprise the Metadataset. This methodology was initially utilized to harmonize data fields for patient demographics, medical history, mechanism of injury, and Glasgow Coma Scale score. Additionally, the team worked to harmonize over 30 clinical outcome assessment (COAs) measures that were utilized across the studies. A complete list of harmonized COAs is found in Appendix 10.

The backbone of the TED Metadataset is the TRACK-TBI study dataset that recently reached its NINDS-mandated target of enrolling 3,000 TBI patients and control subjects. To date, TRACK-TBI has enrolled over 2,700 subjects with TBIs across the injury spectrum and over 300 orthopedic trauma controls. Additionally, over 200 'friend controls' have been enrolled under the TED Friend Control Study protocol. (See *TED Friend Control Study* later in report for details). Further strengthening the efficacy of the Metadataset, the data quality assurance team at the University of Washington has taken the lead in curating TRACK-TBI GOS-E scores. The GOS-E is the primary outcome for the study and over 3,500 assessments have been audited. Auditing of other entered subjects is ongoing, with the plan to have manual audits of all TRACK/TED cases and controls. Automatic checks have also been built into QuesGen to aid in data curation covering over 137,000 CRFs, with over 6,000 rule checks.

In addition, curation efforts include reviewing all outcome data entered from the 6 new TRACK-TBI sites that have been enrolling subjects over the past two years. This includes reviewing the pre-injury interviews as well as data entered at each follow up time point that includes the GOSE, interview, neuropsychological measures, and self-report questionnaires. All data from these new sites have been reviewed, queries sent to sites, and resolved.

The UW curation efforts continue with the goal of reviewing all GOSEs scores collected in TRACK-TBI and comparing these scores with pre-injury information and current work and living situation data. Priority has been placed on the approximately 150 severe TBI participants, as well with Orthopedic Controls for use in upcoming papers.

In addition to this, the data curation team has begun review of BTACT administration dates in relation to the administration dates of the more standard paper and pencil neuropsychological measures.

Imaging Curation.

The Metadataset now contains over 6,000 CT scans, of which, more than 2,200 have been read with CDEs catalogued by TED neuroradiologists. Quantitative interpretation has been completed on more than 200 scans.

To make this process more efficient, the TED Initiative contracted with Rancho Biosciences to develop an imaging annotation and management tool designed to streamline the process of reading, annotating, and cataloging Metadataset images. (Fig. 5,6) This contract was made possible through private philanthropic funding as detailed in the Year 3 Annual Report. The tool will produce a number of solutions to greatly aid our reviewers as they work through the annotation of the images. These solutions include:

- Creation of new data entry form with validation requirements
- Development of online dashboard that will display total number of CT scans to be annotated, total number of reads, number of reads by radiologist/site, ability to generate predefined reports
- User interface design that demonstrates annotation progress on each scan with injury summary detail

Fig. 5. Imaging annotation dashboard

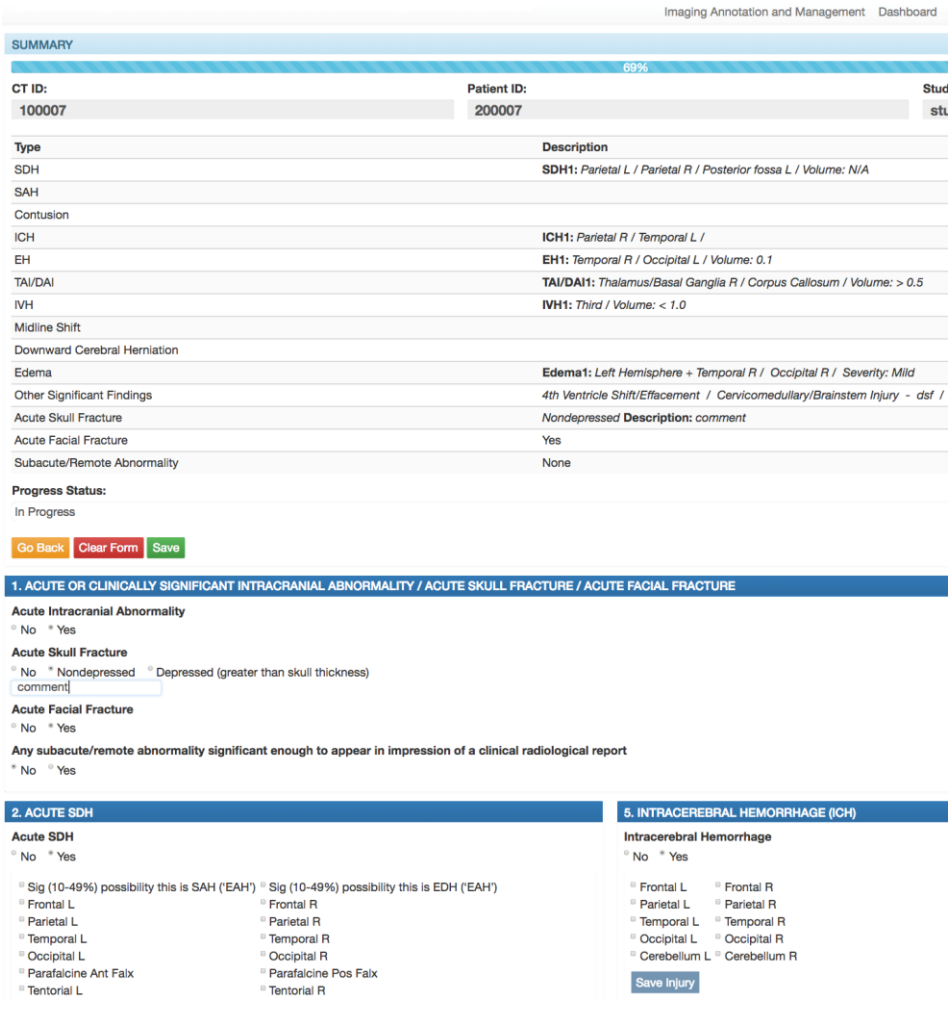
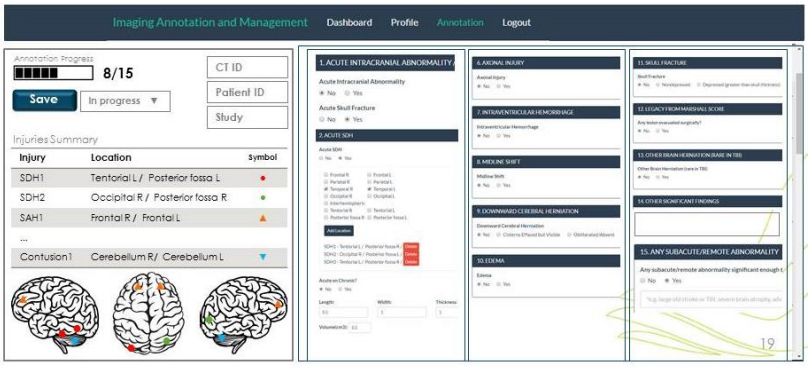


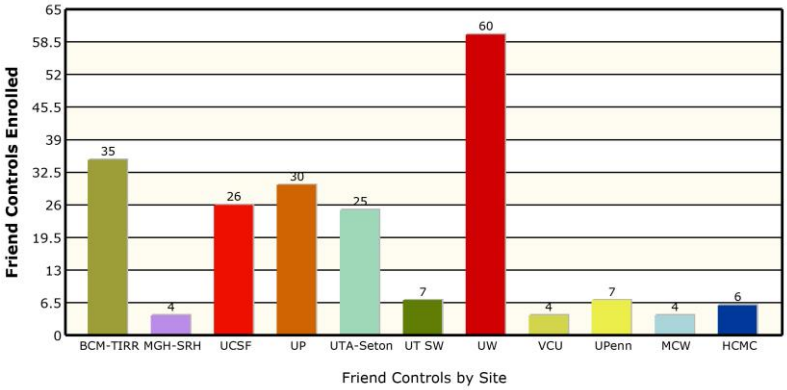
Fig. 6. Imaging annotation dashboard



metadata from all CT scans in the TED Metadataset into the tool's database.

A hard drive containing CT scans from the COBRIT study was recently shipped to board certified neuroradiologists at Massachusetts General Hospital who will be begin reading the scans and remotely logging the CDE data into the imaging annotation and management tool. It is estimated these readers will be able to read 50-100 CT scans per week.

Fig.7. Friend controls enrolled by site



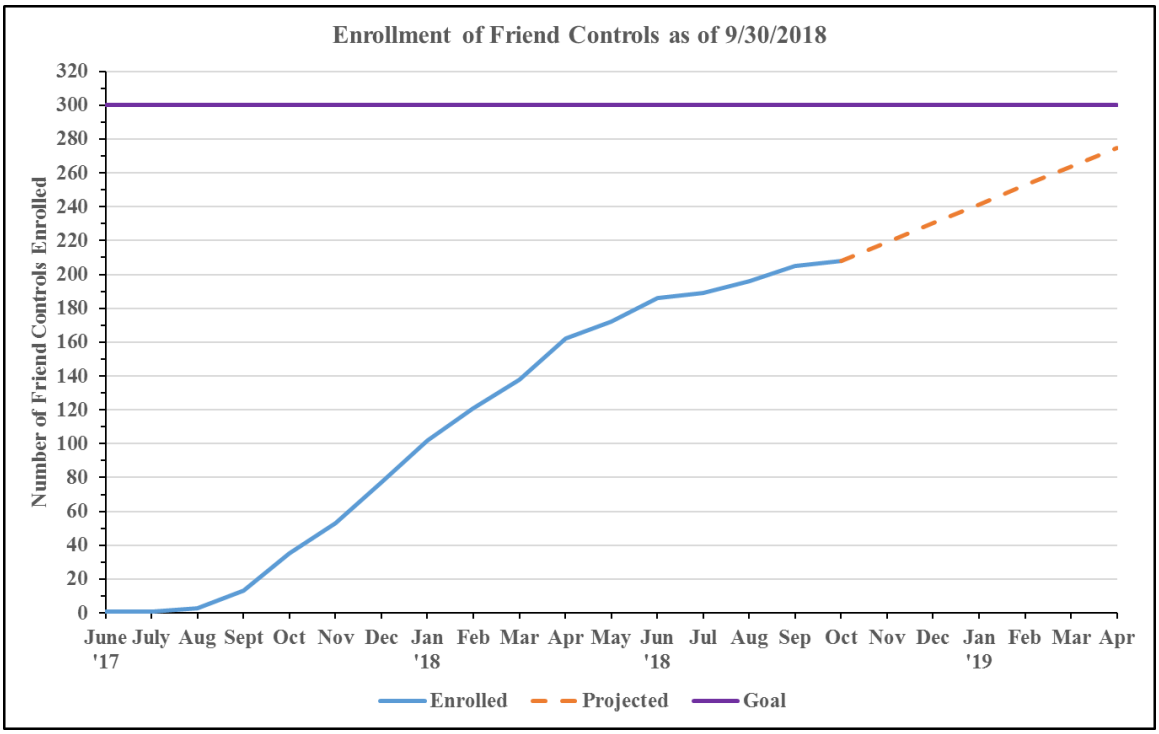
4. TED Friend Control Study

Utilizing and leveraging the existing study infrastructure of TRACK-TBI, enrollment in the TED Friend Control Study has significantly ramped up in Year 4.

After receiving both HRPO and IRB approval, 15 sites are now fully approved to recruit and consent Friend Controls.

Over the past five quarters, 208 Friend Controls have been enrolled. 196 of these Friends Controls have been enrolled in the MRI cohort meaning they have fully or partially completed 2-week. 129 of the 196 have also obtained a fully complete or partially complete matching 6-month MRI. Based on current enrollment averages, the Friend Control Study is estimated to reach its enrollment goal of 300 in April-May 2019.

Fig.8. Friend control enrollment projection



5. New Initiatives

Collaborative Partnership with U.S. Department of Energy (DOE) National Laboratories

Harnessing High Through-put Computing in a Precision Medicine Approach to TBI

A collaborative partnership has developed with the DoE National Labs: Lawrence Livermore National Laboratory (LLNL), Lawrence Berkeley National Laboratory (LBNL), and Argonne National Laboratory

(ANL). The three laboratories have executed Data Use and Human Material Transfer Agreements for the TRACK-TBI Pilot and TRACK-TBI (U) studies. DUAs will also be executed for the TED Metadataset. This collaboration seeks to enhance, extend, and expand our ability to both objectively stratify and develop effective treatments for patients with TBI. Building on expertise in high performance computing and data analytics/artificial intelligence, the National Labs will develop scalable algorithms, tools and capabilities for use on multi-scalar data collected from brain injured and control study subjects, which feature several challenges commonly found in DoE mission data i.e., extremely large, complex, heterogeneous, and with missing and variable quality elements. Early feasibility and utility of such an approach is being demonstrated using the TRACK-TBI Pilot dataset. For this proof-of-concept engagement, DOE computing resources and expertise will be brought to bear to analyze high-resolution multi-modal MRI brain images from the TRACK-TBI dataset, captured over a year following injury, along with other serially collected outcome data, and will apply machine learning approaches to cluster patients and develop prognostics from heterogeneous data collected in the largest longitudinal study of TBI to date.

In a short time, this collaboration has already produced deliverables. The multi-scalar TRACK-TBI Pilot data has been moved from UCSF to the National Laboratories and analysis is underway. Subject matter and technical work groups have been established and have demonstrated a seamless and scalable network connection enabling secure data hosting and high-performance TBI analytics across ANL, LBNL, and LLNL. The TRACK-TBI MR image pipeline has been transferred to a supercomputer system **that has demonstrated a factor of 1000 speedup in analytic capability, to wit: the BEDPOST X analysis of MRIs acquired under our protocols went from 10 hours to 2m37s. Processing scripts for other MRI algorithms are now being written by the National Labs' data scientists to achieve similar reductions in processing times. This suggests the possibility of incorporating MRIs into acute clinical decision making, an impossibility with the former 24-hour or greater lag from acquisition to analysis**.

Progress continues with this partnership as multiple working groups have formed with regular bi-monthly conference calls scheduled. Data use agreements between UCSF and each of the three labs to share TRACK-TBI U01 data have also been fully executed.

In July, Secretary Perry made his second visit to UCSF, where he was given a tour of the Neurotrauma Intensive Care Unit at Zuckerberg San Francisco General Hospital and Trauma Center by Dr. Manley. The Secretary and members of the DOE's Veteran's Relations Committee then participated in half-day conference that included presentations on the UCSF Precision Medicine/National Labs Collaboration, SPOKE: Scalable Precision Open Knowledge Engine, ACTIV, and a presentation by Dr Manley titled, *From Precision Medicine to Personalized Care: Weill Institute of Neuroscience TBI Clinic*. Demonstrating the importance of these initiatives, these sessions were attended by UC President Janet Napolitano and UCSF Chancellor Sam Hawgood. (Appendix 11)

In September 2018, a 'data blitz' meeting was held at the UCSF Mission Bay Campus that was attended by 27 Department of Energy data scientists and the TED Initiative/TRACK-TBI Executive Committee members and key personnel. Progress and key priorities for analysis was documented in the COA EWG update section of this report.

During this meeting, key milestones and timelines were crystallized for connectome computations and development of a CT registration atlas.

The connectome workflow timeline is as follows:

- Finish initial computation pipeline and execute a prototypical patient at LLNL (10-31-2018)
- Develop coarse-grain PARSL version of computation pipeline (10-31-2018)
- Demonstrate container-based computation pipeline at LLNL (11-30-2018)
- Develop fine-grained PARSL pipeline (01-31-2019)
- Process full TRACK-TBI dataset (~1000 MRI scans) using container-based PARSL scripting (03-31-2019)

CT Registration Build-out

There exists no public reference anatomical atlas for CT. Newer methods employing deep-learning techniques have shown successful improvements in both accuracy and processing, but also rely on atlases or the manually segmented volumes the atlases are generated from. While there have been efforts to manually segment CT volumes, the data is not public and communication with the developing groups has been as of yet unforthcoming.

Therefore, the team will utilize the atlases and labeled volumes in the MR domain. For patients with MR volumes available, MRs will be registered to an Atlas, and the MR will be registered to the CT. Doing this for roughly 250 patients with both imaging modalities will provide two useful datasets:

1. Volumetrically aligned cross-modality imaging pairs
2. Anatomical segmentation labels for CT volumes

The labeled CT volumes may be sufficient to compute an atlas for intersubject registration (patient -> atlas). The pairs can further be used to learn the mapping between the imaging domains using generative deep learning techniques. From this, an end-to-end approach to CT anatomical segmentation using scalable, non-rigid, non-linear deep learning models may be employed. The synthesis of MR from CT may be useful for the connectome work, as well as for conditionally synthesizing patient images to improve diagnosis/prognosis accuracy of classification models, and publishing models/data that protects patient privacy.

CT Registration Milestone Completion – target date January 2019

- Register the ~250 pairs of MR & CT scans in the TRACK-TBI Pilot dataset
- Investigate efficacy of derived “CT Atlas”
- Develop model trained on pairs to synthesize MR from CT and vice versa
- Develop end-to-end DL approach for anatomical segmentation using pilot pairs (~250)
- Use existing lesion segmentation (non-localizing) methods and patient scan-level CT annotations to broadly validate and quantify accuracy.
- Obtain as many as possible manually labeled CT images for validation
- Investigate disparities between CT and MR annotations, with minimum goal to predict when an MR may be necessary.

6. Regulatory Successes of TED Initiative Partners

Philanthropic and private industry partners of the TED Initiative have achieved regulatory successes over the past year that have advanced the field of traumatic brain injury research.

In February 2018, FDA granted the De Novo request of Banyan Biomarkers for the commercialization of the Banyan BTI (Brain Trauma Indicator), an *in vitro* diagnostic blood test using GFAP to aid in the evaluation of patients with suspected TBI and concussion. Approval for this assay is a significant step forward for the TBI community. Banyan Biomarkers has been a part of the TED Initiative and the TRACK-

TBI public-private partnership since inception, with Banyan representatives having attended and participated in both TED Consensus Conferences and the FDA TBI Biomarkers Conference in March 2016. In a letter dated April 4, 2018, Ron Hayes, PhD, Founder and Chief Scientific Officer of Banyan, formally acknowledged the pioneering work that TED Initiative investigators have done to lay the groundwork for Banyan's FDA approval. (See Appendix 12)

Following on the Banyan success, FDA then accepted Abbott Laboratories into their Breakthrough Devices Program for its TBI diagnostic test using GFAP and UCHL-1 as TBI biomarkers. The iSTAT TBI test will provide for a more effective and timely diagnosis of potentially life-threatening and irreversibly debilitating effects from a mild traumatic brain injury, relative to the current standard of care in the United States. The brief submitted to FDA in support of this request was founded upon data collected and contributed by, and through direct collaboration with, the TED Initiative and TRACK-TBI research teams. These two initiatives' clinical insights, track record of contribution of information dossiers and tireless communication with FDA about TBI biomarkers, specifically GFAP and UCHL-1, were critical to Abbott's success, as set forth in a letter of thanks from Abbott. (See Appendix 13)

Further recent acknowledgement of the TED Initiative's collaborative methodology came via C-PATH (Critical Path Institute), a nonprofit, public-private partnership with the FDA created under the auspices of the FDA's Critical Path Initiative program in 2005. C-PATH was an early consulting partner with the TED Initiative as we developed strategic relationships with multiple FDA divisions. In March 2018, C-PATH launched the Huntington's Disease Regulatory Science Consortium. (See Appendix 14) The Consortium will work to advance innovation in regulatory science methods, supporting clearer development and regulatory pathways that lead to the approval of Huntington's disease therapeutics. Recent information shared by Diane Stephenson, CPATH Executive Director, Critical Path for Parkinson's Consortium indicated that learnings from TED's regulatory efforts had led to the success of this effort.

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

The Blood-based Biomarker EWG LOS initiative was led by Dr. Fred Korley, whose K Award is supported as part of the TRACK-TBI study, and includes mentors drawn from the TED/TRACK-TBI lead, Ramon Diaz-Arrastia. The TED COA and Imaging EWGs continue to mentor Dr. Raquel Gardner, whose work using latent class growth to identify outcome trajectories in TBI uses the TED Metadataset. COA EWG Lead, Dr. Michael McCrea has mentored Dr. Lindsay Nelson, whose published manuscripts using with TRACK-TBI data, and abstracts presented at both MHSRH and NNS supported her NIH R01 application *Improving Patient Classification and Outcome Measurement in TBI*. Dr. Nelson scored in the 15th percentile on this submission, suggesting a fundable score, and supported by both TED Initiative and TRACK-TBI Investigators.

How were the results disseminated to communities of interest?

<u>Combined TED/TRACK-TBI Investigators Meeting | Toronto, ON</u>

Taking advantage of the 3rd Joint Symposium of the International and National Neurotrauma Societies in Toronto, ON a combined TED Initiative/TRACK-TBI investigators meeting was held. Key personnel from both programs met to discuss programmatic issues that included progress of the Friend Control Study, data management and curation, and synergies between TRACK-TBI and TED Initiative working groups to name a few. (Appendix 5)

<u>2018 Military Health System Research Symposium Presentations</u>

TED Initiative investigators were well represented at the 2018 MHSRS with 14 abstracts, 4 of which were

selected for Oral Presentations. (Appendix 6)

3rd Joint Symposium of the International and National Neurotrauma Societies

TED Initiative investigators were represented at the 3rd Joint Symposium of the International and National Neurotrauma Societies in Toronto, ON with 17 abstracts presented. (Appendix 5)

Neuroimaging Biomarker EWG Manuscripts

The evolution of white matter changes after mild traumatic brain injury: A DTI and NODDI study.

Palacios EM, Owen J, Yuh EL, Wang M, Vassar MJ, Ferguson AR, Diaz-Arrastia R, Giacino J, Okonkwo DO, Robertson CS, Stein MB, Temkin NR, Jain S, McCrea M, Mac Donald C, Levin HS, Manley GT, Mukherjee P. Submitted to *BRAIN*. Preprint published on bioRxiv: https://doi.org/10.1101/345629

Blood-Based Biomarker EWG Manuscripts

Performance evaluation of a multiplex assay for simultaneous detection of four clinically relevant TBI biomarkers.

Korley FK, Yue JK, Wilson D, Hrusovsky K, Diaz-Arrastia R, Ferguson AR, Yuh EL, Mukherjee P, Wang KKW, Valadka A, Puccio A, Okonkwo DO, Manley GT. *J Neurotrauma*. 2018 Jul 23. PMID 29690824.

Age-related differences in diagnostic accuracy of plasma GFAP and Tau for identifying acute intracranial trauma on CT: A TRACK-TBI study.

Gardner RC, Rubenstein R, Wang KKW, Korley FK, Yue JK, Yuh EL, Mukherjee P, Valadka AB, Okonkwo DO, Diaz-Arrastia R, Manley GT; TRACK-TBI Investigators. *J Neurotrauma*. 2018 Jun 29. PMID 29717620.

An update on diagnostic and prognostic biomarkers for traumatic brain injury.

Wang KK, Yang Z, Zhu T, Shi Y, Rubenstein R, Tyndall JA, Manley GT. *Expert Rev Mol Diagn*. 2018 Feb;18(2):165-180. PMID 29338452

Clinical Outcome Assessment EWG Manuscripts

Optimizing outcome assessment in multicenter TBI trials: Perspectives from TRACK TBI and the TBI Endpoints Development Initiative.

Bodien Y, McCrea M, Dikmen S, Temkin N, Boase K, Machamer J, Taylor S, Sherer M, Levin H, Kramer J, Corrigan J, McAllister T, Whyte J, Manley G, Giacino J; and the TRACK-TBI Investigators. *The Journal of Head Trauma Rehabilitation*. 2018 May/Jun;33(3):147-157. PMID 29385010

Validating Multi-Dimensional Outcome Assessment: Using the Traumatic Brain Injury Common Data Elements: An Analysis of the TRACK-TBI Pilot Study Sample.

Nelson LD, Ranson J, Ferguson AR, Giacino J, Okonkwo DO, Valadka AB, Manley GT, McCrea MA, and the TRACK-TBI Investigators. *J Neurotrauma.* 2017 Nov 34:3158–3172. PMID 28595478.

Functional status examination in patients with moderate-to-severe traumatic brain injuries.

Machamer J, Temkin NR, Manley GT, Dikmen S. *J Neurotrauma*. 2018 May 15;35(10):1132-1137. PMID 29415608.

Temporal profile of care following mild traumatic brain injury: Predictors of hospital admission, follow-up referral and six-month outcome.

Yue JK, Winkler EA, Sharma S, Vassar MJ, Ratcliff JJ, Korley FK, Seabury SA, Ferguson AR, Lingsma HF, Deng H, Meeuws S, Adeoye OM, Rick JW, Robinson CK, Duarte SM, Yuh EL, Mukherjee P, Dikmen SS, McAllister TW, Diaz-Arrastia R, Gordon WA, Valadka AB, Okonkwo DO, Manley GT; TRACK-TBI Investigators. *Brain Inj*. 2017;31(13-14):1820-1829. PMID 29166203.

Emergency department blood alcohol level associates with injury factors and six-month outcome after uncomplicated mild traumatic brain injury.
Yue JK, Ngwenya LB, Upadhyayula PS, Deng H, Winkler EA, Burke JF, Lee YM, Robinson CK, Ferguson AR, Lingsma HF, Cnossen MC, Pirracchio R, Korley FK, Vassar MJ, Yuh EL, Mukherjee P, Gordon WA, Valadka AB, Okonkwo DO, Manley GT; TRACK-TBI Investigators. *J Clin Neurosci*. 2017 Nov;45:293-298. PMID 28789959.

TED Initiative Website

The TED website is hosted on the UCSF Drupal platform, which is free for UCSF programs and departments. (https://tbiendpoints.ucsf.edu) The site 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. From October 1, 2017 to September 30, 2018, the website has garnered nearly 5,000 page views.

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

1. Continued collaboration with FDA CDRH review team to address any feedback received from submission of MDDT Qualification Package by Dr. Esther Yuh and team

2. Comprehensive harmonization of studies in the TED Metadataset, primarily focusing on reading/cataloging neuroimaging features of remaining CT scans

3. Continued recruitment, enrollment, and follow-up of subjects for Friend Control study to reach target enrollment of 300

4. Targeted Clinical Outcomes Assessment EWG Interrogations
    1. Submitting Trail Making Test and PTSD Checklist to EB-COP process
    2. Longitudinal performance of multidimensional COAs in TBI over time
        - Manuscript in progress
    3. Utility of multidimensional COAs to stratify TBI patients into clinical phenotypes for targeted intervention trials
        - Pending completion of TRACK-TBI dataset
    4. COAs as predictors of recovery and outcome after TBI
        - Focused analysis of TRACK-TBI dataset and TED Metadataset on COA predictors of outcome led by Drs. McCrea and Nelson

5. COA EWG to complete and submit following manuscripts:
    1. EB-COP process
    2. Natural history of recovery from mild traumatic brain injury in patients presenting to U.S. level 1 trauma centers: a TRACK-TBI study
    3. Feasibility of a Flexible Outcome Assessment Battery for use in Longitudinal Traumatic Brain Injury Research
    4. Identifying and mitigating common threats to the validity of outcome assessment in TBI research: perspectives from TRACK TBI
    5. Glasgow Outcome Scale Extended — Differences Counting Disability From Only Brain Injury Versus Including Peripheral Injuries
    6. The Temporal Relationship of Mental Health Problems and Functional Limitations Following mTBI: A TRACK-TBI Study

6. Neuroimaging EWG to complete and submit following manuscripts:
    1. Inter-Rater Reliability for TBI Common Data Elements (CDEs) on MRI Scans
    2. Inter-Rater Reliability for TBI Common Data Elements (CDEs) on CT Scans

7. Biofluid Biomarker EWG to complete and submit following manuscripts:
    1. Validation of GFAP as a diagnostic biomarker for TBI (compared to CT as FDA standard for diagnosis)
    2. To definitively determine the prognostic accuracy of day-of-injury GFAP and UCHL1 and their combination for identifying TBI patients with a high probability of having delayed functional recovery.
    3. Validation of GFAP as a diagnostic biomarker for TBI in CT-negative subjects (subgroup MRI+ and MRI- TBI subjects) vs Orthopedic Controls and Healthy Volunteer Controls

8. Blood-based biomarker validation studies looking at GFAP and UCHL-1 that will utilize data collected from approximately 1,500 TBI patients, 100 trauma controls, 50 healthy controls, and newly enrolled friend controls

Impact

The importance of the TED collaborative as a paradigm for "a new way of doing business" is already taking hold. We continue to expand our pre-competitive research ecosystem in which academic collaboration is advanced by synergistic contribution by historically siloed private industry competitors, and guided by 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 four years since our launch, we have brought together over 40 academic institutions, more than 20 private industry partners, and 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. By way of the TED Metadataset, we have created an informatics platform that contains harmonized data on thousands of subjects from multiple studies of mild, moderate, and severe TBI. With the progression of the TRACK-TBI study, the Metadaset continues to grow in size and richness. 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 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 leave a lasting imprint on the field of TBI research. The last large-scale effort to create a harmonized database was the IMPACT study, which concluded a decade ago. While IMPACT was a major achievement, the studies upon which this metadataset was build were conducted in 1980's and 1990's. The TED Metadataset includes ongoing observational studies and recent interventional studies that are likely more generalizable to future clinical trials. 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. At the conclusion of this initiative, the TED Metadataset will be publically accessible via FITBIR.

In the field of neuroimaging, the continued development of the Yuh et al OsiriX CDE software module provides a standardized way to locate, count, measure, and record imaging biomarkers that we can show

provide a prognostic correlation to negative outcomes. The software will assist expert raters e.g., neuroradiologists, to classify pathoanatomic lesions using CDE criteria and label abnormalities on the appropriate MR images to enhance and standardize clinical assessment of contusions and hemorrhagic axonal injury on MRI. By targeting patients with these biomarkers, medical product developers will have a more enriched patient population in which to study therapeutic effectiveness. Identification of these imaging biomarkers will lead to reliable enrichment of therapeutic clinical trials through association of those biomarkers to negative patient outcomes at 3 months. With the tool, the field will have greater certainty that patients have presented with definitive identification of pathoanatomic lesions, with reduced subjectivity toward interpretations of imaging results, and that the therapy being evaluated will be able to make specific claims towards the improvement in outcomes. We are confident that the tool will receive FDA Qualification during Year 5 of the grant.

Designed in collaboration with Rancho Biosciences, the imaging annotation tool designed to streamline the process of reading, annotating, and cataloging Metadataset images will possess great utility for TED investigators as they work their way through the roughly 56,000 CT scans in the Metadataset. This web-based platform is currently being utilized by multiple neuroradiologists in different geographic locations.

The development of the Giacino et al EB-COP Platform will provide the field with an evidence-based platform for assessment of COAs, placing particular emphasis on the validity of the COA as it pertains to a specific concept of interest within a given context of use. EB-COP, as a semi-automated tool, is designed to enable an efficient, transparent, and systematic process for selection and validation of clinical outcome assessment measures. Its research impact will be to identify which COAs are best equipped to address specific types of research questions (ie, COU-specific); its clinical impact will serve to evaluate COA performance separately for different clinical applications (eg, diagnosis, prognosis), and its regulatory impact will be to provide a pipeline for vetting COAs (including CDEs) nominated for use in drug and device trials.

The Wang et al work to produce quantified high-purity antigen protein gold standard solution (0.50 mg/mL) for a set of identified blood-based biomarker (UCH-L1, S100β, GFAP, NFL, and Tau) will permit assay cross-referencing, a first in the field. Testing of serum samples in all assay formats for each of the 4 biomarkers to establish a cross-referencing capacity and obtaining a complete assay performance and reproducibility profile for the four biomarkers across all assay platforms will be an ongoing contribution to the field.

The partnership with DOE national labs has the potential to significantly clinical practice in the TBI field. The demonstrated ability to speed up the imaging pipeline by a factor of 1000 shows the immense potential of this collaboration.

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 Metadataset 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 and to our MDDT submission. 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 avoided 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. As an objective metric of TED's success, in 2015 we received no inquiries from pharmaceutical companies regard clinical trial planning, cohort enrichment/stratification, or selection of outcome measures. To date, in 2018 we have received inquiries from over 10 biotech/pharmaceutical companies and 2 device companies. There is a growing awareness of the progress being made in TED and the importance of our ongoing efforts that is encouraging a return of industry to TBI.

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. Given the recent flurry of activity in the drug and device clinical trial space by our public-private partners, lessons learned from TED are contributing to the design of these studies that will likely lead to improved diagnostic tools and new therapeutics for TBI.

CHANGES/PROBLEMS:

Nothing to report

PRODUCTS

Publications

The evolution of white matter changes after mild traumatic brain injury: A DTI and NODDI study.
Palacios EM, Owen J, Yuh EL, Wang M, Vassar MJ, Ferguson AR, Diaz-Arrastia R, Giacino J, Okonkwo DO, Robertson CS, Stein MB, Temkin NR, Jain S, McCrea M, Mac Donald C, Levin HS, Manley GT, Mukherjee P. Submitted to *BRAIN*. Preprint published on bioRxiv: https://doi.org/10.1101/345629

Temporal lobe contusions on computed tomography are associated with impaired 6-month functional recovery after mild traumatic brain injury: A TRACK-TBI study.
Yue JK, Winkler EA, Puffer RC, Deng H, Phelps RRL, Wagle S, Morrissey MR, Rivera EJ, Runyon SJ, Vassar MJ, Taylor SR, Cnossen MC, Lingsma HF, Yuh EL, Mukherjee P, Schnyer DM, Puccio AM, Valadka AB, Okonkwo DO, Manley GT; TRACK-TBI Investigators. *Neurol Res*. 2018 Sep 3:1-10. PMID 30175944.

Optimizing outcome assessment in multicenter TBI trials: Perspectives from TRACK TBI and the TBI Endpoints Development Initiative.
Bodien Y, McCrea M, Dikmen S, Temkin N, Boase K, Machamer J, Taylor S, Sherer M, Levin H, Kramer J, Corrigan J, McAllister T, Whyte J, Manley G, Giacino J; and the TRACK-TBI Investigators. *The Journal of Head Trauma Rehabilitation*. 2018 May/Jun;33(3):147-157. PMID 29385010

Performance evaluation of a multiplex assay for simultaneous detection of four clinically relevant TBI biomarkers.
Korley FK, Yue JK, Wilson D, Hrusovsky K, Diaz-Arrastia R, Ferguson AR, Yuh EL, Mukherjee P, Wang KKW, Valadka A, Puccio A, Okonkwo DO, Manley GT. *J Neurotrauma*. 2018 Jul 23. PMID 29690824.

Age-related differences in diagnostic accuracy of plasma GFAP and Tau for identifying acute intracranial trauma on CT: A TRACK-TBI study.
Gardner RC, Rubenstein R, Wang KKW, Korley FK, Yue JK, Yuh EL, Mukherjee P, Valadka AB, Okonkwo DO, Diaz-Arrastia R, Manley GT; TRACK-TBI Investigators. *J Neurotrauma*. 2018 Jun 29. PMID 29717620.

Functional status examination in patients with moderate-to-severe traumatic brain injuries.
Machamer J, Temkin NR, Manley GT, Dikmen S. *J Neurotrauma*. 2018 May 15;35(10):1132-1137. PMID 29415608.

An update on diagnostic and prognostic biomarkers for traumatic brain injury.
Wang KK, Yang Z, Zhu T, Shi Y, Rubenstein R, Tyndall JA, Manley GT. *Expert Rev Mol Diagn*. 2018 Feb;18(2):165-180. PMID 29338452

Temporal profile of care following mild traumatic brain injury: Predictors of hospital admission, follow-up referral and six-month outcome.
Yue JK, Winkler EA, Sharma S, Vassar MJ, Ratcliff JJ, Korley FK, Seabury SA, Ferguson AR, Lingsma HF, Deng H, Meeuws S, Adeoye OM, Rick JW, Robinson CK, Duarte SM, Yuh EL, Mukherjee P, Dikmen SS, McAllister TW, Diaz-Arrastia R, Gordon WA, Valadka AB, Okonkwo DO, Manley GT; TRACK-TBI Investigators. *Brain Inj*. 2017;31(13-14):1820-1829. PMID 29166203.

Validating Multi-Dimensional Outcome Assessment: Using the Traumatic Brain Injury Common Data Elements: An Analysis of the TRACK-TBI Pilot Study Sample.
Nelson LD, Ranson J, Ferguson AR, Giacino J, Okonkwo DO, Valadka AB, Manley GT, McCrea MA, and the TRACK-TBI Investigators. *J Neurotrauma.* 2017 Nov 34:3158–3172

Apolipoprotein E epsilon 4 (APOE-ε4) genotype is associated with decreased six-month verbal memory performance after mild traumatic brain injury.
Yue JK, Robinson CK, Burke JF, Winkler EA, Deng H, Cnossen MC, Lingsma HF, Ferguson AR, McAllister TW, Rosand J, Burchard EG, Sorani MD, Sharma S, Nielson JL, Satris GG, Talbott JF, Tarapore PE, Korley FK, Wang KKW, Yuh EL, Mukherjee P, Diaz-Arrastia R, Valadka AB, Okonkwo DO, Manley GT; TRACK-TBI Investigators. *Brain Behav*. 2017 Aug 9;7(9):e00791. PMID 28948085.

Emergency department blood alcohol level associates with injury factors and six-month outcome after uncomplicated mild traumatic brain injury.
Yue JK, Ngwenya LB, Upadhyayula PS, Deng H, Winkler EA, Burke JF, Lee YM, Robinson CK, Ferguson AR, Lingsma HF, Cnossen MC, Pirracchio R, Korley FK, Vassar MJ, Yuh EL, Mukherjee P, Gordon WA, Valadka AB, Okonkwo DO, Manley GT; TRACK-TBI Investigators. *J Clin Neurosci*. 2017 Nov;45:293-298. PMID 28789959.

Presentations

Contact PI Dr. Geoff Manley

1. Invited Speaker, Craig Brain Injury Summit, Vail, Co; Title: Paving the Way for a New Era in Brain Injury Medicine and Neurorehabilitation
2. Invited Speaker, Indiana Spinal Cord and Brain Injury Research Fund Board Conference, Indianapolis, IN; Title: Paving the Way for a New Era in Brain Injury Medicine and Neurorehabilitation
3. Invited Speaker, Brain Injury Alliance of Washington, Seattle, WA, Title: Mechanisms of Traumatic Brain Injury
4. Invited Speaker, 4th Federal Interagency Meeting on TBI, Washington, DC, Title: Biomarkers for Traumatic Brian Injury: Lessons Learned from TRACK-TBI and TED
5. Invited Speaker AAN 5th Annual Sports Concussion Conference, Indianapolis, IN; Title: Magnetic Resonance Imaging
6. Invited Speaker: NeuroTrauma2018, Toronto, ON; Title: TRACK-TBI: Transforming Clinical Research and Knowledge in Traumatic Brain Injury

Biofluid-Based Biomarker EWG Co-Lead Dr. Ramon Diaz-Arrastia

1. Workshop Chair and Speaker, American Neurological Association 142nd Annual Meeting, San Diego, CA; Title: Endophenotypes of Traumatic Brain Injury: What we need to know for the next generation of clinical trials
2. Invited Speaker, Powering Precision Health Summit 2017, Boston, MA; Title: Towards precision medicine in neurotrauma: Progress Report from TRACK-TBI
3. Invited Speaker, Craig Hospital Brain Injury Summit 2018, Vail, CO; Title: TBI Biomarker Research and Clinical Applications: An update
4. Invited Speaker, Craig Hospital Brain Injury Summit 2018, Vail, CO; Title: Dementia, Aging, and Neurodegenerative Consequences after TBI
5. Invited Speaker and Session Chair, North American Brain Injury Society, 2018, Houston, TX; Title: Towards Precision Medicine in TBI: Lessons from TRACK-TBI
6. Invited Speaker and Meeting Organizer, 8th Annual Arrowhead Traumatic Brain Injury Conference, Arlington, VA; Title: Endophenotypes of Traumatic Brain Injury: Early Lessons from TRACK-TBI and the Path Forward
7. Keynote Speaker, Yale Critical Care and Emergency Neuroscience Symposium, New Haven, CT; Title: Brain Tissue Oxygen Monitoring in Severe TBI (BOOST)
8. Invited Speaker, Zlotowski Neuroscience Center, Ben Gurion University of the Negev, Beer-Sheva, Israel; Title: Traumatic Microvascular Injury: A Potentially Treatable Endophenotype of TBI
9. Invited Speaker, Gordon Research Conference on Neurobiology of Brain Disorders, Barcelona, Spain; Title: Traumatic Microvascular Injury: An Overlooked Endophenotype of Trauma-Related Neurodegeneration
10. Invited Speaker, 3rd Joint Symposium of the International and National Neurotrauma Societies - Neurotrauma2018, Toronto, ON; Title: Genomics and Proteomics Research in TBI—The Power of Standardization and Collaboration
11. Invited Speaker, Department of Neurology Grand Rounds, Johns Hopkins University, Baltimore, MD; Title: Endophenotypes of traumatic brain injury: What we need to know for the next generation of clinical trials in TBI
12. Invited Speaker, Society for Neuroscience in Anesthesia and Critical Care, 46th Annual Meeting, Neurotrauma Symposium, San Francisco, California; Title: Does Boosting Cerebral Oxygenation Boost TBI Outcomes
13. Invited Keynote Speaker, Traumatic Brain Injury and Protection Research Symposium, Temple

University, Philadelphia, Pennsylvania; Title: Traumatic Microvascular Injury: A Potentially Treatable Endophenotype of TBI

Clinical Outcome Assessment EWG Co-Lead and Seed Project Recipient Dr. Joseph Giacino

1. Invite Speaker, American Congress of Rehabilitation Medicine Conference, Atlanta, GA; Title: An Evidence-Based Clinical Outcome Assessment Platform (EB-COP) for the Validation of TBI Assessment Measures
2. Invite Speaker, 4th Federal Interagency Conference on Traumatic Brain Injury, Washington D.C; Title: An Evidence-Based Clinical Outcome Assessment Platform (EB-COP) for the Validation of TBI Assessment Measures

Clinical Outcome Assessment EWG Co-Lead Dr. Harvey Levin

1. Poster Presentation, 3rd Joint Symposium of the International and National Neurotrauma Societies, Toronto, ON; Title; Location of Brain Contusions and Outcome of GCS 9-15 TBI Patients in TRACK-TBI Pilot Study
2. Invited Speaker, Old Servants Symposium on Head Trauma in Sports and Risk of Dementia, Stockholm, Sweden; Title: Cognitive Rehabilitation Post-trauma
3. Poster Presentation, 2018 Military Health System Research Symposium; Title: White Matter Hyperintensities and Mild TBI in Post-9/11 Veterans and Service Members
4. Invited Speaker, National Brain Injury Society, Houston, TX; Title: Towards a Comprehensive and Practical Assessment Battery for Mild TBI
5. Invited Speaker, NINDS Workshop on Understanding Traumatic Brain Injury in Women, Bethesda, MD; Title: Sex Differences in Recovery from TBI Among High School Athletes

Clinical Outcome Assessment EWG Co-Lead Dr. Michael McCrea

1. Invited Speaker, NIH Clinical Center Grand Rounds, Bethesda, MD; Title: Neurobiological Effects and Recovery after Concussion: Emerging Evidence from the CARE Consortium
2. Invited Speaker, University of Pittsburgh Medical Center Grand Rounds, Pittsburgh, PA; Title: Advances in Sport-related Concussion: Emerging Evidence from the CARE Consortium
3. Invited Speaker, Brain Injury Research Day, Milwaukee, WI; Title: Realizing the Neurobiopsychosocial Model of TBI
4. Invited Speaker, Texas Institute for Brain Injury and Repair at UT Southwestern, Dallas, TX; Title: Advances in Sport-Related Concussion: Emerging Evidence from the CARE Consortium
5. Invited Speaker, Minnesota Brain Injury Research Conference, Minneapolis, MN; Title: Toward Realizing a Neurobiopsychosocial Model of Injury and Recovery
6. Invited Speaker, Vanderbilt Sports Concussion Center, Nashville, TN; Title: Neurobiological Effects of Sport-Related Concussion: Implications for Clinical Translation
7. Invited Speaker, Fourth Federal Interagency Conference on TBI, Washington, DC; Title: Advances in the Natural History of Concussion: Emerging Evidence from the NCAA-DoD CARE Consortium
8. Invited Speaker, Medical College of Wisconsin Department of Neurosurgery Grand Rounds, Milwaukee, WI; Title: Gaps and Progress Toward Achieving a Precision Medicine Model in TBI.
9. Invited Speaker, American Academy of Neurology Sport-Related Concussion Conference, Indianapolis, IN; Title: NCAA-DoD CARE Consortium Advanced Research Core: Neurobiological Effects & Recovery.
10. Invited Speaker: DoD TBI National Provider Training Conference, Fort Belvoir, VA; Title: Knowledge Translation from Sideline to Battlefield: Findings from the Care Consortium and the Mind Matters Challenge

Neuroimaging Core Lead Pratik Mukherjee

1. Invited Speaker, 102nd Scientific Assembly and Annual Meeting, Radiological Society of North America, Chicago, IL; Title: Impact of Large Scale Research Trials
2. Invited Speaker, Society for Brain Mapping and Therapeutics, Los Angeles, CA; Title: Precision Imaging of Traumatic Brain Injury
3. Invited Speaker, 12th Annual Meeting of the American Society of Functional Neuroradiology, San Diego, CA; Title: Advances in Imaging of White Matter Microstructure and the Macroscale Connectome: Applications to Traumatic Brain Injury

Clinical Outcome Assessment EWG Co-Lead Dr. Murray Stein

1. Invited Speaker, Grand Rounds, University of Manitoba Department of Psychiatry; Title: Traumatic Mind Injury
2. Invited Speaker, Public Health Grand Rounds, UCSD School of Medicine; Title: Military Mental Health
3. Invited Speaker, Research Colloquium on PTSD, Medical Epidemiology and Biostatistics department at the Karolinksa Institute in Stockholm, Sweden; Title: Traumatic Mind Injury

Biofluid-Based Biomarker EWG Co-Lead Dr. Kevin Wang

1. Invited speaker: 23rd Annual EMN Congress (Euroacademia Multidisciplinaria Neurotraumatologica) Pecs, Hungary; Title: The Next Generation of TBI biofluid biomarkers
2. Invited speaker: IRCCS-Mario Negri Institute, Milan, Italy; Title: Tau and Phospho-Tau as TBI biomarkers
3. Invited speaker: 3rd Joint Symposium of the International and National Neurotrauma Societies - Neurotrauma2018, Toronto, ON; Title: Clinical biomarkers for TBI– from acute to subacute-chronic phases and utilities in clinical trials
4. Seminar Speaker, Clinical Translational Aging Research Seminar, University of Florida Institute on Aging, Gainesville, FL; Title: From Traumatic Brain Injury to Chronic Neurodegenerative Disorders
5. Invited speaker, International Initiative for Traumatic Brain Injury Research (InTBIR) 7th Annual Meeting, Brussels, BE; Title: Looking into the future: Clinical utilities of the next generation of TBI biomarkers
6. Invited speaker: State of the Science Meeting on Blood Based Biomarkers for TBI Workshop/ Symposium– jointly sponsored by NIH/DOD/FDA/CDC; Title: Second generation TBI biomarkers

Website

https://tbiendpoints.ucsf.edu

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Personnel Name	Role	Person month worked (Calendar Months)	**Contribution to project** (ex. Ms. Smith has performed work in the area of combined error-control and constrained coding)	Comments
University of California, San Francisco				
Geoffrey Manley	Princpal Investigator	1.2	Lead and contact Principal Investigator	5% cost-sharing support from departmental funds
Pratik Mukherjee	Co-Investigator	1.2	Dr. Mukherjee leads the Neuroimaging Biomarkers Core and serves on the Executive and Steering Committees. Dr. Mukherjee has been involved in all stages of the project in support of the work for the Consensus and Implementation Conferences and Validation studies.	
Yuh, Esther	Co-Investigator	2.4	Dr. Yuh extracts CT and MRI common data elements from the metadataset, performs consensus interpretations on a subject of the CT and MRI exams, and also works with Dr. Harvey Levin and Dr. Temkin on analysis of the CDE imaging data for interrater reliability and validation as prognostic biomarkers.	
Tosun-Turgut, Duygu	Co-Investigator	4.2	Dr. Tosun provides technical and analytical expertise for the proposed high-resolution MRIs and the Tau and amyloid PET scans.	
Palacios, Eva	Specialist	5.75	Dr. Palacios provides support to the Neuroimaging EWG and has been co-author on several high profile manuscripts	
Taylor, Sabrina	Clinical Project Manager	9.6	Dr. Taylor oversees the day-to-day project operations. She provides support to study personnel at all sites regarding implementation of the Core protocols. She supervises all apects of the project at UCSF including enrollment, follow-up, and the meeting of all milestones for the TED Validation Stage II studies.	
Fabian, Jeffrey Brian	Research Administrator	8.4	Mr. Fabian support 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. He serves as a liaison between Dr. Manley and other Core Leaders, Co-PIs, DOD, industry, public-private partners.	
Bajouri, Zabiullah	Clinical Research Coordinator	2.19	Mr. Bajouri was responsible for subject screening and enrollment; completion of the electronic case report forms; subject retention efforts; scheduling of the TED supplemental neuroimaging and follow-up for outcome assessment; processing of subject stipends.	
Morrissey, Molly Rose	Clinical Research Coordinator	2.59	Ms. Morrissey was responsible for subject screening and enrollment; completion of the electronic case report forms; subject retention efforts; scheduling of the TED supplemental neuroimaging and follow-up for outcome assessment; processing of subject stipends.	
Coss, Nathan	Clinical Research Coordinator	2.21	Mr. Coss is responsible for subject screening and enrollment; completion of the electronic case report forms; subject retention efforts; scheduling of the TED supplemental neuroimaging and follow-up for outcome assessment; processing of subject stipends.	
Ma, Herman	Finance Manager	4.5	Mr. Ma suppots the financial operations of the project. He is responsible for managing reimbursement for subcontracts, developing and managing budgets, and approving purchase orders, travel and research subject reimbursements.	
Northern California Institute for Research and Education				
Weiner, Mike	Co-Investigator	1.08	Dr. Weiner is involved in all phases of the project in support of the work for the Consensus and Implementation Conferences and Validation studies. He provided leadership and expertise in neuroimaging and clinical trials.	
Rossi, Stephanie	Staff Research Assistant II	1.6	Ms. Rossi is responsible for acquiring the 3T multimodal MRI sequences followed by perform data quality reviews on all incoming data. She is performing the pipeline processing of multimodality MRI data. She also transform results of image processing into database format and query data for statistical analyses. In addition, she is responsible for data archiving and backup. This position will be supervised by Dr. Tosun-Turgut.	
Kurlander, Danielle	Staff Research Assistant II	7.1	Ms. Kurlander is responsible for acquiring the 3T multimodal MRI sequences followed by perform data quality reviews on all incoming data. She is performing the pipeline processing of multimodality MRI data. She also transform results of image processing into database format and query data for statistical analyses. In addition, she is responsible for data archiving and backup. This position will be supervised by Dr. Tosun-Turgut.	
Lang, Alex	Staff Research Assistant II	7.71	Mr. Lang is responsible for acquiring the 3T multimodal MRI sequences followed by perform data quality reviews on all incoming data. He is performing the pipeline processing of multimodality MRI data. He also transform results of image processing into database format and query data for statistical analyses. In addition, he is responsible for data archiving and backup. This position will be supervised by Dr. Tosun-Turgut.	
Ellis, Ryan	Staff Research Assistant I	8	Mr. Ellis is responsible for performing the pipeline processing of multimodality MRI data. He also transform results of image processing into database format and query data for statistical analyses. In addition, he is responsible for data archiving and backup. This position is supervised by Dr. Tosun-Turgut.	
Truran-Sacrey, Diana	Imaging Manager	3.4	Ms. Truran-Sacrey oversees the management of the image processing and is responsible for training of the imaging staff. She is responsible for the quality of MRI processing and coordinates the co-analysis of processed MRI images. Ms. Truran-Sacrey meets with Derek Flenniken to review database management, priorities and issues. This position is supervised by Dr. Tosun-Turgut.	
Wu, I-Wei	Staff Research Assistant II	1.52	Ms. Wu is responsible for transforming results of image processing into database format and query data for statistical analyses. In addition, she is responsible for data archiving and backup. This position is supervised by Dr. Tosun-Turgut.	
University of Florida				
Wang, Kevin	Co-Investigator	1.2	Biomarker work group CO-lead, biomarker selection, assay optimization	
Yang, Zhihui	Sr. Scientist	2.16	Biomarker assays, data analysis	
Lin, Fan	Res. Assistant	3.6	Biomarker assays, sample organization, archiving and tracking	
Albert Einstein Healthcare Network				
Whyte, John	Co-Investigator	1.2	Dr. Whyte attends all scheduled teleconferences and reviews and advises on all outcomes measurement strategies	
University of Texas - Austin				
Goeke, Esther	Coordinator	5.5	In charge of all patient recruitment and follow up scheduling and quality control	
Griffith, Ebanie	Research Assistant	5	Conducted outcome assessments and neuroimaging sessions, data upload and entry - MRI phantoms	

Medical College of Wisconsin				
McCrea, Michael	Co-Investigator	1.2	Serves on the TED Executive and Steering Committees and Outcomes Core providing expertise in neuropsychology and long term effects on sports related brain injuries	
Nelson, Lindsey	Co-Investigator	2.4	Dr. Nelson led a paper investigating the Glasgow Outcome Scale Extended (GOSE) and its overlap with a multidimensional set of clinical outcome measures (Nelson et al., 2017, J Neurotrauma, 34, 3148-3172). Dr. Nelson has led work investigating the possibility of stratifying patients on the basis of different symptom dimensions using the Rivermead symptom questionnaire (poster presented and manuscript in preparation, in collaboration with Dr. Kramer at MCW and post-doc Stephanie Agtarap from UCSD). Dr. Nelson and Dr. Ranson investigated the psychometric strengths/weaknesses of the GOSE using item-response theory (IRT; poster presented and manuscript under review). Dr. Nelson has used IRT to compare the GOSE to a possible alternative functional outcome measure (manuscript in preparation). Dr. Nelson is leading a project to investigate the performance of a phone-based cognitive outcome measure (the BTACT) versus in-person neurocognitive tests.	
Kramer, Mark	Staff Researcher	2.13	Dr. Kramer has conducted advanced modeling analyses of the project with Dr. Nelson deriving clinical phenotypes from symptom ratings from the Rivermead questionnaire. Dr. Kramer is contributing the modeling analyses of phone (BTACT) vs. in-person cognitive outcomes project with Dr. Nelson.	
Han, Hsiao-Ping	Post doc	3.36	Dr. Han is applying advanced longitudinal modeling techniques to discern the prevalence, course, and clinical significance of an acute depression phenotype in athletes with sport-related concussion.	
Ranson, Jana	Post doc	2.25	Dr. Ranson contributed analyses and writing to the publication on the relationship between GOSE and other clinical outcome measures (Nelson et al., 2017, J Neurotrauma) and lead the analysis and drafting of the initial manuscript (under review) using IRT to evaluate the fitness of the GOSE as a measure of TBI-related disability.	
University of California, San Diego				
Stein, Murray	Co-Investigator	1	Dr. Stein continues to provide expert input into planning for biomarker validation. He regularly attends planning calls and meetings, with an emphasis on mental health input.	
Agtarap, Stephanie	Post Doc	12	Dr. Stephanie Agtarap, under the supervision of Dr. Stein, conducts literature searches and composes summaries of the searches, conducts analyses using project multiple databases, and participates in planning and manuscript writing.	
University of Washington				
Nancy Temkin	Co-Investigator	1.8	Oversee and participate in the Expert Working Group, analyze data and design studies	
Sureyya Dikmen	Co-Investigator	1.8	Work on the design and execution of studies	
Christine Mac Donald	Co-Investigator	1	Advance the qualification of imaging markers as diagnostic and therapeutic endpoint	
Sara Wellnitz	Study Coordinator	8.4	Work on all aspects of the subject screening, enrollment, data collection and follow-up	
Joan Machamer	Research Scientist	1.08	Data curation, data analysis, and preparation of manuscripts	
Laurel Peabody	Study Coordinator	1.2	Work on all aspects of the subject screening, enrollment, data collection and follow-up	
Evan Zahniser	Pre-doc Fellow	3.6	Evaluate methods for analyzing different types off data and on performing the analyses	
Massachusetts General Hospital				
Duhaime, Ann-Christine	Co-Investigator	1.15	Oversight and management of all trial work	
Fortes-Monteiro, Carla	Clinical Research Coordinator	4.2	Clinical trial coordinator – enrolling patients and	
University of Southern California				
Toga, Arthur W.	Co-Investigator	1.19	Dr. Toga was involved in the project in support of the Consensus and Implementation Conferences and Validation studies.	
Nizni, Sander	Programmer	1.42	Sander performed system interface design, testing and quality assessment.	
Agop, Hovsep	Programmer	1.97	Hovsep assisted in system interface design, testing and quality assessment.	
Estrada, Monica	Project Assistant	1.62	Monica provided user support for image upload activities, processing all required follow up	
Baylor College of Medicine				
Robertson, Claudia	Co-Investigator	0.6	Dr. Robertson participates in the Consensus and Implementation Conferences. She provides the infrastructure and oversee the clinical enrollment.	
Levin, Harvey	Co-Investigator	1.2	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.	
Spaulding Rehabilitation Hospital				
Giacino, Joseph T.	Sub PI	1.17	In collaboration with Dr. Michael McCrea, Dr. Giacino continues to oversee all outcomes research activities related to TED and TRACK-TBI.	
Bodien, Yelena	Postdoctoral Fellow	3.6	Dr. Bodien continued data curation for the TRACK-TBI severe TBI cohort and co-authored TED/TRACK-TBI manuscripts.	
Christoforou, Andrea	Postdoctoral Fellow	4.8	Dr. Christoforou continued work with personnel from the Practice Division of the American Academy of Neurology to finalize web-based data entry tool for the Evidence-Based Clinical Outcome assessment Platform (EB-COP) and accompanying manual of operating procedures. She has completed EB-COP validation study of the Rivermead Post-Concussion Questionnaire (RPQ) and presented findings at the Military Health System Research Symposium and NeuroTrauma meetings	
Christopher Malone, Sc.D	Postdoctoral Fellow	2.4	Dr. Malone assisted with user validation testing of the EB-COP and reviewed the manual of operating procedures. He reviewed the data in the TED Metadataset in preparation for selected COA validation studies. He has also begun his role as the TED/TRACK-TBI Outcomes Core liaison for the DOE National Laboratories team and will be responsible for day-to-day communication between the TED/TRACK-TBI Outcomes Core and the DOE investigators during planned data analytic activities. Dr. Malone will also collaborate with the TED postdoc fellow from MCW on selected COA validation studies assigned by the Outcomes Core leadership.	
Minneapolis Medical Research Foundation				
Rafter, Daniel	Coordinator	1.8	Oversaw and participated in all TED Friend Control Study activities	
Sturtevant, Dylan	Ast. Coordinator	6	Oversaw and participated in all TED Friend Control Study activities	
Chettupally, Tabitha	Research Assistant	6	Oversaw and participated in all TED Friend Control Study activities	
University of Pittsburgh Medical Center				
Okonkwo, David	Co-Investigator	0.6	Dr. Okonkwo has overall responsibility for the conduct of this project as PI of the Pittsburgh Site. He is responsible for the recruitment overseeing enrollment of the participants at the Pittsburgh Site. Dr. Okonkwo is a member of the TED Steering Committee's Clinical & Rehabilitation Core and meets regularly with the other investigators.	
Puccio, Ava	Co-Investigator	0.12	Dr. Puccio has overall responsibility for the Biospecimen Repository of samples collected from the TBI subjects from all participating sites as well as overseeing IRB submissions and compliance.	
Sharpless, Jane	HRPO Coordinator	3.84	Ms. Sharpless is responsible for securing site-specific IRB and HRPO approval to initiate human-subject recruitment at each participating military site. Additionally, she works with the FITBIR team to upload data collected under this protocol into FITBIR compliant form structures.	
Hahner, Thomas	Psychometrician	9.6	Mr. Hahner is responsible for subject screening, enrollment and for conducting neuropsychological testing and follow-up on enrolled study participants at scheduled time points.	
Brooks, Jordan	Lab Technician	1.8	Mr. Brooks' responsibilities included biomarker sample processing and cataloging for storage in the biorepository. He was also responsible for the coordination and procurement of all study related materials and research supplies. Please note that Mr. Brooks left the University in early August.	
Creppage, Kathleen	Graduated Student Researcher	2.88	Data Harmonization	
Lyons, Jason	Data Manager	2.76	Data Harmonization	

University of Pennsylvania				
Diaz-Arrastia, Ramon	Co-Investigator	1.7	Analyze data; critically review manuscripts for publication	
Kumar, Monisha	Co-Investigator	1.1	Analyze data; critically review manuscripts for publication	
Haber, Margalt	Post-doctoral Fellow	8	Conduct biomarker assays; Analyze data; Prepare poster presentations and manuscripts for publication	
Carb, Kodiak	Research Assistant	3	Data entry; collect data	
Morrison, Justin	Student Worker	3	Datra entry; collect data	
Rock, James	Research Assistant	3	Data entry; collect data	

OTHER SUPPORT PAGES

MANLEY, GEOFFREY T.

CURRENT

Title:	Transforming Research and Clinical Knowledge in Traumatic Brain Injury Network (TRACK-TBI NET) (A131954)
Time Commitment:	3.60 calendar months
Support Agency:	Medical Technology Enterprise Consortium
Grants Officer:	Rebecca Harmon Advanced Technology International 315 Sigma Drive, Summerville, SC 29483 Telephone: 843-760-3358 Email: mtec-contracts@ati.org
Performance Period:	10/01/2018 – 11/30/2023
Total Costs of the Project:	$24,999,999
Project Goals:	This project will leverage the network capability and infrastructure capacity of the largest precision natural history study of TBI: TRACK-TBI and TED Initiative to characterize the clinical, neuroimaging, and blood-based biomarker features of TBI in a network that is immediately prepared to launch an innovative Phase 2 TBI clinical trials network that delivers on the recommendations of the DoD and NIH workshops and expert panels.
Specific Aims:	1) Adapt the current TRACK-TBI study network into a Phase 2 clinical trial network and work with DoD, FDA, and industry partners to identify key drug candidates for randomized controlled trials. 2) Enroll 504 participants into a Phase 2 multi-arm, multi-stage (MAMS) adaptive platform design for randomized, controlled clinical trial(s). 3) Complete study close-out, analyses, dissemination of findings, and meet with MTEC, FDA, and industry partners to begin plans for Phase 3 clinical trials.
Overlap:	None

Title:	Transforming Research and Clinical Knowledge in Traumatic Brain Injury Longitudinal (TRACK-TBI LONG) (A131769)
Time Commitment:	Effort as needed
Support Agency:	National Football League
Grants Officer:	Joshua Keidan, Finance Manager Telephone: 212-450-2309 Email: Joshua.Keidan@nfl.com
Performance Period:	07/01/2018 – 06/30/2021
Total Costs of the Project:	$3,454,080
Project Goals:	This project will extend TRACK-TBI's current 1-year follow-up for 3 additional years, adding data ranging from 2-7 years post-injury depending on participants' original enrollment date. These data will validate endpoints for acute and chronic

	diagnosis, and advance knowledge of the epidemiology, risk factors, and pathology of TBI's long-term sequelae.
Specific Aims:	1) Extend examination of existing injured and control TRACK-TBI participants with 3 annual telephonic and Web-based follow-ups: capturing neuropsychological and cognitive symptoms and life function/quality and screening for neurodegenerative and post-traumatic disorders; 2) Characterize long-term trajectory of imaging biomarkers in brain-injured and control subjects ("MRI Cohort") using DTI, rs-fMRI, and high-resolution structural studies; 3) Characterize long-term trajectories of neurocognitive/psychological function and their relationship to e.g., plasma-CSF proteomic markers related to inflammation and neurodegeneration, and imaging; 4) Apply PET imaging to characterize prevalence and extent of Aβ plaques and neurofibrillary tangles in a subset of the MRI Cohort age >50y; 5) Apply traditional and novel neuroimaging-guided and quantitative neuropathologic approaches to donated brains to interrogate TBI-associated structural and biological changes correlated with antemortem phenotyping.
Overlap:	None

Title:	Co-Design for Artificial Intelligence Coupled with Computing at Scale for Extremely Large, Complex Datasets (A131066)
Time Commitment:	0.60 calendar months
Support Agency:	Lawrence Livermore National Laboratory
Grants Officer:	Gary M. Ward, LLNS Contract Analyst Telephone: (925)-423-5952 Email: ward31@llnl.gov
Performance Period:	05/01/2018 – 07/31/2019
Total Costs of the Project:	$400,000 (pending approval of additional $300,000 supplement)
Project Goals:	The overall objective of this collaborative project is to develop and demonstrate a "cognitive simulation" approach that tightly couples artificial intelligence, simulations, and computing at scale with extremely large datasets and pilot it to the specific challenge of learning actionable insights from growing complex Traumatic Brain Injury (TBI) datasets. Longer term, this will serve as a premier platform and test bed to develop and demonstrate scalable scientific machine learning approaches and tools suited for the analysis of extremely large, highly complex and uncertain datasets, including other TBI, VA and UCSF data.
Specific Aims:	1) establish enclaves capable of securely handling sensitive data and to perform data management. 2) to develop and perform new classes of scalable analytics on provided pilot TRACK-TBI data 3) to run analysis experiments at multiple DOE sites and generation of actionable insights for TBI.
Overlap:	None

Title:	Subrecipient PI: 010376-002 / W81XWH-16-2-0020 Development and Validation of Spreading Depolarization Monitoring for TBI Management (SDII) (A129063)

Time Commitment:	0.12 calendar months
Support Agency:	University of Cincinnati (Subaward)
Grants Officer:	Katherine Carey, Senior Accountant Telephone: (513)-558-3915 Email: careyk@ucmail.uc.edu
Performance Period:	09/15/2016 – 09/14/2019
Total Costs of the Project:	$509,075
Project Goals:	The objective of the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Research Collaboration Policy is to establish a framework to support the conduct of collaborative research projects involving the TRACK-TBI Investigators, the TRACK-TBI Dataset, and external parties
Specific Aims:	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
Overlap:	None

Title:	Co-Investigator: Clinical Center of Excellence in Spinal Cord Injury: TRACK-SCI (A128168)
Time Commitment:	0.06 calendar months
Support Agency:	Craig H. Neilsen Foundation
Grants Officer:	Tracey Wheeler Telephone: 517-281-3018 Email: tracey@chnfoundation.org
Performance Period:	09/30/2016 – 09/29/2021
Total Costs of the Project:	$1,000,000
Project Goals:	This project will provide new data for driving evidence-based recommendations and guidelines for the treatment of acute SCI. The ultimate aim is to provide a sustainable, coordinated network of trauma centers with shared SCI treatment guidelines capable of providing high quality data on SCI patients from admission through rehab and community integration.
Specific Aims:	1) To prepare practice guidelines based on our retrospective and prospective datasets and evolving best practices and submit application for certification. 2) To expand and solidify our clinical research effort and infrastructure at the Brain and Spinal Injury Center at ZSFG 3) To disseminate Joint Commission approved ZSFG practice guidelines to our affiliates trauma centers 4) Begin enrolling patients at these additional network centers in the TRACK SCI database/ registry. 5) Improve our ability to track SCI patients to and through discharge, rehabilitation and community placements by strengthening our collaborations with Laguna Honda Hospital and Santa Clara Valley Medical Center.
Overlap:	None

Title:	Co-Investigator: Early Critical Care Decisions and Outcomes after SCI: Track-SCI (A127941)
Time Commitment:	0.24 calendar months
Support Agency:	DoD US Army Med. Res.
Grants Officer:	Christopher Meinberg Telephone: 301-619-2657 Email: christopher.l.meinberg.civ@mail.mil
Performance Period:	08/15/2016 – 08/14/2019
Total Costs of the Project:	$2,376,474
Project Goals:	The objective of this proposal is to understand the critical care practices and outcomes for SCI patients and to build a knowledge network for acute SCI.
Specific Aims:	1) Diagnosis: Building a knowledge network for acute SCI 2) Prognosis: Predictive models and biomarkers 3) Data analysis and sharing
Overlap:	None

Title:	PI: U01NS086090 Transforming Research and Clinical Knowledge in Traumatic Brain Injury (A127834)
Time Commitment:	2.76 calendar months
Support Agency:	NIH National Institution Neurological Disord and Stroke
Grants Officer:	Aaron Kinchen, Grants Management Officer P.O. Box 6021 Rockville, MD 20852 Telephone: (301)-451-7966 Email: aaronkinchen@ninds.nih
Performance Period:	05/16/2016 – 08/31/2019
Total Costs of the Project:	$7,657,982
Project Goals:	TRACK-TBI is built from the foundational NINDS-funded TRACK-TBI Pilot study, which collected clinical data from 3 sites and 600 subjects. With over a dozen publications and growing, the TRACK-TBI Pilot dataset is the first to populate the Federal Interagency Traumatic Brain Injury Research (FITBIR) repository and with the current TRACK-TBI data, is compatible with the International Initiative for Traumatic Brain Injury Research (InTBIR), a collaborative effort of the European Commission (EC), the Canadian Institutes of Health Research (CIHR) and the National Institutes of Health (NIH). TRACK-TBI also forms one of the core datasets of the Department of Defense-funded TBI Endpoints Development (TED) Initiative, which has established an interrogatable Metadataset of high quality studies across civilian, sports, and military populations. TED's goals, aligned with TRACK-TBI, are to identify and validate the FDA regulatory readiness of candidate clinical outcome assessments and proteomic and

	neuroimaging biomarkers and technologies that may serve as endpoints in the design of precision clinical trials.
Specific Aims:	1) Improve TBI classification/taxonomy for targeted clinical treatment trials 2) Improve TBI outcome assessments, such that the size and costs of clinical trials can be reduced 3) Identify the health and economic impact of Mild TBI patient disposition 4) Create a legacy database with analytic tools and resources to support TBI research
Overlap:	None

Title:	PI: TRACK-TBI biospecimen collection and transfer (A124817)
Time Commitment:	1.20 calendar months
Support Agency:	Abbott Laboratories
Grants Officer:	Beth A. Schodin, PhD., Manger, Global Scientific Affairs Abbott Diagnostics 100 Abbott Park Road Dept 09AA/CPI-5 Abbott Park, IL 60064 Telephone: (224)-668-1020 Email: Beth.Schodin@abbott.com
Performance Period:	12/18/2014 – 11/30/2018
Total Costs of the Project:	$1,738,000
Project Goals:	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
Specific Aims:	1) Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) is an ongoing study that aims to create a large, high quality database that integrates clinical, imaging, proteomic, genomic and outcome biomarkers to establish more precise methods for TBI diagnosis and prognosis, refine outcome assessment, and compare the effectiveness and costs of TBI care.
Overlap:	None

Title:	Subrecipient PI: 0043845-1 / W911QY-14-C-0070 Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) - High Definition Fiber Tracking Neuroimaging, Biospecimen and Data Informatics Repositories (A124574)
Time Commitment:	0.12 calendar months
Support Agency:	The University of Pittsburgh
Grants Officer:	Heather Bragg Office of Research 123 University Place R21 UCLUB / Lower Lobby Pittsburgh, PA 15213-2303 Telephone: (412)-624-7009 E-mail: hmb30@pitt.edu
Performance Period:	09/05/2014 – 09/04/2019

Total Costs of the Project:	$787,065
Project Goals:	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. This will be accomplished by the creation of 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. The Bioinformatics Core will submit TRACKTBI data into the Federal Interagency Traumatic Brain Injury Research Informatics System (FITBIR). Utilizing TBI-Common Data Elements (CDEs), along with uniform standards for acquiring multi-site MRI data, the TRACK Information Commons will serve as a resource for current and future TBI research and international collaborations.
Specific Aims:	1) Deliverable 1: Develop Data Management Plan for TRACK Repository. We will develop an integrated data management plan across the Cores for data quality control and quality assurance. This will involve convening Core leaders via conference calls and in-person meetings to determine priorities and resources for harmonization of data across Cores. 2) Deliverable 2: Implementation of Data Management Plan. As subject enrollment is ongoing during the 4-year project period, there will be extensive ongoing efforts to 3) clean and curate the datasets across the Cores at baseline enrollment and again at each milestone. 4) Deliverable 3: Submission of Baseline Data to FITBIR. Data will be prepared for end users, and ultimate mapping and migration of TRACK-TBI data into the Federal Interagency Traumatic Brain Injury Research (FITBIR) informatics system. Core and Basic data will be submitted on a quarterly schedule for a total of 3,000 subjects. 5) Deliverable 4: Provide Technical Support to Users. As an "Information Commons" a goal of TRACK-TBI is to promote the sharing of data among investigators and to all qualified and approved researchers as determined by the Data Access and Quality Committee. The Informatics Repository will manage requests associated with Data Use Agreements to provide access to and training on the tranS MART platform for conducting analysis. The Informatics Repository team will also serves as a "help desk" for the collaborators and clinical study sites to address technical problems and other requests.
Overlap:	None

Title:	PI: W81XWH-14-2-0176 TBI Endpoints Development (TED) (A124306)
Time Commitment:	1.20 calendar month
Support Agency:	U.S. Department of Defense
Grants Officer:	Susan Dellinger, Grant Officer USA Med Research ACQ Activity 820 Chandler Street, Fort Detrick, MD 21702-5014 Telephone: (301)-619-2090 Email: susan.m.dellinger.civ@mail.mil

Performance Period:	09/30/2014 – 09/29/2019
Total Costs of the Project:	$17,109,805
Project Goals:	To identify and validate candidate COAs and biomarkers for future DDT qualification.
Specific Aims:	1) AIMS: Stage I (Years 1-2) Technical 2) 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. 3) 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.
Overlap:	None

Title:	PI: Supplemental Funding for TRACK TBI (A123381)
Time Commitment:	Effort as needed
Support Agency:	One Mind for Research, Inc.
Grants Officer:	Joan Demetriades One Mind for Research Inc. 120 Lakeside Avenue, Suite 100 Seattle, WA 95122 Telephone: (206)-457-8400 Email: joan.demetriades@onemind.org
Total Costs of the Project:	03/01/2014 – 08/31/2019
Level of Funding:	$421,049
Project Goals:	This grant is designed to supplement the research of the TRACK-TBI U01 NS086090 study
Specific Aims:	1) To supplement the TRACK TBI study by providing funds for patient stipend payments and travel reimbursements 2) To accelerate the data curation for FDA submission
Overlap:	None

Title:	Subrecipent PI: Center-TBI: Collaborative European NeuroTrauma Effectiveness Research in TBI (A122281)
Time Commitment:	0.12 calendar months
Support Agency:	Antwerp University Hospital subcontract (PI: Andrew Maas) European Commission 7th Framework Programme (PI: Maas)
Grants Officer:	Annina Sorgner, International Projects Management CABO; milliarium mbH & Co. KG Oskar-von-Miller-Ring 29, D-80333 Munich Telephone: (49)-89-288-104-22 Email: annina.sorgner@gabo-mi.com

Performance Period:	10/01/2013 – 03/31/2020
Total Costs of the Project:	$161,375
Project Goals:	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.
Specific Aims:	1) Moreover, information on provider profiles will be captured. These data sets will be subjected to extensive analyses aimed at improving characterization of injury and outcome and 2) 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).
Overlap:	None

PENDING

Title:	TRACK-TBI Precision Medicine - Pathomechanistic Classification of Traumatic Brain Injury: The Bridge to Targeted Therapies
Time Commitment:	1.20 calendar months
Support Agency:	U.S. Department of Defense
Grants Officer:	TBD
Performance Period:	08/01/2018 – 07/31/2021
Total Costs of the Project:	$4,500,000
Project Goals:	Validate blood-based and imaging biomarkers to improve the characterization of TBI, and elucidate factors to influence design of future precision medicine clinical trials and inform patient responsiveness to targeted therapeutics.
Specific Aims:	1) Validate biomarkers of Diffuse Axonal Injury (DAI), Microvascular Injury (MVI), and Neuroinflammation using advanced blood-based assay platforms and MR imaging sequences in prospectively collected data from existing TRACK-TBI subjects. 2) Validate early and ultra-early blood-based and novel imaging biomarkers of DAI, MVI, and neuroinflammation that may serve as predictive and pharmacodynamic biomarkers in a new cohort of moderatesevere TRACK-TBI subjects. 3) Conduct a multicenter double-blind, placebocontrolled exploratory clinical trial comparing the impact of Cyclosporine A on blood-based and imaging biomarkers of DAI and neuroinflammation in moderate-severe TBI patients admitted to the ICU.
Overlap:	None

Title:	TRACK-TBI Epileptogenesis Project
Time Commitment:	0.27 calendar months
Support Agency:	University of Pennsylvania (DOD USAMRAA prime)
Grants Officer:	TBD
Performance Period:	04/01/2019 – 03/31/2023
Total Costs of the Project:	$31,320
Project Goals:	To efficiently integrate extended follow-up evaluation and study of existing and prospective subjects in the TRACK-TBI study
Overlap:	None

Title:	Blood RNA Biomarkers to Predict Outcome and Monitor Treatment in SCI (PI: Beattie)
Time Commitment:	0.12 calendar months
Support Agency:	U.S. Department of Defense
Grants Officer:	TBD
Performance Period:	07/01/2019 – 06/30/2022
Total Costs of the Project:	$485,577
Project Goals:	The major goals of this project are to identify RNA biomarker(s) that can be translated into usable convenient testing platforms using microfluidics or other approaches and that will yield new insights into SCI pathophysiology, and that can be back-translated into preclinical studies of mechanism as well as be used as surrogate markers of therapeutic interventions.
Overlap:	None

PREVIOUS (within the last 5 years)

Title:	Co-Investigator: U10NS058931 SF-NETT: San Francisco Neurological Emergencies Trials Network (A127796)
Time Commitment:	0.12 calendar month
Support Agency:	NIH National Institution Neurological Disord and Stroke
Grants Officer:	Joanna Vivalda, Program Official P.O. Box 6021 Rockville, MD 20852 Telephone: (301)-496-9135 Email: Joanna.vivalda@nih.gov
Performance Period:	09/01/2012 – 07/31/2017
Total Costs of the Project:	$305,651
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.
Specific 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) 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) 3) To enhance the participation of underserved minorities in clinical trials of new treatments for neurological emergencies
Overlap:	None

Title:	Co-Investigator: R01NS067092 Bioinformatics for Translational Spinal Cord Injury (SCI) (A114558)
Time Commitment:	0.12 calendar month
Support Agency:	National Institute of Health
Grants Officer:	Joanna Vivalda, Program Official P.O. Box 6021 Rockville, MD 20852 Telephone: (301)-496-9135 Email: Joanna.vivalda@nih.gov
Performance Period:	05/01/2010 – 04/30/2017
Total Costs of the Project:	$1,644,785
Project Goals:	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.
Specific 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 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.

Overlap:	None

Title:	CO-Investigator: R21NS087458 Contribution of infiltrating macrophages on synaptic function after TBI (A123947)
Time Commitment:	0.12 calendar month
Support Agency:	National Institute of Health
Grants Officer:	Joanna Vivalda, Program Official P.O. Box 6021 Rockville, MD 20852 Telephone: (301)-496-9135 Email: Joanna.vivalda@nih.gov
Performance Period:	09/01/2014 – 08/31/2016
Total Costs of the Project:	$435,250
Project Goals:	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
Specific 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.
Overlap:	None

Title:	PI: Manley, Geoffrey Codman Neuro Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) (A126352)
Time Commitment:	Effort as needed
Support Agency:	Codman Neuro
Grants Officer:	Worldwide Director of Clinical Research Codman Neuro, a division of DePuy Orthopaedics, Inc. Clinical Research Department, MS34 325 Raynham, MA 02767 Telephone: (508)-880-8274 Email: RA-DPYUS-ClinRsrCod@its.jnj.com
Performance Period:	10/16/2015 – 02/16/2016
Total Costs of the Project:	$64,400

Project Goals:	TRACK-TBI is built from the foundational NINDS-funded TRACK-TBI Pilot study, which collected clinical data from 3 sites and 600 subjects. With over a dozen publications and growing, the TRACK-TBI Pilot dataset is the first to populate the Federal Interagency Traumatic Brain Injury Research (FITBIR) repository and with the current TRACK-TBI data, is compatible with the International Initiative for Traumatic Brain Injury Research (InTBIR), a collaborative effort of the European Commission (EC), the Canadian Institutes of Health Research (CIHR) and the National Institutes of Health (NIH). TRACK-TBI also forms one of the core datasets of the Department of Defense-funded TBI Endpoints Development (TED) Initiative, which has established an interrogatable Metadataset of high quality studies across civilian, sports, and military populations. TED's goals, aligned with TRACK-TBI, are to identify and validate the FDA regulatory readiness of candidate clinical outcome assessments and proteomic and neuroimaging biomarkers and technologies that may serve as endpoints in the design of precision clinical trials.
Specific Aims:	1) Improve TBI classification/taxonomy for targeted clinical treatment trials 2) Improve TBI outcome assessments, such that the size and costs of clinical trials can be reduced 3) Identify the health and economic impact of Mild TBI patient disposition 4) Create a legacy database with analytic tools and resources to support TBI research
Overlap:	None

Title:	PI: W81XWH-13-1-0441 Transforming Research and Clinical Knowledge in Traumatic Brain Injury (A122361)
Time Commitment:	0.84 calendar month
Support Agency:	U.S. Department of Defense
Grants Officer:	Dana Herndon, Contracting Officer USA MED Research MAT CMD 1077 Patchel Street Bldg 1056 Fort Detrick, MD 21702 Telephone: (301)-619-7140 Email: dana.l.herndon.civ@mail.mil
Performance Period:	09/26/2013 – 09/25/2016
Total Costs of the Project:	$1,463,453
Project Goals:	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 Pittsburg, Mt. Sinai and University of Texas, Austin
Specific Aims:	1) To develop improved prognostic, diagnostic and outcome models for TBI; 2) To identify neuroimaging biomakers for diagnosis and prognosis in TBI; 3. To identify proteomic and genomic associations with TBI phenotypes

Overlap:	None

Title:	PI: U01NS086090 Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK TBI) (A122283)
Time Commitment:	2.26 calendar month
Support Agency:	NIH National Institution Neurological Disord and Stroke
Grants Officer:	Joanna Vivalda, Program Official P.O. Box 6021 Rockville, MD 20852 Telephone: (301)-496-9135 Email: Joanna.vivalda@nih.gov
Performance Period:	09/30/2013 – 08/31/2016
Total Costs of the Project:	$9,687,014
Project Goals:	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.
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.
Overlap:	None

Title:	Subreceipt PI: T062576 ProTECT III (A113421)
Time Commitment:	1.20 calendar month
Support Agency:	Emory University NIH (U01NS062778) (PI: David Wright)
Grants Officer:	Claire French, Office of Sponsored Programs 1599 Clifton Road NE, 4th Floor 1599-001-1BA Atlanta, GA 30322 Telephone: (404)-727-4054 Email: cvfrenc@emory.edu

Performance Period:	07/01/2009 – 06/30/2014
Total Costs of the Project:	$157,449
Project Goals:	The major goal of this multicenter Phase III clinical trial is to determine the efficacy of administering intravenous (IV) progesterone (initiated within 4 hours of injury and administered for 72 hours, followed by an additional 24 hour taper) versus placebo for treating victims of moderate to severe acute traumatic brain injury.
Specific Aims:	1) The Clinical Standardization Team will examine and refine the goal directed therapy protocols for ProTECT III at all the NETT sites; 2) Oversee the implementation of these protocols; 3) Monitor compliance with the protocls and 4) Resolve any issues related to real or perceived variability in neurological treatment.
Overlap:	None

Title:	PI: RC2NS069409 Transforming Traumatic Brain Injury Research and Clinical Care (A113086)
Time Commitment:	2.40 calendar month
Support Agency:	NIH National Institution Neurological Disord and Stroke
Grants Officer:	Joanna Vivalda, Program Official P.O. Box 6021 Rockville, MD 20852 Telephone: (301)-496-9135 Email: Joanna.vivalda@nih.gov
Performance Period:	09/30/2009 – 08/31/2013
Level of Funding:	$3,466,236
Project Goals:	The major goals of this project are to test and refine standards for data collection in TBI studies, suitable for use across the broad spectrum of TBI, and to explore novel approaches for TBI classification and outcome after TBI, making use of emerging technology
Specific Aims:	1) The global aim of this proposal is to test and refine standards for data collection in TBI studies, suitable for use across the broad spectrum of TBI; 2) To explore novel approaches for TBI classification; 3) Outcome after TBI, making use of emerging technology. 4) In addition, we aim to develop a pilot set of performance indicators for assessment of the health care quality and effectiveness in TBI.
Overlap:	None

Title:	Co-PI: R21AG042016-01A1 Effects of traumatic brain injury on hippocampal network activity: age difference (A121632)
Time Commitment:	0.14 calendar months
Support Agency:	National Institute of Health
Grants Officer:	Joanna Vivalda, Program Official P.O. Box 6021 Rockville, MD 20852 Telephone: (301)-496-9135

	Email: Joanna.vivalda@nih.gov
Performance Period:	09/01/2012 – 08/31/2014
Total Costs of the Project:	$432,834
Project Goals:	From these studies we will establish the role and the effect of age on the progression of TBI-related cognitive impairments from a behavioral, cellular and network prospective.
Specific Aims:	1) Identify the dynamics of the post transcriptional infrastructure of gene expression involved in synaptic plasticity and memory after TBI in behaviorally characterized young and old mice; 2) 2) determine how age at the time of TBI affects hippocampal networks mediating contextual and spatial information processing
Overlap:	None

Title:	Co-Investigator R01 NS060776 Macrostructural and Microstructural Imaging Biomarkers of Traumatic Brain Injury (A112322)
Time Commitment:	0.24 calendar months
Support Agency:	National Institutes of Health
Grants Officer:	Joanna Vivalda, Program Official P.O. Box 6021 Rockville, MD 20852 Telephone: (301)-496-9135 Email: Joanna.vivalda@nih.gov
Performance Period:	07/15/2009 – 06/30/2014
Total Costs of the Project:	$1,761,547
Project Goals:	The major goals of this project are to establish quantitative macrostructural and microstructural imaging biomarkers for predicting patient outcome after TBI.
Specific Aims:	1) The hypothesis will be tested that increasing spatial extent of progressive focal atrophy detected by DBM of serial MRI and/or progressive white matter microstructural injury on serial DTI is correlated with worse neurocognitive and functional outcomes at one year after injury, after controlling for clinical measures of injury severity including Glasgow Coma Scale, duration of unconsciousness, and duration of post-traumatic amnesia. These macrostructural and microstructural imaging biomarkers will also be correlated with functional and metabolic imaging data using fMRI and 3D MR spectroscopic imaging, respectively. If the proposed investigation is successful in establishing these quantitative macrostructural and microstructural imaging biomarkers of long-term outcome in TBI, then they could potentially serve as surrogate endpoints for clinical intervention trials. They might also yield endophenotypes for studies of genetic susceptibility factors that worsen outcome after TBI. Towards this purpose, DNA will be banked from patients in this study for genotype analysis. Specifically, we will examine whether ApoE genotype influences the degree of regional brain atrophy and microstructural white matter injury. The allelic variants of ApoE are already known to modulate clinical outcome after TBI, and this study will determine if DBM and DTI can provide "intermediate phenotypes" for the effect of ApoE genotype on TBI outcome.

Overlap:	None

Title:	Co-Investigator: Sanofi-Aventis Collaboration with UCSF on Traumatic Brain Injury (TBI) (A119072)
Time Commitment:	0.12 calendar months
Support Agency:	Sanofi-Aventis
Grants Officer:	Marie-Noelle Castel 185 Berry Street, San Francisco, CA 94107 Telephone: (415)-856-5000 Email: Marie-Noelle.Castel@sanofi.com
Performance Period:	11/28/2011 – 06/30/2014
Total Costs of the Project:	$171,662
Project Goals:	The major goal of this project is to study effects of SAR127963 on proNGF versus LPS-induced Tumor Necrosis Factor production in whole blood and peripheral blood monocytes in healthy volunteers and TBI patients.
Specific Aims:	1) Ex-vivo human assay to test the effects of SAR127963 on proNGF versus LPS-induced TNF production in the whole blood and by Peripheral Blood Monocytes from healthy volunteers and Trauma brain injury patients.
Overlap:	None

Title:	Co-Investigator: W81XWH-13-1-0297 Effects of Early Acute Care on Autonomic Outcomes in SCI: Bedside to Bench and Back (A122126)
Time Commitment:	0.12 calendar month
Support Agency:	U.S. Department of Defense
Grants Officer:	Susan Dellinger, Grant Officer USA Med Research ACQ Activity 820 Chandler Street, Fort Detrick, MD 21702-5014 Telephone: (301)-619-2090 Email: susan.m.dellinger.civ@mail.mil
Performance Period:	09/30/2013 – 09/29/2016
Total Costs of the Project:	$1,108,987
Project Goals:	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
Specific 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.
Overlap:	None

Title:	PCORI: ME-1306-02735 Semiparametric Causal Inference Methods for Adaptive Statistical Learning in Trauma Patient-Centered Outcomes Research (A123709)
Time Commitment:	0.12 calendar month
Support Agency:	University of California, Berkeley/PCORI
Grants Officer:	Deborah Howard University of California, Berkeley Berkeley, CA 94720 Telephone: (510)-642-6000 Email: subcontracts@berkeley.edu
Performance Period:	04/01/2014 – 08/31/2016
Total Costs of the Project:	$266,396
Project Goals:	Combine the expertise physicians/surgeons in critical care facilities, along with computational biostatistics to develop methods for targeting patient-centered parameter estimation.
Specific Aims:	1) 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.
Overlap:	None

Ramon Diaz-Arrastia, MD PhD

ACTIVE

Title: **Brain Oxygen Optimization in Severe TBI—Phase 3 (BOOST-3)** (Diaz-Arrastia, Protocol PI)
Time Commitment: 2.4 calendar months
Supporting Agency: NIH/NINDS U01 NS099046
Program Official: Scott Janis (janiss@ninds.nih.gov)
Performance Period: 8/1/2018 – 7/31/2023
Level of Funding: $32,532,017
Project Goals: BOOST-Phase 3 is designed to obtain definitive data regarding the clinical efficacy of a treatment protocol based on$PbtO_2$ monitoring.
Specific aims: We propose one primary and several secondary hypotheses:
Primary Hypothesis: The prescribed treatment protocol, based on $PbtO_2$ monitoring, results in improved neurologic outcome measured by the Glasgow Outcome Scale-Extended (GOS-E) 6 months after injury.
Secondary Hypotheses:

- The prescribed treatment protocol, based on $PbtO_2$ monitoring, results in improved neurologic outcome 6 months after injury based on functional, cognitive, and behavioral assessments.
- Safety hypotheses: Adverse events associated with $PbtO_2$ directed therapy are low.
- The prescribed treatment protocol, based on $PbtO_2$ monitoring, results in improved survival at discharge
- The prescribed treatment protocol, based on $PbtO_2$ monitoring, results in shortened time to follow commands (Glasgow Coma Scale Motor Score).
- The prescribed treatment protocol, based on $PbtO_2$ monitoring, results in reduction of total hypoxia exposure, measured by the area under the curve $PbtO_2$ below 20 mm Hg
- Total hypoxia exposure is correlated with worse neurological outcome as measured with the GOS-E.
- Total hypoxia time is correlated with worse neurological outcome as measured by a composite outcome measure based on functional, cognitive, and behavioral assessments.

Overlap: None

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 U01 NS086090
Program Official: Patrick Bellgowan (PatricFrostBellgowan@nih.gov)
Performance Period: 9/1/2013 – 8/30/2019
Level of Funding: $19,000,000 overall
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: **TBI Endpoints Development (TED)** (Diaz-Arrastia Co-PI) (Manley PI)
Time Commitment: 1.0 calendar month
Supporting Agency: DoD/USAMRAA
Program Official: Elizabeth Hirst
Performance Period: 09/01/2014-08/31/2019
Level of Funding: $17 million
Project Goals: The goals of this project is to identify and validate candidate clinical outcome measures and biomarkers that could be qualified by FDA as Drug Development Tools for future TBI clinical trials to benefit military and civilian populations.
Specific Aims: (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.
(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.
Overlap: None

Title: **Penn Center for Excellence in Neuroscience Clinical Trials (Penn NeuroNEXT)** (Diaz-Arrastia, PI)
Time Commitment: 1.0 calendar months
Supporting Agency: NIH/NINDS U24 NS107199
Program Official: Janice Cordell (cordellj@ninds.nih.gov)
Performance Period: 9/1/2018 – 8/31/2023
Level of Funding: $1,549,626
Project Goals: The goal of the proposed Penn Center for Excellence in Neuroscience Clinical Trials (Penn NeuroNEXT) is to bring together and optimize the contributions of a large group of experienced investigators focused in the clinical neurosciences at the University of Pennsylvania Perelman School of Medicine (UPennSOM), across four major teaching hospitals: the Hospital of the University of Pennsylvania (HUP), the Children's Hospital of Philadelphia (CHOP), Pennsylvania Hospital (PAH) and Penn Presbyterian Medical Center (PPMC). UPennSOM has long been a leading Center for clinical research in the neurosciences, and internationally recognized leaders in neurology, neurosurgery, neuroradiology, and psychiatry have a strong track record of collaboration, evidenced by existing multiple program projects, collaborative agreements, successful participation in federally and industry-sponsored multi-center clinical trials, and a large number of investigator-initiated studies. The expertise of Penn NeuroNEXT investigators covers the lifespan, and they have been leading contributors to our understanding of and development of innovative therapies for neurological disorders from infancy through old age. The four hospitals collaborating in Penn NeuroNEXT compromise the largest health system in the Philadelphia area, the nation's fifth largest city which anchors a metropolitan area of over 6 million people, which does not currently have a NeuroNEXT site. Additionally, UPennSOM has long been one of the leading Centers for training talented clinical neuroscientists, with large residencies and fellowship programs that routinely attract very promising young physician scientists, a large number of whom go on to highly productive academic careers.
Specific aims:
Specific Aim 1: To be an outstanding enrolling site for NeuroNEXT trials. Penn NeuroNEXT will participate in a minimum of 4 NeuroNEXT clinical trials over the next 5 years. We intend to meet or exceed recruitment and retention goals. We will ensure a high level of data quality in the context of specific protocols and regulatory standards.
Specific Aim 2: To optimize efficiency of clinical research in neurosciences at UPennSOM.
Specific Aim 3: To promote career enhancement of early stage clinical investigators. The University of Pennsylvania and our four hospitals are recognized as leading training centers in the clinical neurosciences, and we have been particularly successful in attracting talented young people interested in obtaining the necessary experience for launching academic careers.

Overlap: None

Title: **Pennsylvania Consortium on TBI (PACT).”** (D. Smith, Univ. of Pennsylvania, PI)
Time Commitment: 0.6 calendar months
Supporting Agency: Pennsylvania Department of Health
Performance Period: 1/1/2018 – 12/31/2020
Overall Level of Funding (3 years): $4 million
Project Goals: The goal of this project is to develop novel diagnostic techniques for acute and chronic neuropathologies of moderate to severe TBI.
Specific aims:
Specific Aim 1: Develop novel diagnostic techniques and approaches for acute and chronic *mild TBI/concussion* in humans that will predict which individuals will have poor outcomes.
Specific Aim 2: Develop novel diagnostic techniques for acute and chronic moderate-severe TBI in humans that are predictive of outcome.
Specific Aim 3: Preclinical analysis of novel diagnostic techniques to identify acute and chronic neuropathologies after TBI that can be extrapolated to Aims 1 and 2.
Specific Aim 4: Community outreach and education for TBI. This will include expanding our grade school demonstrations and public seminars as well as enhancing our strong commitment to education of underrepresented minorities in our well-established TBI research training program.

Overlap: None

Title: **Transforming Research and Clinical Knowledge in TBI Clinical Trials Network (TRACK-TBI NET)** Diaz-Arrastia Co-PI (with Geoff Manley, MD (UCSF)) MTEC-18-03-DTTBI-0001
Time Commitment: 1.2 calendar months
Supporting Agency: Department of Defense/Medical Technology Enterprise Consortium
Performance Period: 9/1/2018 – 8/31/2023
Overall Level of Funding: $25 million
Project goals: We propose to leverage the TRACK-TBI and TED infrastructure and experience, in partnership with globally recognized CRO ICON, to establish the TRACK-TBI NETWORK (TRACK-TBI NET), an innovative Phase 2 TBI adaptive clinical trials network that delivers on DoD and NIH recommendations. We propose a 5-year (4 years of enrollment), Phase 2 multi-arm, multi-stage (MAMS) adaptive platform design for multi-site, randomized, controlled clinical trials for patients with moderate to severe TBI. An adaptive trial permits design modifications to be made after subjects have been enrolled and some responses have been observed, without compromising the validity of the scientific method and trial integrity. In this flexible, precision medicine approach to TBI Phase 2 trials, numerous hypotheses may be addressed, from dose-finding to selection of a therapeutic intervention for a confirmatory Phase 3 trial. The study cohort will first be enriched for TBI using objective imaging and blood-based biomarkers and then, based on the drug/drugs selected, stratified into cohorts based on pathoanatomic features (e.g., presence/absence of contusion) and pathophysiologic features (e.g., presence/absence of neuroinflammation).

Overlap: None

Title: **Transforming Research and Clinical Knowledge in Traumatic Brain Injury-Longitudinal (TRACK-TBI LONG)** (G. Manley, UCSF, PI)
Time Commitment: 1.2 calendar months
Supporting Agency: National Football League (NFL)
Program Officer: Nancy Smith-Shaw (nancy.smithshaw@onemind.org) One Mind, 120 Lakeside Avenue, Ste. 200, Seattle, WA 98122
Performance Period: 07/01/2018 – 6/30/2021
Overall level of funding (3 years) Direct Cost: $11.6 million
Project Goals: TRACK-TBI LONG will extend TRACK-TBI’s current 1-year follow-up for 3 additional years, adding data ranging from 2-7 years post-injury. These data will validate endpoints for acute and chronic

diagnosis, and advance knowledge of the epidemiology, risk factors, and pathology of TBI's long-term sequelae.
Specific Aims:
1) To extend examination of existing injured and control TRACK-TBI participants;
2) to characterize the long-term trajectory of imaging biomarkers in brain-injured and control subjects;
3) to characterize the long-term trajectories of neurocognitive/psychological function and their relationship to plasma-CSF proteomic markers related to inflammation and neurodegeneration, and imaging;
4) apply traditional and novel neuroimaging-guided and quantitative neuropathologic approaches to donated brains to interrogate TBI-associated structural and biological changes correlated with antemortem phenotyping.
OVERLAP: none

PENDING:

Title: **Biomarkers in Brain Oxygen Optimization in Severe TBI Trial (Bio-BOOST)** (Diaz-Arrastia, PI)
Time Commitment: 0.96 calendar months
Supporting Agency: DOD/USAMRMC
Program Officer: TBN
Performance Period: 4/1/2018 – 3/30/2023
Level of Funding: $2,863,689
Project Goals: The recently funded BOOST-3 (Brain Oxygen Optimization in Severe TBI Phase 3) trial. BOOST-3 offers a unique opportunity to study and validate biomarkers and therefore accelerate our understanding of the pathophysiology of severe TBI, and promote the development of effective interventions. Capitalizing on the infrastructure and the rich study population for BOOST-3, we propose conducting an ancillary biomarker study, Bio-BOOST. Bio-BOOST will profile longitudinal changes in target molecular biomarkers measured in blood and cerebrospinal fluid (CSF), to identify unique molecular signatures that classify severe TBI with improved precision. Given that BOOST-3 will study severe TBI only, Bio-BOOST will fill an important gap in the field, since ongoing biomarker collections efforts through the Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) and TBI Endpoints Development (TED) efforts are primarily focused on mild TBI.
Specific aims: Our primary objective is to quantify the effect of brain tissue hypoxia exposure on brain injury using fluid-based biomarkers of brain injury. We hypothesize that total brain tissue hypoxia exposure within 48 hours of randomization (defined as the hours of $PbtO_2 < 20$ mmHg and the area over the curve (hours * mm Hg) (Fig 6) during the first 48 hours of injury is independently associated with higher peak levels of biomarkers of astrocytic (GFAP) and axonal (UCH-L1, Total Tau and NFL) injury, after adjusting for age, gender, and time between injury and randomization. We will also explore the association between lower cutoffs for brain tissue hypoxia ($PbtO_2 < 15$ mmHg and $PbtO_2 < 10$ mmHg) and brain injury.
Our secondary objectives are:

- To determine the effect of total cerebral hypoperfusion exposure (defined as the depth and duration of cerebral perfusion pressure (CPP) < 60 mmHg within 48 hours of randomization, quantified using the AUC methodology) on peak levels of GFAP, UCH-L1, Total Tau and NFL.
- To determine whether a prescribed treatment protocol based on $PbtO_2$ monitoring results in a decrease in blood and CSF levels of GFAP, UCH-L1, Total Tau and NFL.
- To determine whether in severe TBI patients, the initial CSF and blood levels of brain injury biomarkers (GFAP, UCH-L1, Total Tau and NFL) are associated with unfavorable functional outcome as measured by the Glasgow Outcome Scale Extended (GOSE) 6 months after injury.
- To determine whether the rate of increase in brain injury biomarker levels during the first 24 hours of randomization are associated with unfavorable functional outcome.
- To determine the time-point at which GFAP, UCH-L1, Total Tau and NFL levels provide the best discriminative ability for TBI outcome.

- To create a biorepository at the NINDS funded BioSpecimen Exchange for Neurological Disorders (BioSEND) of longitudinal serum, plasma, CSF, RNA and DNA samples of severe TBI patients for validating novel brain injury biomarkers. These samples will be available for future research on TBI biomarkers.

Overlap: None

Completed: (past 5 years)

Title: **Phase II, randomized clinical trial of brain tissue oxygen monitoring in severe TBI.** (Diaz-Arrastia, PI)
Time Commitment: 1.2 calendar months
Supporting Agency: NIH/NINDS R01 NS061860
Program Official: Ramona Hicks (HicksRA@ninds.nih.gov)
Performance of Period: 10/1/2009 – 9/30/2014
Level of Funding: $2,978,915
Project's Goals: The goal of this project is to conduct a pilot clinical trial of brain tissue oxygen monitoring in patients with severe TBI. Dr. Diaz-Arrastia remains as overall PI for this project. No direct support for Dr. Diaz-Arrastia's salary is coming from this project after his move to CNRM.
Specific aim: Primary Hypothesis:
(1) Treatment protocol is effective in reducing the fraction of time that pBrO2 values are below the critical threshold of 20 mm Hg.
Secondary Hypotheses:
(2). Safety hypotheses: Adverse events associated with pBrO2 monitoring are rare (< 3% for combination of infectious, hemorrhagic, or other monitoring-related adverse events) and pBrO2 directed therapy does not result in increased risk of pulmonary or systemic complications (such as acute lung injury/Adult Respiratory Distress Syndrome (ALI/ARDS).
(3). Feasibility hypotheses: Episodes of decreased pBrO2 can be identified and treatment protocol instituted comparably across 3 Clinical sites, and protocol violations will be low (<10% and uniform across different clinical sites).
(4). Non-futility hypothesis. A relative risk of good outcome measured by the Glasgow Outcome Scale-Extended (GOS-E) at 6 months post-injury of 2.0 in those randomized to management guided by pBrO2 monitoring is compatible with the outcome of this Phase II study.
Overlap: None

Title: **Neuroimaging Biomarkers of Outcome for Diffuse Axonal Injury.** (C. Marquez de la Plata, PI, Diaz-Arrastia, Primary Mentor)
Time Commitment: 0.5 calendar months.
Supporting Agency: NIH/NINDS K23 NS060827
Program Official: Ramona Hicks (HicksRA@ninds.nih.gov)
Performance Period: 7/1/2008 – 6/30/2013
Level of Funding: $669.871.
Project Goals: The goal of this project is to identify novel MRI biomarkers of functional recovery in patient with diffuse axonal injury after TBI. Dr. Diaz-Arrastia is the primary mentor for this career development award. No direct support for Dr. Diaz-Arrastia's salary is coming from this project after his move to CNRM.
Specific Aims: (1). Obtain MRI scans on patients with DAI in the acute period (within 48 hours after injury).
(2). Obtain repeat MRI scans 6-months after injury.
(3). Obtain functional and neurocognitive outcome data.
Overlap: None

Title: **Exercise training in depressed traumatic brain injury survivors.** (A. Hudak, PI, Diaz-Arrastia, Primary Mentor)
Time Commitment: 0.5 calendar months.

Supporting Agency: NIH/NICHD K23 HD067553-01A1
Program Official: Beth Ansel, PhD (AnselB@mail.nih.gov)
Performace Period: 7/1/2011 – 6/30/2015
Level of Funding: $654,955
Project goals: The goal of this project is to determine whether exercise is beneficial in the treatment of depressed TBI survivors, and to identify MRI and biochemical biomarkers of exercise-induced plasticity. Dr. Diaz-Arrastia is the primary mentor for this career development award. No direct support for Dr. Diaz-Arrastia's salary is coming from this project after his move to CNRM.
Specific aims: (1). Primary Aim: Establish the aerobic exercise group's ability to complete the exercise protocol.
(2). Secondary Aim 1: Investigate the impact of moderate exercise on BDNF and VEGF in depressed TBI subjects.
(3). Secondary aim 2. Investigate the impact of moderate exercise on regional brain volumes measured by MRI.
(4). Secondary Aim 3: Determine the impact of moderate exercise versus placebo on depressive symptoms after TBI.
(5). Secondary Aim 4: Determine the impact of moderate exercise on cognitive abilities of TBI subjects with depressive symptoms.
Overlap: None

Title: **Translational Research in Traumatic Brain Injury** (Diaz-Arrastia, PI)
Time Commitment: 0.6 calendar months
Supporting Agency: USUHS/CNRM, 4301 Jones Bridge Road, Bethesda, MD 20814
Program Official: Walter Tinling (walter.tinling@usuhs.edu)
Performance Period: 7/1/2011 – 6/30/2015
Level of Funding: $254,124
Project's Goals: To conduct pre-clinical and clinical research aimed to develop diagnostic and therapeutic strategies for TBI.
Specific aim: (1). To develop immunoassays to detect Tau fragments in serum of patients with chronic traumatic encephalopathy
(2). To establish a rodent model of cerebrovascular dysfunction after TBI.
(3). To conduct a pilot clinical trial of sildenafil for the treatment of cerebrovascular dysfunction after TBI.
Overlap: None

Title: **Transcriptome Profiling of TBI and PTSD in a Post-Deployment Military Population** (Diaz-Arrastia PI)
Time Commitment: 0.3 calendar months
Supporting Agency: NIH/NINR/USUHS
Performance Official: Kirsten Youngren
Performance Period: 07/01/2013-9/30/2015
Level of Funding: $108,501
Project Goals: This is a prospective case-control cohort study of mild traumatic brain injury exclusive (mTBI-PTSD) and co-morbid with PTSD (mTBI+PSD), and PTSD exclusive of mTBI (PTSD-mTBI) in male and female active duty soliders with recent return form either OIF/OEF>18 years of age with a history of combat exposure; and meets criteria for mTBI (per Department of Defense definition).
Specific Aims: NA
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 measured 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: **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

Sureyya Dikmen, PhD

CURRENT SUPPORT

1R01NS080648 (CPI Chesnut) 9/30/12/12-7/31/19 1.14 cal mos
NIH/NINDS and Fogarty $2,516,005
Grants Officer: Patrick Bellgowan, 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) 10/01/17 – 09/30/22 0.36 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-14-2-0176 (Manley, site PI: Temkin) 9/30/14-9/29/19 0.96 cal mos
DOD US Army Med. Res. Acq. Activity $123,212
Program Officer – Susan Dellinger
Traumatic Brain Injury Endpoints Development (TED)
The goals are to harmonize and curate data from military, civilian and sports-related TBI studies to create the TED Metadataset in order to identify endpoints to validate as measures for diagnostic and therapeutic trials for TBI. Existing research networks will be leveraged to validate endpoints and once validated will be submitted for the FDA qualification process for Drug Development Tools for TBI trials.
Role: Investigator

U01 NS099084 (Barsan; Site PI: Chesnut) 4/1/18—3/31/23 0.9 to 2.4 cal mos
NIH/NINDS $32,532,017 (UW: $1,760,014)
Grants Officer: Scott Janis, 9000 Rockville Pike, Bethesda, MD 20892
Project Title: **Brain Oxygen Optimization in Severe Traumatic Brain Injury—Phase 3 (BOOST-3)**
Brief Description of the Project's Goals: This is a Phase 3 clinical trial comparing management of severe TBI based on brain tissue oxygen levels as well as intracranial pressure vs. intracranial pressure alone.
Role: Investigator

PENDING SUPPORT

#TBD (Manley) 07/01/18 – 06/30/21 TBD
National Football League (NFL) $3,454,080Joshua Keidan, Finance Manager, Telephone: 212-450-2309, Email: Joshua.Keidan@nfl.com
Project Title: **Transforming Research and Clinical Knowledge in Traumatic Brain Injury-Longitudinal** (TRACK-TBI LONG)

Brief Description of Project Goals: TRACK-TBI LONG will extend TRACK-TBI's current 1-year follow-up for 3 additional years, adding data ranging from 2-7 years post-injury. These data will validate endpoints for acute and chronic diagnosis, and advance knowledge of the epidemiology, risk factors, and pathology of TBI's long-term sequelae.
Aims: 1) To extend examination of existing injured and control TRACK-TBI participants; 2) to characterize the long-term trajectory of imaging biomarkers in brain-injured and control subjects; 3) to characterize the long-term trajectories of neurocognitive/psychological function and their relationship to plasma-CSF proteomic markers related to inflammation and neurodegeneration, and imaging; 4) to apply PET imaging to characterize prevalence and extent of Aβ plaques and neurofibrillary tangles in a subset of the cohort age >50y; and 5) apply traditional and novel neuroimaging-guided and quantitative neuropathologic approaches to donated brains to interrogate TBI-associated structural and biological changes correlated with antemortem phenotyping.
Role: Investigator

#TBD (Manley) 10/01/2018 – 11/30/2023 2.2 cal mos
Medical Technology Enterprise Consortium $24,999,999
Rebecca Harmon, Advanced Technology International, 315 Sigma Drive, Summerville, SC 29483, Telephone: 843-760-3358, Email: mtec-contracts@ati.org
Project Title: **Transforming Research and Clinical Knowledge in Traumatic Brain Injury Network (TRACK-TBI NET)**
Brief Description of Project Goals: This project will leverage the network capability and infrastructure capacity of the largest precision natural history study of TBI: TRACK-TBI and TED Initiative to characterize the clinical, neuroimaging, and blood-based biomarker features of TBI in a network that is immediately prepared to launch an innovative Phase 2 TBI clinical trials network that delivers on the recommendations of the DoD and NIH workshops and expert panels.
Specific Aims:

1) Adapt the current TRACK-TBI study network into a Phase 2 clinical trial network and work with DoD, FDA, and industry partners to identify key drug candidates for randomized controlled trials.
2) Enroll 504 participants into a Phase 2 multi-arm, multi-stage (MAMS) adaptive platform design for randomized, controlled clinical trial(s).
3) Complete study close-out, analyses, dissemination of findings, and meet with MTEC, FDA, and industry partners to begin plans for Phase 3 clinical trials.

OVERLAP: none

PREVIOUS, CURRENT, AND PENDING SUPPORT

Joseph Giacino

ACTIVE

Spaulding-Harvard Traumatic Brain Injury Model System
National Institute on Disability, Independent Living, and Rehabilitation Research
Contracting/Grants Officer: Leslie Caplan, PhD, 400 Maryland Ave., S.W., Washington, DC
Performance Period: 10/1/17-9/30/22
Annual Funding: $441,500
Level of effort: 2.40 Calendar Months
The aims of this 5-year program grant are to contribute prospective demographic, clinical and outcome data acquired from patients with moderate to severe TBI to the TBI National Data and Statistical Center, develop and validate an abbreviated version of the Coma Recovery Scale-Revised for use in the ICU and participate in multi-site collaborative projects in concert with other funded TBI model systems.
Overlap: There is no overlap.

Central thalamic stimulation for traumatic brain injury
National Institutes of Health
Contracting/Grants Officer: Amy Lane, Asst. Director, Office of Sponsored Research, 1300 York Avenue Box 89, New York, NY 100654805
Performance Period: 9/30/2015 - 8/31/2020
Annual Funding: $71,820
Level of effort: 1.44 Calendar Months
The goal of the research is to develop a deep brain stimulation system that will recover cognitive capacity following brain injury sufficient to improve daily function and vocational or academic reentry.
Aims: 1. To establish the safety of CT-DBS in patients with severe-to-moderate brain injuries and outcomes of GOSE 6-7.
2. To establish measures of efficacy of CT-DBS stimulation in patients with severe-to moderate brain injuries and outcomes of GOSE 6-7.
3. To obtain and analyze critical human subject data to guide device design enabling effective and robust modulation of the DTTm in the human central thalamus.
Overlap: There is no overlap.

Traumatic Brain Injury Endpoints Development Award (TED)
Dept. of the Army - United States Army Medical Research Acquisition Activity
Contracting/Grants Officer: Janet P Kuhns, 820 Chandler St., Fort Detrick, MD 21702-5014
Performance Period: 9/30/2014 - 9/29/2019
Annual Funding: $108,958
Level of effort: 0.96 Calendar Months
The objective of this study is to identify (Stage I) and validate (Stage II) candidate clinical outcome assessments and biomarkers that could be qualified by the Food and Drug Administration as drug development tools for future TBI trials to benefit military and civilian populations.
Aims: 1. To 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.

2: To 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.

3: Continue FDA qualification process for validated COAs and biomarkers, and develop an Implementation and Dissemination Transition Plan.

Overlap: There is no overlap.

Multicenter evaluation of memory remediation after traumatic brain injury with donepezil National Institute on Disability and Rehabilitation (MEMRI-TBI-D)

National Institute on Disability, Independent Living, and Rehabilitation Research

Contracting/Grants Officer: Leslie Caplan, PhD, 400 Maryland Ave., S.W., Washington, DC

Performance Period: 10/1/13-9/30/19 (NCE)

Annual Funding: $101,377

Level of effort: 1.08 Calendar Months

The objective of this 5-year, four-site, randomized, placebo-controlled trial is to test the effectiveness of donepezil for treatment of declarative memory problems experienced by individuals who have sustained mild to severe traumatic brain injury.

Aims: 1. To evaluate the effects of donepezil on neuropsychologically identified, clinically important, verbal memory impairments among persons with complicated mild, moderate, or severe non-penetrating TBI in the subacute to chronic recovery period.

2: To evaluate the effects of donepezil on everyday memory functioning among persons with clinically important declarative memory impairments in the subacute or chronic recovery period following complicated mild, moderate, or severe non-penetrating TBI.

3: To acquire data that inform on the effects of donepezil on attention, processing speed, executive function, neuropsychiatric symptoms, community participation, quality of life, and caregiver burden among persons with complicated mild, moderate, or severe non-penetrating TBI in the subacute to chronic recovery period.

Overlap: There is no overlap.

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

National Institute of Neurological Disorders and Stroke

Contracting/Grants Officer: Aaron Kinchen, 6001 Executive Blvd MSC 9525, Bethesda, MD 20892-9525

Performance Period: 9/30/2013-8/31/19 (NCE)

Annual Funding: $254,509

Level of effort: 3.72 Calendar Months

The overall goal of TRACK-TBI II is to determine the relationships among the clinical, neuroimaging, cognitive, genetic and proteomic biomarker characteristics for the entire spectrum of TBI from concussion to coma, across the entire age spectrum and to validate biomarkers and outcome measures for use in clinical trials.

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.

Overlap: There is no overlap.

PENDING

TRACK-TBI Precision Medicine - Pathomechanistic Classification of Traumatic Brain Injury: The Bridge to Targeted Therapies

U.S. Department of Defense
Contracting/Grants Officer: TBD
Performance Period: 08/01/2018 – 07/31/2021
Total Award: $4,500,000
Level of effort: TBD

The goals of this 3-year project are to validate blood-based and imaging biomarkers to improve the characterization of TBI and elucidate factors to influence design of future precision medicine clinical trials and inform patient responsiveness to targeted therapeutics.

Aims: 1. Validate biomarkers of Diffuse Axonal Injury (DAI), Microvascular Injury (MVI), and Neuroinflammation using advanced blood-based assay platforms and MR imaging sequences in prospectively collected data from existing TRACK-TBI subjects.
2. Validate early and ultra-early blood-based and novel imaging biomarkers of DAI, MVI, and neuroinflammation that may serve as predictive and pharmacodynamic biomarkers in a new cohort of moderate severe TRACK-TBI subjects.
3. Conduct a multicenter double-blind, placebo-controlled exploratory clinical trial comparing the impact of Cyclosporine A on blood-based and imaging biomarkers of DAI and neuroinflammation in moderate-severe TBI patients admitted to the ICU.

Overlap: There is no overlap.

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

National Football League
Contracting/Grants Officer: TBD
Performance Period: 08/01/2018 – 07/31/2021
Total Award: $3,500,000
Level of effort: TBD

This project will extend TRACK-TBI's current 1-year follow-up for 3 additional years, adding data ranging from 2-7 years post-injury depending on participants' original enrollment date. These data will validate endpoints for acute and chronic diagnosis, and advance knowledge of the epidemiology, risk factors, and pathology of TBI's long-term sequelae.

Aims: 1. Extend examination of existing injured and control TRACK-TBI participants with 3 annual telephonic and Web-based follow-ups: capturing neuropsychological and cognitive symptoms and life function/quality and screening for neurodegenerative and post-traumatic disorders;
2. Characterize long-term trajectory of imaging biomarkers in brain-injured and control subjects ("MRI Cohort") using DTI, rs-fMRI, and high-resolution structural studies;
3. Characterize long-term trajectories of neurocognitive/psychological function and their relationship to e.g., plasma-CSF proteomic markers related to inflammation and neurodegeneration, and imaging;

4. Apply PET imaging to characterize prevalence and extent of Aβ plaques and neurofibrillary tangles in a subset of the MRI Cohort age >50y;
5. Apply traditional and novel neuroimaging-guided and quantitative neuropathologic approaches to donated brains to interrogate TBI-associated structural and biological changes correlated with antemortem phenotyping.

Overlap: There is no overlap.

Transforming Research and Clinical Knowledge in Traumatic Brain Injury Network (TRACK-TBI NET)
U.S. Department of Defense- Medical Technology Enterprise Consortium
Contracting/Grants Officer: TBD
Performance Period: 08/10/2018 – 08/09/2023
Total Award: $25,000,000
Level of effort: TBD
This project will leverage the network capability and infrastructure capacity of the largest precision natural history study of TBI: TRACK-TBI and TED Initiative to characterize the clinical, neuroimaging, and blood-based biomarker features of TBI in a network that is immediately prepared to launch an innovative Phase 2 TBI clinical trials network that delivers on the recommendations of the DoD and NIH workshops and expert panels.
Aims: 1. Adapt the current TRACK-TBI study network into a Phase 2 clinical trial network and work with DoD, FDA, and industry partners to identify key drug candidates for randomized controlled trials.
2. Enroll 504 participants into a Phase 2 multi-arm, multi-stage (MAMS) adaptive platform design for randomized, controlled clinical trial(s).
3. Complete study close-out, analyses, dissemination of findings, and meet with MTEC, FDA, and industry partners to begin plans for Phase 3 clinical trials.

Overlap: There is no overlap.

<u>PREVIOUS (within the last 5-years)</u>

Spaulding-Harvard Traumatic Brain Injury Model System
National Institute on Disability, Independent Living, and Rehabilitation Research
Contracting/Grants Officer: Cate Miller, PhD, 400 Maryland Ave., S.W., Washington, DC
Performance Period: 10/1/12-9/30/18 (NCE)
Annual Funding: $430,100
Level of effort: 1.0 Calendar Months
The aims of this 5-year center grant are to contribute prospective demographic, clinical and outcome data acquired from patients with moderate to severe TBI to the TBI National Data and Statistical Center, complete a site-specific functional neuroimaging study entitled, “Looking for Consciousness: A Novel Functional Neuroimaging Approach for Detection of Visual Cognition in Patients with Severe TBI and Disorders of Consciousness” and participate in collaborative “module” projects in concert with other funded TBI model systems.
Overlap: There is no overlap.

Huperzine A for the Treatment of Cognitive, Mood and Functional Deficits After Moderate and Severe TBI
US Department of Defense
Contracting/Grants Officer: Jennifer Shankie, US Army Medical Research and Materiel Command, 820 Chandler Street Fort Detrick, MD 21702

Performance Period: 9/1/11-8/31/18 (NCE)
Annual Funding: $409,000
Level of effort: 1.08 Calendar Month
The primary objective of this study is to conduct a phase II, randomized, double-blind, placebo-controlled clinical trial to investigate the effects of Huperzine A on memory function, TMS-induced neurophysiologic markers, EEG event related potentials (P50 and p300), seizure frequency and incidence of adverse effects in civilian and military personnel who sustain moderate to severe traumatic brain injury.
Aims: 1. To determine whether Huperzine A, as compared to placebo, has a differential effect on learning and memory functions after moderate to severe TBI.
2. To determine whether administration of Huperzine A produces significant differences in neurophysiologic markers (as indexed by EEG event related potentials (P50 and P300) and TMS-indexed cortical excitability (cholinergic activity)) associated with cognition relative to a placebo.
3. To determine whether Huperzine A reduces the prevalence/frequency of post-traumatic seizures after moderate and severe TBI as compared to placebo.
4. To evaluate the safety and tolerability of Huperzine A in this patient population as compared to placebo. Safety and tolerability will be assessed by a comparison of the frequency and intensity of adverse effects.
Overlap: There is no overlap.

An Evidence-Based Clinical Outcome Assessment Platform to Advance the Identification and Validation of Clinical Outcome Assessment Measures for Use as FDA-Qualified Drug Development Tools: A Traumatic Brain Injury Endpoints Development (TED) SEED Award
Dept. of the Army - United States Army Medical Research Acquisition Activity
Contracting/Grants Officer: Susan Dellinger, 820 Chandler St., Fort Detrick, MD 21702-5014
Performance Period: 02/01/2016- 01/31/2017
Annual Funding: $274,981
Level of effort: 1 Calendar Month
The objective of this study is to design, build and pilot test an evidence-based platform for assessment of COAs, placing particular emphasis on the validity of the COA as it pertains to a specific concept of interest within a given context of use.
Aims: 1. Facilitate completion of Stage 1 of TED by designing and building an evidence-based clinical outcome assessment platform that will enable efficient, transparent and systematic grading of COAs to aid selection of suitable candidates for regulatory acceptance or FDA qualification.
2: Pilot test the EB-COP platform on the Glasgow Outcome Scale- Extended (GOSE), the only COA designated as a “core” CDE for TBI, and the only measure currently accepted by the FDA for use in clinical trials.
Overlap: There is no overlap.

The INjury and TRaumatic STress (INTRuST) Consortium Neuroimaging Acquisition and Archival
US Department of Defense
Contracting/Grants Officer: Pamela Fisher, USA MED Research Acq Activity, 820 Chandler Street Fort Detrick, MD 21702
Performance Period: 3/31/2013-9/30/2014
Annual Funding: $315,230
Level of effort: 1 Calendar Month

The primary goal of this project is to acquire and archive neuroimages representing a diverse population (civilian and military) and a spectrum of traumatic brain injuries (e.g., blast vs. impact in the military population).
Overlap: There is no overlap.

Zolpidem and Restoration of Consciousness: An Exploration of the Mechanism of Action
H133G080066 National Institute on Disability and Rehabilitation Research
Contracting/Grants Officer: Leslie Caplan, PhD, 400 Maryland Ave., S.W., Washington, DC
Performance Period: 1/01/08-12/31/13 (NCE 2013)
Annual Funding: $675,000
Level of effort: 0.01 Calendar Months
The primary goal of this multicenter trial is to determine the incidence of behavioral improvement immediately following administration of zolpidem.
Overlap: There is no overlap.

Harvey Levin, PhD

ACTIVE

W81XWH-13-PHTBI-TED (Manley) 09/1/2014-08/31/2019 1.2 CM
DOD, USAMRMC (PT13078) $64,735

TBI Endpoints Development (TED)
Goals: The major goal of this study is to facilitate the qualification of diagnostic and prognostic biomarkers of traumatic brain injury by analyzing meta-databases of recent observational studies and clinical trials.
Aims: Secondary analysis of meta-databases of recent observational studies and clinical trials to identify imaging, fluid, and neuropsychological biomarkers of mild to moderate traumatic brain injury.
Role: Site PI

PT120517 (Cifu, D.) 9/30/13 - 9/29/18 (NCE) 0.6 CM
CENC/DoD/VA $306,300

Chronic Effects of Neurotrauma Consortium (CENC) Longitudinal Study 1
Goals: To establish a large longitudinal case-control cohort Veterans to comprehensively evaluate for the late effects of combat related mTBI, describe the late outcomes and change over time of Veterans with single and repeated mTBI, and establish whether, and to what extent, mTBI(s) is associated with poorer outcome among combat-exposed Veterans.
Role: Co-Investigator

R44-HD090817-01A1 (Southern, S./Peacock) 08/15/17-07/31/19 1.2 CM
NIH $246,997

Rapid Saliva Test for Diagnostics of Neuro-Cogntivie Disorder due to TBI
Goals: Nearly 4 million traumatic brain injuries (TBI) happen in the USA each year due to motor vehicle accidents, falls, assaults and sport injuries. Most TBI are classified as mild (mTBI). mTBI is a major public health care concern because about 20% patients develop physical, cognitive, emotional and sleep symptoms after mTBI. These persistent sequelae are called Neuro Cognitive Disorder due to TBI (NCDT). Objective NCDT test is key element for valid NCDT diagnostics, and development of targeted therapy. Currently, there is no objective diagnostic test for NCDT, and no specific treatment for NCDT. Symptomatic patients are diagnosed using neuropsychological tests in hospital. The standard practice has significant weaknesses: low accuracy, high cost and inconvenience. The goal of this project is to develop a rapid NCDT test based on saliva biomarkers. The proposed test will provide an objective, simple, affordable and convenient aid for NCDT diagnostics. N=10 candidate saliva biomarkers of NCDT were identified in Phase I R&D using N=475 saliva samples from human subjects. The candidate biomarkers have diagnostic accuracy¡Ý80% for early NCDT (4-6 months after mTBI) as well as late NCDT (12-36 months after mTBI). Specific objectives for Phase II: Specific Aim 1 will collect N=2,610 longitudinal saliva samples from N=500 patients (N=120 NCDT, N=230 mTBI

without NCDT, N=130 orthopedic injury controls and N=20 healthy controls) at 3 clinical sites: Baylor College of Medicine, University of Pittsburgh Medical Center and University of California San Diego. Specific Aim 2 will measure 10 candidate NCDT biomarkers in saliva samples from SA1 using 3 orthogonal assays. Results will cross-validate the molecular specificity and diagnostic accuracy of the candidate biomarkers, and validate the best 3-4 biomarkers for the commercial NCDT test. SA3 will develop a rapid NCDT test using a proven commercial device platform based on a lateral-flow immunoassay with onboard digital reader.
Role: Co-Investigator

1 R43 HD 097039 (Southern/Levin) TBD .36 CM
NIH $56,434

Saliva Biomarkers for MTBI Diagnostic in Children
The major goals of this project are to (1) Collect serial saliva samples from school children with medically diagnosed mild traumatic brain injury (mTBI, n=40), controls with orthopedic injury (OI, n=30) who are evaluated in Emergency Medicine, Texas Children's Hospital (TCH) and from uninjured, healthy controls (HC, n=15) to measure salivary biomarkers for brain injury; and (2)Determine diagnostic accuracy of saliva mTBI biomarkers in classifying the mTBI and OI groups. Saliva samples will be obtained on three occasions (within 48 hours after injury, 7 to 14 days, and 30 days); postconcussion symptoms will also be measured on each visit. As a secondary goal, we will evaluate the accuracy of the biomarkers measured within 48 hours in predicting persistent postconcussion symptoms (PPCS) based on the day 30 outcome assessment; functional status on day 30 of the children with mTBI will also be analyzed in relation to the biomarkers measured within 48 hours . The ultimate goal is to develop a new point-of-care (POC) test for diagnostics of mTBI) in children. Salivary samples from healthy children and existing baseline samples from pre-season high school athletes will define normal range and daily/diurnal variability in biomarker concentrations. This project addresses the need for objective, noninvasive, and practical biomarkers for mTBI.

OVERLAP

None.

For New and Renewal Applications (PHS 398) – DO NOT SUBMIT UNLESS REQUESTED
For Non-competing Progress Reports (PHS 2590) – Submit only Active Support for Key Personnel

PHS 398/2590 OTHER SUPPORT

Provide active support for all key personnel. **Other Support includes all financial resources, whether Federal, non-Federal, commercial or institutional, available in direct support of an individual's research endeavors, including but not limited to research grants, cooperative agreements, contracts, and/or institutional awards.** Training awards, prizes, or gifts do not need to be included.

There is no "form page" for other support. Information on other support should be provided in the *format* shown below, using continuation pages as necessary. ***Include the principal investigator's name at the top and number consecutively with the rest of the application.*** The sample below is intended to provide guidance regarding the type and extent of information requested.
For instructions and information pertaining to the use of and policy for other support, see Other Support in the PHS 398 Part III, Policies, Assurances, Definitions, and Other Information.
Note effort devoted to projects must now be measured using person months. Indicate calendar, academic, and/or summer months associated with each project.

McCrea, M.
ACTIVE

U0-1NS086090 (Manley) 9/1/16-8/31/19 0.12 calendar
NINDS
(Subcontract with UCSF) $125,000
Transforming Research and Clinical Knowledge in TBI (TRACK TBI)

The goal of this project is 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.

W911QY-14-C-0070 (Okonkwo) 9/8/17-9/4/18 0.12 calendar
Naval Health Research Center $283,500
(Subcontract with Pitt)
TRACK-TBI - High Definition Fiber Tracking Neuroimaging, Biospecimen and Data Informatics Repositories

The goal of this project is to deliver on three core missions that will harmonize TRACK-TBI resources and infrastructure with ongoing DoD-funded initiatives, broadening the impact to military health priorities.

W81XWH-14-2-0151 (Broglio, McAllister, McCrea) 9/15/14-9/14/18 (NCE) 4.8 calendar
USAMRMC and NCAA (Subcontract with IU) $7,407,407 Co-PI
The NCAA-DOD Grand Alliance: Concussion Assessment, Research and Education (CARE)

The goal of this study is to create a national consortium of researchers who will conduct a large-scale, longitudinal, multi-site, multi-sport investigation that integrates biomechanical, clinical, neuroimaging, and genetic markers of injury to delineate the natural history of concussion in male and female athletes.

--- (McCrea) 4/1/14-9/30/18 (NCE) 0.24 calendar
NFL-GE Head Health Challenge $800,000
A Prospective Study of Advanced MRI Biomarkers to Determine Acute Physiological Effects and Longitudinal Recovery After Sport-Related Concussion

The goal of this project is to further characterize and validate noninvasive, quantitative neuroimaging biomarkers of acute physiological effects and longitudinal physiological recovery after sport related concussion. Specific Aims

W81XWH-14-1-0561 (McCrea) 9/29/14-9/30/18 3 calendar
USAMRMC $6,158,636
Comprehensive Study of Acute Effects and Recovery After Concussion: An Integrated Investigation of Head Impact Sensor Technology, Blood Biomarkers, Advanced Neuroimaging, Genetic Testing and Clinical Outcome Metrics (Project Head to Head 2)

The goal of this study is to understand the relative influence of various neurobiopsychosocial factors in the response to and recovery following sport-related concussion by integrating advanced multi-modal neuroimaging, blood biomarkers, head impact sensor biomechanics, genetic testing, and clinical measures in a single sample of concussed contact sport athletes and matched non-concussed controls.

--- (Register-Mihalik, Guskiewicz, McCrea) 5/1/16-4/30/19 0.36 calendar
National Football League $787,865
Role of Rehabilitation in Concussion Management: A Randomized, Controlled Trial

The goal of this project is to conduct a randomized clinical trial to yield preliminary data on the added benefits of active rehabilitation during recovery after SRC in professional and amateur athletes.

W81XWH-14-2-0176 (Manley) 10/1/14-9/30/19 1.2 calendar
CDMRP (Subcontract with UCSF) $665,955 Co-I
TBI Endpoints Development (TED)

The goal of this project is to validate candidate endpoints and improve clinical trial design to inform and accelerate FDA approval of diagnostic tools and therapeutic agents for TBI.

BA170608 (Broglio, McAllister, McCrea) 2 years 4.8 calendar
NCAA (Subcontract with IU) $7,737,972
Cumulative and Persistent Intermediate Effects of Concussion and Head Impact Exposure in CARE Consortium Military Service Academy Members and NCAA Athletes

The goal of this proposal is to answer three critical questions related to the intermediate-term effects of concussion and/or repetitive head impact exposure in MSA cadets and NCAA student-athletes.

PENDING
--- (McCrea, Mukherjee, Yang) 5 years 1.2 calendar
NINDS (Subcontract with UCSF) $1,867,372
Microstructural and Connectomic Imaging Biomarkers of Mild TBI

The goals of this project are to: (1) better characterize the dynamic white matter microstructural changes after mTBI using biologically meaningful metrics of DAI and neuroinflammation; (2) better delineate the alterations of the structural and functional connectome after mTBI using novel diffusion and rs-fMRI metrics; and (3) test the clinical utility of these novel microstructural and connectomic imaging measures as early prognostic biomarkers of patient outcome after mTBI.

--- (Manley) 3 years 1.2 calendar
USAMRMC (Subcontract with UCSF) $333,264
TRACK-TBI Precision Medicine - Pathomechanistic Classification of Traumatic Brain Injury: The Bridge to Targeted Therapies

The goal of this proposal is to characterize magnetic resonance imaging (MRI) and blood-based biomarker features of traumatic brain injury (TBI) to inform the design of a next-generation precision medicine TBI exploratory clinical trial and evaluate the use of serum biomarkers and MRI for the diagnosis of TBI.

--- (Meehan) 5 years 2.4 calendar
National Football League (Subcontract with BCH) $4,035,768
Neurologic Function across the Lifespan: A Prospective, LONGitudinal, and Translational Study for Former National Football League Players: NFL-LONG

The goal of this project is to assess the association between concussion, sub-concussive exposure, cerebral tau, and clinical outcomes.

--- (Manley) 5 years 11.94 calendar

MTEC (Subcontract with UCSF) $475,000
Transforming Research and Clinical Knowledge in Traumatic Brain Injury Network (TRACK-TBI NET)

The goal of this project is leverage the TRACK-TBI and TED infrastructure and experience establish the TRACK-TBI NETWORK (TRACK-TBI NET), an innovative Phase 2 TBI adaptive clinical trials network that delivers on DoD and NIH recommendations.

--- (Pasquina) 4 years 1.2 calendar
UHSUS (Subcontract with IU) $4,035,768
Service Academy Longitudinal TBI Outcomes Study (SALTOS)

The goal of this project is to assess the association between concussion, sub-concussive exposure, cerebral tau, and clinical outcomes.

OVERLAP
None

Pratik Mukherjee, MD PhD

ACTIVE

Title: Transforming Research and Clinical Knowledge in Traumatic Brain Injury
Grant number: U01 NS086090 A#122283
Principal Investigator: (PI: Pratik Mukherjee, Geoffrey Manley-Contact PI)
Time commitment: *effort as needed
Supporting agency: NIH/NINDS/NIBIB/NICHD/NIDCD
Grants management specialist: Yvonne C. Talley; talleyy@mail.nih.gov
Performance period: 09/30/2013 - 08/31/2019 (NCE)
Level of funding: $3,378,488 total directs
Project Goals: 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.
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
Project Overlap: None

Title: TBI Endpoints Development (TED)
Grant number: W81XWH-14-2-0176
Principal investigator: Geoffrey Manley
Time commitment: 1.62 calendar months
Supporting agency: DOD US Army Med. Res. Acq. Activity
Grants management specialist: Susan Dellinger; susan.m.dellinger.civ@mail.mil
Performance period: 09/30/2014-09/29/2019
Level of funding: $3,335,742 total directs
Project Goals: To improve diagnosis, treatment, and rehabilitation strategies for mTBI to mod TBI.
Specific Aims:
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 FDAqualified drug development tools (DDTs), and initiate development of CDISC data standards for trials involving diagnosis and treatment of mTBI to modTBI.
Aims:
1.1. 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.
1.2. 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.
1.3. 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).
1.4. Establish Expert Working Groups (EWGs) to organize the analyses of individual studies and the TED Metadataset, and review existing TBI COA and biomarker literatures.
1.5. 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.
1.6. Solicit, evaluate, and collaboratively develop “seed projects” to further the TED goals of identification

and validation of endpoints for diagnostic and therapeutic trials.
1.7. Organize and host a Consensus Conference Year 2 (CC2) to review work product of EWGs and utilize a Delphi process that incorporates scientific rationale as well as regulatory feasibility to reach consensus as to COAs and biomarkers to be validated in Stage II.
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.
Aims:
2.1 Validate COA endpoints that provide more sensitive outcome assessments and support the design of more effective clinical trials.
2.2 Validate biomarkers that can provide diagnostic, prognostic, predictive, and pharmacodynamic endpoints for clinical trials.
Technical Objective 3: Continue FDA qualification process for validated COAs and biomarkers, and develop an Implementation and Dissemination Transition Plan.
Project Overlap: None

Title: Foundations of MRI Corticography for mesoscale organization and neuronal circuitry
Grant number: R01MH111444
Principal Investigator: (Feinberg)
Time commitment: 0.60 calendar months
Supporting agency: NIH
Grants management specialist: Heather Weiss; weissh@mail.nih.gov
Performance period: 9/16/2016-6/30/2021
Level of funding: $50,000 total directs
Project goals: The improved technologies developed in this project will lead to MRI scans with expanded diagnostic information in potentially the less time than traditional methodologies. The emphasis on ultra-high resolution MRI for mapping the mesoscale organization and circuitry of the human brain in this grant will support efforts currently underway at the VA to characterize, diagnose, and treat neurovascular and neurodegenerative diseases which is of prime importance to our aging veterans.
Specific Aims:
Aim 1: Implement product pulse sequences for SMS phase contrast imaging
M-1 Demonstrate SMS in cine-GRE and in real-time EPI PC imaging can increase number of slices N fold.
M-2 Segmented cine-SMS GRE PC to reduce acquisition time
M-3 Centric k-space in segmented SMS EPI PC to shorten TE, increase SNR and/or spatial resolution.
M-4 Implement in-plane acceleration to increase spatial resolution and/or reduced acquisition time.
M-5 Determine if radial sampling in SMS PC reduces motion artifacts.
Aim 2: Variable slice angles in simultaneous acquisitions
M-6 Create pulse sequence for angled non-parallel slices in SMS PC using sequential selective RF pulses
Aim 3: Create SMS PC sequence with two velocity ranges (VENC)
M-7:. Measure 20cm/s and 90cm/s velocity ranges within one acquisition of SMS PC imaging
Aim 4: Improve quantitation, image quality and temporal resolution
M-8 Test flow compensation gradients in SMS PC to improve image SNR and velocity quantification.
M-9 Compare image reconstruction algorithm for separating images to reduce artifact and increase SNR.
M-10 Determine best use of CAIPIRHINA, blipped-CAIPI, radial-CAIPI to reduce artifact and raise SNR.
M-11 Develop undersampled acquisition and reconstruction strategy to reduce scan time while minimizing aliasing artifact.
Aim 5: Implement SMS 4D Phase Contrast Imaging
M-12: Use SMS-radial or Cartesian to replace 3D radial trajectory to increase speed and reduce artifact.
Aim 6: Create Product software interface
M-13: Create control switches for pulse sequences and data acquisition in scanner graphic user interface.
Aim 7: Imaging Protocol Optimization.
M-14 Create protocols and a technical manual on vascular imaging with SMS PC pulse sequences including imaging protocols for a) coronary arteries, b) aorta and great vessels, c) carotid and vertebral arteries, d) cerebral vessels including Circle of Willis.
M-15 Create protocols and a technical manual on CSF imaging with SMS PC imaging protocols.
Project Overlap: None

Title: Multi-level assessment and rehabilitation of combat mild traumatic brain injury
Grant number: I01RX002300
Principal Investigator: (Mukherjee)
Time commitment: 1.20 calendar months
Supporting Agency: Department of Veterans Affairs
Grants management specialist: Stuart W. Hoffman; stuart.hoffman@va.gov
Performance period: 02/01/2017 – 09/30/2021
Leveling of funding: $166,575 total directs
Project goals: The objectives of this proposal are to investigate the potential short- and longer-term effects of GOALS training program in Veterans with mild traumatic brain injury (mTBI) and cognitive difficulties, and to use to use advanced imaging to investigate changes in brain structure and function in: (1) attention and executive control networks, (2) working memory and short-term memory pathways important for complex real-world tasks, and (3) frontolimbic circuits that regulate emotion that may accompany cognitive training in mTBI.
Specific Aims:
AIM 1: To determine the short and long term effects of GOALS training on neuro-cognitive performance and neural plasticity of attention and executive control networks in mTBI.
AIM 2: To determine the short and long term effects of GOALS training on complex functional task performance and daily functioning, and on plasticity in pathways related to memory function, in mTBI.
AIM 3: To determine the short and long term effects of GOALS training on measures of emotional regulation, and on plasticity of frontolimbic networks related to emotion processing, in mTBI
Project Overlap: None

Title: Multimodal modeling framework for fusing structural and functional connectome data
Grant number: 1R01 EB022717-01
Principal Investigator: Ashish Raj, Srikantan Nagarajan
Time commitment: 0.29 calendar months
Supporting Agency: NIH/NIBIB
Grants management specialist: Florence Turska; ft7p@nih.gov
Performance period: 07/01/2016-06/30/2019
Leveling of funding: $296,810 total directs
Project goals: The goal of this project is to develop a novel framework for fusion of MEG and dMRI datasets.
Specific Aims: Drs. Nagarajan and Mukherjee will work closely with Dr. Raj on algorithm development. Dr. Nagarajan will be involved in the model development work for Aim 1, as well as inference work in Aim 2. He will also coordinate algorithm application and testing in patients with callosal agenesis and with early onset Alzheimer's disease. Dr. Mukherjee will provide the much need clinical perspective on algorithm development and testing, and input on applications to patients with callosal agenesis and early onset Alzheimer's disease.
Project Overlap: None

Title: Artificial intelligence to characterize head computed tomography studies in neurological emergencies
Grant number: OPR0141109
Principal Investigator: Atul Butte
Time commitment: *effort as needed
Supporting Agency: CIAPM (California Precision Medicine Initiative)
Grants management specialist: Elizabeth Baca; Elizabeth.baca@opr.ca.gov
Performance period: 02/07/2017-12/31/2018
Leveling of funding: $1,200,000 total directs
Project goals: To identify effective measures of brain injury and recovery, using genomics, biomarkers from blood, new imaging equipment and software, and other computational tools
Specific Aims:
Aim 1: develop, train, test deep learning models
Aim 2: develop cloud-based AI, robust to differences in scanner hardware and protocols
Aim 3: demonstrate superiority to subjective head CT grading schemes for outcome prediction
Project Overlap: None

Title: Co-design for artificial intelligence coupled with computing at scale for extremely large, complex datasets

Grant number: B628729
Principal Investigator: Geoffrey Manley
Time commitment: 0.84 calendar months
Supporting Agency: Lawrence Livermore National Laboratory
Grants management specialist: Gary M. Ward; ward31@llnl.gov
Performance period: 05/01/2018-7/31/2019
Leveling of funding: $319,174 total directs
Project goals: The Subcontractor shall focus its research activities toward the following goals: (i) establish enclaves capable of securely handling sensitive data and to perform data management; (ii) develop and perform new classes of scalable analytics on provided pilot TRACK-TBI data; and (iii) run analysis experiments at multiple DOE sites and generation of actionable insights for TBI.
Specific Aims:
Project Overlap: None

Title: Transforming research and clinical knowledge in traumatic brain injury network (TRACK-TBI)
Grant number: 2018-674
Principal Investigator: Geoffrey Manley
Time commitment: 1.2 calendar months
Supporting Agency: MTEC
Grants management specialist: Rebecca Harmon; mtec-contracts@ati.org
Performance period: 10/1/2018-11/30/2023
Leveling of funding: $1,631,270 total directs
Project goals: The goal of the Drug Treatment for TBI (DTTBI) program is to improve the quality and quantity of candidate drugs entering Phase 3 trials for the treatment of TBI.
Specific Aims:
Project Overlap: None

PENDING

Title: A biophysical, connectome-based model of global and regional functional rerouting in recovery from traumatic brain injury
Grant number: TBD R21
Principal Investigator: Kuceyeski
Time commitment: 0.6 calendar months
Supporting Agency: NIH
Grants management specialist:
Performance period: 07/01/16-06/30/18
Leveling of funding: $13,125 total directs
Project goals: To create a brain network connectivity model of brain injury and recovery in head trauma.
Specific Aims: Dr. Mukherjee will provide data for this project, including demographic, MRI and neuropsychological data from a mild to moderate TBI subjects, collected at baseline and 1-year follow-up. Dr. Mukherjee will provide advice to Dr. Kuceyeski for dealing with any issues that arise in image processing and will also be a key contributor in providing neurological interpretation of and clinical relevance to the findings.
Project Overlap: None

Title: MRI Corticography: Developing Next Generation Microscale Human Cortex MRI Scanner
Grant number: U01 EB025162
Principal Investigator: Feinberg
Time commitment: 0.6 calendar months
Supporting Agency: NIH
Grants management specialist:
Performance period: 9/1/2017- 8/31/2022
Leveling of funding: $23,375 total directs

Project goals: The goal of this project is is to create a significantly higher-resolution MRI scanner for imaging the cortex of human brain as a new tool for studying neural circuitry.
Specific Aims:
Project Overlap: None

Title: Neural Mechanisms of Sensory Over-Responsivity
Grant number: P0518378
Principal Investigator: (Multi PI: Marco, Contact PI and Mukherjee)
Time commitment: 1.2 calendar months
Supporting Agency: NIH
Grants management specialist:
Performance period: 07/01/18 – 06/30/23
Leveling of funding: $499,471 total directs
Project goals: The major goal of this project is to identify the neural architecture of auditory and tactile sensory over-responsivity and to identify potential biomarkers.
Specific Aims:
Project Overlap: None

OVERLAP

None.

Nancy Temkin, PhD

CURRENT SUPPORT

R01HD083126 (Mac Donald) 7/1/2015 - 6/30/2020 0.6 cal mos
NIH/NINDS
Grants Officer: Patrick Bellgowan. 9000 Rockville Pike, Bethesda, MD 20892
Project Title: **EValuation Of Longitudinal outcomes in mild TBI Active-Duty Military and Veterans – The EVOLVE Study**
Brief Description of the Project's Goals: 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

5U48 DP00191104 (SIP-12-057) (Fraser) 9/30/12 - 9/29/19 0.24 cal mos
CDC $120,000
Grants 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

1R01NS080648 (CPI Chesnut, Temkin MPI) 9/30/12/12-7/31/19 1.2 cal mos
NIH/NINDS and Fogarty $2,516,005
Grants Officer: Patrick Bellgowan, 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

H133A980023 (Hoffman) 10/01/17 – 09/30/22 0.36 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

U01 NS099084 (Barsan; Site PI: Chesnut) 4/1/18—3/31/23 0.9 to 2.4 cal mos
NIH/NINDS $32,532,017 (UW: $1,760,014)
Grants Officer: Scott Janis, 9000 Rockville Pike, Bethesda, MD 20892

Project Title: **Brain Oxygen Optimization in Severe Traumatic Brain Injury—Phase 3 (BOOST-3)**
Brief Description of the Project's Goals: This is a Phase 3 clinical trial comparing management of severe TBI based on brain tissue oxygen levels as well as intracranial pressure vs. intracranial pressure alone.
Role: Investigator

PENDING SUPPORT

#TBD (Manley) 07/01/18 – 06/30/21 TBD
National Football League (NFL) $3,454,080
Joshua Keidan, Finance Manager, Telephone: 212-450-2309, Email: Joshua.Keidan@nfl.com
Project Title: **Transforming Research and Clinical Knowledge in Traumatic Brain Injury-Longitudinal (TRACK-TBI LONG)**
Brief Description of Project Goals: TRACK-TBI LONG will extend TRACK-TBI's current 1-year follow-up for 3 additional years, adding data ranging from 2-7 years post-injury. These data will validate endpoints for acute and chronic diagnosis, and advance knowledge of the epidemiology, risk factors, and pathology of TBI's long-term sequelae.
Specific Aims: 1) To extend examination of existing injured and control TRACK-TBI participants; 2) to characterize the long-term trajectory of imaging biomarkers in brain-injured and control subjects; 3) to characterize the long-term trajectories of neurocognitive/psychological function and their relationship to plasma-CSF proteomic markers related to inflammation and neurodegeneration, and imaging; 4) apply traditional and novel neuroimaging-guided and quantitative neuropathologic approaches to donated brains to interrogate TBI-associated structural and biological changes correlated with antemortem phenotyping.
Role: Investigator

#TBD (Manley) 10/01/2018 – 11/30/2023 2.2 cal mos
Medical Technology Enterprise Consortium $24,999,999
Rebecca Harmon, Advanced Technology International, 315 Sigma Drive, Summerville, SC 29483, Telephone: 843-760-3358, Email: mtec-contracts@ati.org
Project Title: **Transforming Research and Clinical Knowledge in Traumatic Brain Injury Network (TRACK-TBI NET)**
Brief Description of Project Goals: This project will leverage the network capability and infrastructure capacity of the largest precision natural history study of TBI: TRACK-TBI and TED Initiative to characterize the clinical, neuroimaging, and blood-based biomarker features of TBI in a network that is immediately prepared to launch an innovative Phase 2 TBI clinical trials network that delivers on the recommendations of the DoD and NIH workshops and expert panels.
Specific Aims:

1) Adapt the current TRACK-TBI study network into a Phase 2 clinical trial network and work with DoD, FDA, and industry partners to identify key drug candidates for randomized controlled trials.
2) Enroll 504 participants into a Phase 2 multi-arm, multi-stage (MAMS) adaptive platform design for randomized, controlled clinical trial(s).
3) Complete study close-out, analyses, dissemination of findings, and meet with MTEC, FDA, and industry partners to begin plans for Phase 3 clinical trials.

#TBD (Manley) 10/01/18 --09/30/21 1.2 cal mos
U.S. Department of Defense $4,500,000
Grants Officer TBD
Project title: **TRACK-TBI Precision Medicine - Pathomechanistic Classification of Traumatic Brain Injury: The Bridge to Targeted Therapies**
Brief Description of Project Goals: Validate blood-based and imaging biomarkers to improve the characterization of TBI, and elucidate factors to influence design of future precision medicine clinical trials and inform patient responsiveness to targeted therapeutics.
Specific Aims:

1) Validate biomarkers of Diffuse Axonal Injury (DAI), Microvascular Injury (MVI), and Neuroinflammation using advanced blood-based assay platforms and MR imaging sequences in prospectively collected data from existing TRACK-TBI subjects.
2) Validate early and ultra-early blood-based and novel imaging biomarkers of DAI, MVI, and neuroinflammation that may serve as predictive and pharmacodynamic biomarkers in a new cohort of moderatesevere TRACK-TBI subjects.
3) Conduct a multicenter double-blind, placebocontrolled exploratory clinical trial comparing the impact of Cyclosporine A on blood-based and imaging biomarkers of DAI and neuroinflammation in moderate-severe TBI patients admitted to the ICU.

OVERLAP: none

Murray B. Stein, MD, MPH: Current/Pending Research Support

Current Research Support

Title: San Diego Clinical and Translational Research Institute
Role: Co-Investigator (PI: Gary Firestein MD, UCSD)
Time commitment: 2.4 cal months
Supporting Agency: NIH/NCATS; Type: UL1 TR001442
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: NCATS Grants Management Specialist, National Center for Advancing Translational Sciences (NCATS), 6701 Democracy Boulevard, Bethesda MD 20892-4874
Performance period: 08/31/2015 – 03/31/2020
Level of funding: ~ $5,000,000 DC current year
Project Goals/Specific Aims: The major goals of this grant are to foster innovative research and research partnerships and advance the science of collaborative research.

Title: TBI Endpoints Development (TED)
Role: Consortium PI (PI: Manley)
Time commitment: 1.35 cal months
Supporting Agency: Department of Defense (DoD) Type: W81XWH-13-PHTBI-TED
Performance period: 09/30/2014 – 09/29/2019
Level of funding: $112,356 DC current year
Project Goals/Specific Aims: The major goal of this award is the support of the Consensus and Implementation Conferences and validation studies pertinent to TBI endpoints and outcomes.

Title: Army Study to Assess Risk and Resilience in Service Members-Longitudinal Survey (STARRS-LS)
Role: Co Investigator (with Ursano, HJF)
Time commitment: 3.15 cal months
Supporting Agency: US Department of Defense
Performance period: 07/01/2015 – 11/30/2019
Level of funding: ~$343,080 DC current year
Project Goals/Specific Aims: The major goals of this award are to develop models and report actionable findings pertinent to suicide and related mental health problems and resilience in the military. This iteration of the project focuses on longitudinal follow-up of the inception cohort.

Title: Novel Behavioral Intervention to Target Social Reward Sensitivity and Attachment
Role: Co-Investigator (Taylor)
Time commitment: 1.8 cal months
Supporting Agency: NIH/NIMH Type: R61MH113769
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: James Pugh, NIMH Grants Management Specialist, 6001 Executive Boulevard Rockville, MD 20852
Performance period: 08/05/2017 – 05/31/2019
Level of funding: $485,715 annual direct costs
Project Goals/Specific Aims: The goal of this project is to test the hypothesis that social approach training can up-regulate social reward sensitivity, investigate optimal dosing of social

approach training to maximally engage the target, and establish further psychometric support such as test-retest reliability for the proposed measures of target engagement.

Title: Enhancing Fear Extinction via Angiotensin Type 1 Receptor Inhibition: A Randomized Controlled Trial in Posttraumatic Stress Disorder
Role: PI
Time commitment: 2.4 cal months
Supporting Agency: Department of Defense (DoD) Type: W81XWH-15-2-0090
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Allison Milutinovich, U.S. Army Medical Research Acquisition Activity, 820 Chandler St., Fort Detrick, MD 21702-5014
Performance period: 09/30/2015 – 09/29/2019
Level of funding: $6,973,352.00 Total Costs for Entire Project Period
Project Goals/Specific Aims: The goal of this project is to conduct a multi-site randomized controlled trial to determine the efficacy of losartan for symptoms of PTSD.

Title: The impact of traumatic stress on the methylome: implications for PTSD
Role: Co-Investigator (Smith)
Time commitment: 0.48 cal months
Supporting Agency: NIH/NIMH Type: R01MH108826
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Maggie Paolini, NIMH Grants Management Specialist, 6001 Executive Boulevard Rockville, MD 20852
Performance period: 08/18/2016 – 05/31/2020
Level of funding: $2,222,029.00 Total Costs for Entire Project Period
Project Goals/Specific Aims: The goal of this project is to facilitate a multi-site, epigenome-wide analysis of PTSD, with the long-term goal of developing an epigenetic panel that informs the prediction or treatment of PTSD.

Pending:

Title: PTSD Genomewide: Genetics, Expression, and Epigenetics
Role: Consortium PD/PI
Time commitment: 1.8 cal months
Supporting Agency: NIH/NIMH via Yale
Performance period: 04/01/2019 – 03/31/2024
Level of funding: $105,315 annual direct cost
Project Goals/Specific Aims: The major goals of this project is to parse heterogeneity in the PTSD by exploring its genetic links to other traits and diseases, en route to developing testable hypotheses about precision treatment.

Completed:

Title: Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK TBI)
Role: Consortium PI (PI: Manley)
Time commitment: 0.5 cal months

Supporting Agency: National Institute of Health (NIH) Type: U01 NS086090
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Krista Roznovsky, UC San Francisco, 3333 California St, San Francisco, CA 94118
Performance period: 09/30/2013 – 08/31/2018
Level of funding: $12,415 DC current year
Project Goals/Specific Aims: The goal of this project is to test and refine data elements by conducting clinical studies on victims of traumatic brain injury.

Title: PTSD-TBI Clinical Consortium (INTRuST)
Role: Director of Biostatistics (PI: Stein)
Time commitment: 3.0 cal months
Supporting Agency: Department of Defense (DoD); Type: W81XWH08-2-0159
Performance period: 09/15/2008 – 10/14/2016
Level of funding: $1,829,370 DC
Project Goals/Specific Aims: The major goal of this 10-Site Clinical Consortium was to conduct clinical research that will advance therapeutics in posttraumatic stress disorder (PTSD) and traumatic brain injury (TBI).

Title: A GEWIS Study of Smoking, Hazardous Drinking, and Other Health Risk Behaviors
Role: MPI (Kaufman/Stein MPI)
Time commitment: 0.9 cal months
Supporting Agency: NIH/NIAAA Type: R21 AA024404
Performance period: 04/01/2015 – 03/31/2017
Level of funding: ~$25,000 DC current year
Project Goals/Specific Aims: The major goal of this award is to conduct genome-wide gene-environment interaction analyses in a large, population-based extant dataset on risks for smoking, hazardous drinking and other health risk behaviors.

Title: Latent Constructs: Negative-Positive Valence Domains in Anxiety and Depression
Role: Co-Investigator (PI: Martin P. Paulus)
Time commitment: 0.9 cal months
Supporting Agency: National Institute of Mental Health (NIH); Type: R01 MH101453
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Joel Sherrill, PhD; 6001 Executive Boulevard, Room 7145, MSC 9633, Bethesda, MD 20892-9633
Performance period: 09/09/2013 – 05/31/2017
Level of funding: $373,768 DC current year
Project Goals/Specific Aims: The major goal of this award is to develop constructs that connect across units of analysis to gain a deeper understanding of psychiatric conditions.

What other organizations were involved as partners?

One Mind

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 to support conversion of the TBI CDEs to CDISC standards.

Clinical Data Interchange Standards Consortium (CDISC)

Located in Austin, TX, CDISC is 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.

Rancho Biosciences

Rancho Biosciences is a data curation company located in San Diego, CA. Through a donation from a private partner, the TED Initiative has contracted with Rancho Biosciences to design and build a custom an imaging annotation and management tool designed to streamline the process of reading, annotating, and cataloging Metadataset images.

Appendix 1

TBI Endpoints Development Initiative

A collaborative for advancing diagnosis and treatment of TBI

Principal Investigators

Ramon Diaz-Arrastia, MD, PhD
University of Pennsylvania

Sureyya Dikmen, PhD
University of Washington

Joseph Giacino, PhD
Spaulding Rehabilitation Hospital
Harvard Medical School

Harvey Levin, MD
Baylor College of Medicine

Geoffrey Manley, MD, PhD
University of California
San Francisco

Michael McCrea, PhD
Medical College of Wisconsin

Murray Stein, MD, MPH
University of California
San Diego

Nancy Temkin, PhD
University of Washington

Stephen Wisniewski, PhD
University of Pittsburgh

Date: July 26, 2018

Subject: **MDDT QUALIFICATION PACKAGE**

MDDT Type: **BIOMARKER TEST**

MDDT Tracking Record Number: **MDDT027**

Submission Type: **Q-SUBMISSION: INFORMATIONAL MEETING REQUEST**

A supplement to Q-SUBMISSION Number: **Q161252**

Division: **DIVISION OF RADIOLOGICAL HEALTH**

Branch: **MAGNETIC RESONANCE AND ELECTRONIC PRODUCTS BRANCH**

Lead reviewer: **Daniel Krainak, Ph.D.**

MDDT Name: **OsiriX CDE Software Module**

Context of Use: This MDDT applies to the COU in which patients aged 18-65 years with acute nonpenetrating head trauma and GCS 13-15 have undergone acute head CT (e.g., as part of standard clinical care according to ACEP/CDC criteria) at a U.S. Level 1 trauma center and who participate in a TBI clinical trial

Complete submitter contact information:

Geoff Manley, MD PhD
Contact PI, TBI Endpoints Development (TED) Initiative
Chief of Neurosurgery, San Francisco General Hospital
Professor and Vice-Chairman, Department of Neurological Surgery,
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415-203-5815

Esther Yuh, MD, PhD
Co-PI TBI TED Initiative and TRACK-TBI Study
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TABLE OF CONTENTS

1. DESCRIPTION OF THE MDDT

Overall executive summary. In this qualification package, we validated the prognostic significance of an MRI biomarker, brain contusion, for 3-month outcome after mild traumatic brain injury. The impact of this is significant. An estimated 2.8 million patients in the U.S. alone are treated in emergency departments annually for mild TBI, and no prognostic imaging biomarker has been validated to identify patients at risk for persistent impairment. Physicians and other medical professionals, other than those engaged in TBI research, are generally unaware of the prognostic significance of imaging findings in mild TBI, including findings on both CT and MRI. This study shows that a specific imaging biomarker can be reliably measured and can identify at- risk patients, an important step in finding ways to treat mild TBI and reduce its social and economic costs. In our study, brain contusion on MRI was prognostic not only for 3-month GOS-E, the primary outcome measure, but remained prognostic out to 6 months, and was also prognostic at 2 weeks. These results were based on a carefully collected and curated data set from 10 U.S. Level 1 trauma centers.

We studied a second biomarker, diffuse axonal injury (DAI) on MRI. Like contusion, DAI was prognostic for 2-week outcome, but was no longer prognostic at 3 or 6 months. This suggests a possible differential recovery rate for these two different pathologies, and supports that identification of specific pathoanatomic lesions is important to understanding prognosis after mild TBI and attempting to find effective treatments for it.

Background. Two structural MRI features had been identified as promising biomarkers for poorer 3-month outcomes in traumatic brain injury (TBI), based on data from the TRACK-TBI pilot study. These candidate biomarkers were brain contusions and ≥4 foci of hemorrhagic axonal injury, as evaluated by a physician on a brain MRI exam performed approximately 2 weeks after injury.[1]

Based on these results from the TRACK-TBI pilot study, we aimed to validate the utility of these imaging biomarkers for clinical trials of therapies for mild TBI. By allowing medical product developers to enroll patients at greater risk for poor outcome, in which to study therapeutic effectiveness of their products, product developers would have a greater chance of demonstrating a statistically significant improvement in outcome in a study population of a given size. This would be highly beneficial for TBI clinical trials, whose 100% failure rate[2-6] has been attributed to heterogeneous pathology not accounted for by grading CT scans as "positive" or "negative."[5]

This MDDT consists of a software module that facilitates identification and measurement of the number of brain contusions, in conjunction with validation of the prognostic utility of this biomarker for the purpose of identifying patients at higher risk for poor outcome for participation in clinical trials of therapies for mild TBI.

a. Measurements provided

The OsiriX CDE software module allows for collection of information on the biomarkers in a reliable and reproducible manner. The software assists expert raters, e.g., neuroradiologists, by providing a standardized way to demarcate and classify pathoanatomic lesions using CDE criteria, and to label the abnormalities on the appropriate MR images.[‡] The clear labeling results in documentation of each biomarker, and enables later review and verification of biomarker lesions. The tool also ensures use of standardized CDE terms and definitions and thereby promotes more standardized assessment of the biomarker lesions.

[‡]T2*-weighted gradient echo (T2* GRE) or susceptibility-weighted imaging (SWI), T2-weighted spin-echo (T2), T2-weighted Fluid Attenuated Inversion Recovery (FLAIR) and 3D T1-weighted gradient echo (3D T1)

b. Describe tool principle and method of measurement

A TBI Imaging Common Data Elements (CDE)[7-9] plug-in module for OsiriX (64-bit version, Pixmeo, Geneva, Switzerland), software was developed. It assists expert raters, e.g., neuroradiologists, by providing a standardized way to demarcate and classify pathoanatomic lesions using CDE criteria and to label abnormalities on MR images[‡] in order to enhance and standardize clinical assessment of contusions and hemorrhagic axonal injury on MRI. The clear labeling aids in reduced subjectivity of interpretation of the prognostic pathoanatomic biomarker lesions.

OsiriX has an architecture that allows users to expand its capabilities through custom plug-in software modules. The TBI Imaging CDE plug-in facilitates the standardized demarcation and recording of the TBI CDE biomarkers on brain imaging exams, allowing the reader to assign a CDE descriptive item to each pathoanatomic abnormality that he or she delineates directly on the images. The reader uses the plug-in module to specify a region of interest (ROI) using an arrow, or an oval or polygon enclosing the abnormality, on at least one image that demonstrates the abnormality. Each ROI has a corresponding pop-up dialog box in which the reader then enters the CDE for the lesion. After completing evaluation of a brain imaging exam, the reader saves the CDE/ROI information as a file. Each reader's CDE/ROI files can be stored for later review and/or imported into a database.

By unifying the descriptive and imaging data, the plug-in module ensures alignment of each CDE textual entry with the correct corresponding lesion as designated directly on the images. This is not possible using conventional textual forms, whether paper or electronic, as these usually require readers to record the names of each CDE lesion but do not allow a convenient or intuitive way to document the specific location of each lesion. The plug-in module allows a quick method for the reader to record a lesion's location, and allows verification that CDE items entered by different readers that *apparently* refer to the same pathoanatomic finding actually refer to the same abnormality on the images. This approach is particularly important when two or more lesions are in close proximity to one another, and their locations are not differentiated by the CDE textual descriptors alone. On conventional paper or electronic forms, recording

of image slice numbers on which lesions are located is cumbersome and error-prone, and may not allow later distinction between two or more lesions located in the same region, or lesions that span multiple images.

2. CONTEXT OF USE, INCLUDING THE DISEASE AND/OR DEVICE AREA FOR APPLICATION OF MDDT

This MDDT applies to the COU in which patients aged 18-65 years with acute nonpenetrating head trauma and GCS 13-15 have undergone acute head CT (e.g., as part of standard clinical care according to ACEP/CDC criteria)[10] at a U.S. Level 1 trauma center and participate in a TBI clinical trial.

3. EVIDENCE GATHERED TO SUPPORT QUALIFICATION

Study Design Overview. **Part 1**. For 517 patients, we analyzed 3-month GOS-E in relation to the following MRI CDEs: 1) presence vs. absence of ≥1 brain contusion, and 2) ≥4 foci of axonal injury. The MRI CDEs were determined independently by each of 3 board-certified neuroradiologists. The individual prognostic performance of each neuroradiologist was determined. **Part 2**. Since the FDA qualification process requires proof that a biomarker can be measured reliably, we determined the interrater reliability for evaluation of these same two MRI CDEs across the 3 neuroradiologists.

Both the interrater reliability study (Part 2) and prognostic validity study (Part 1) were performed on data that were completely distinct from the TRACK-TBI pilot data[1, 11] used to identify the two candidate MRI CDE prognostic biomarkers.

Part 1. Validation of the MRI CDE, brain contusion, as prognostic biomarker in mild TBI.

Approach. For 517 patients at 10 Level 1 trauma centers participating in the TRACK-TBI study within the TED Metadataset, we analyzed 3-month GOS-E in relation to the following MRI CDEs: 1) presence vs. absence of ≥1 brain contusion, and 2) ≥4 foci of axonal injury. These MRI CDEs were determined independently by each of 3 board-certified neuroradiologists and annotated using the OsiriX TBI Imaging CDE software module. The individual prognostic performance of each of the 3 neuroradiologist readers was then determined.

Outcome measure. 3-month GOS-E, a widely-used, FDA-approved clinical outcome assessment (COA) for global functional outcome after mild to moderate TBI.[12-14]

Study population. The TRACK-TBI study is a prospective longitudinal observational study of TBI patients who presented to the ED at one of 11 Level 1 U.S. Level 1 trauma centers (Ben Taub General Hospital in Houston, TX; Massachusetts General Hospital in Boston, MA; Zuckerberg San Francisco General Hospital in San Francisco, CA; University of Cincinnati Medical Center in Cincinnati, OH; R Adams Cowley Shock Trauma Center in Baltimore, MD; Ryder Trauma Center in Miami, FL; University of

Pittsburgh Medical Center in Pittsburgh, PA; Seton Medical Center in Austin, TX; Parkland Memorial Hospital in Dallas, TX; Harborview Medical Center in Seattle, WA; and Virginia Commonwealth University Medical Center in Richmond, VA).

Inclusion criterion for the TRACK-TBI study was acute non-penetrating head trauma that prompted an ED physician to order a clinical head computed tomography (CT) scan within 24 hours of injury.

Exclusion criteria for the TRACK-TBI study included pregnancy, incarceration, nonsurvivable physical trauma, debilitating mental health disorders or neurological disease, MRI contraindications (e.g., cardiac pacemakers, aneurysm clips, insulin pumps), and pre-existing medical conditions that could interfere with outcomes assessments.

Patient recruitment process for TRACK-TBI study. For the TRACK-TBI study, research coordinators scanned the electronic records system and radiology PACS system for patients with head computed tomography performed from the Emergency Department, as these were the main inclusion criteria for the study. Once potential TBI patients were identified, coordinators approached them in the Emergency Department, hospital wards, or ICU, and explained the study to prospective participants or their legally authorized medical decisionmakers. Eligibility was assessed based on the stated inclusion/exclusion criteria, and hospital medical personnel were also involved in that decision when necessary. The Galveston Orientation and Amnesia Test (GOAT) was administered to determine ability for self-consent. For those without a passing score, the patient's legally authorized representative gave initial consent, and competency screening was repeated at all followup visits.

Three-month GOS-E. The 3-month GOS-E was obtained from the patient, or if the patient were cognitively unable, the caregiver. Evaluators of the 3-month GOS-E were not blinded to the patient's clinical data.

Study population for this MDDT application (subset of TRACK –TBI study population). As this MDDT application focuses on the COU of adult mild TBI patients, while the TRACK study included both adult and pediatric TBI patients with all injury severity levels, the study population for the MDDT includes a *subset* of enrolled TRACK-TBI patients. Specifically, the MDDT study population consisted of *all 517 adult TBI patients aged 18-65 years enrolled at 10 of 11 TRACK-TBI sites between 2/26/2014 and 5/4/2016 with GCS ED arrival scores of 13-15, initial head CT performed upon ED admission, and completion of both 2-week MRI exam and 3-month GOS-E score*.

Protocol violations. Participants from one of the 11 original TRACK-TBI study sites (R Adams Cowley Shock Trauma Center in Baltimore, MD) were excluded from the MDDT study population, and are generally being omitted from other TRACK-TBI publications that require analysis of outcome data, because of concerns that the GOSE was not administered according to standard study protocols at that single study site.

Patients screened and consented for participation, who did not complete study and were not evaluated for the proposed MRI biomarkers. Patients who were initially enrolled in TRACK-TBI but did not ultimately complete the planned 2-week MRI were not included in the 517 patients who were analyzed for this MDDT application. However, their

available demographic and clinical data are included in the enclosed .csv file, **Appendix5_CSVfile_Demographics_BiomarkerEvals_3moGOSE.csv.**

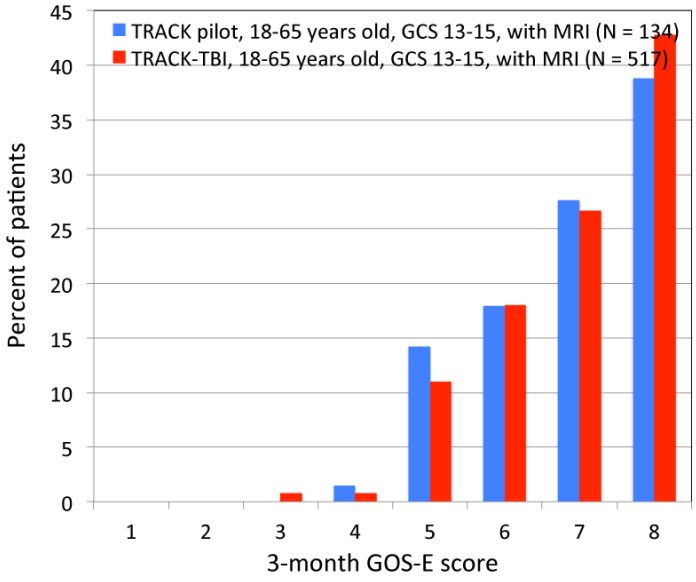

Figure 1. 3-month GOS-E scores for the current MDDT study population (TRACK-TBI patients aged 18-65 years with GCS scores of 13-15 upon ED arrival, red bars, N = 517) and TRACK-TBI pilot (blue, N = 134) studies. Two-sided Wilcoxon rank sum test showed no statistically significant difference in these distributions (p = 0.35).

Distribution of 3-month GOS-E scores: Comparison to distribution expected for proposed context of use (COU). The intended COU for this MDDT proposal consists of patients aged 18-65 years with acute nonpenetrating head trauma and GCS scores of 13-15 upon ED arrival who have undergone acute head CT (e.g., as part of standard clinical care according to ACEP/CDC criteria)[10] at a U.S. Level 1 trauma center, and who participate in a TBI clinical trial. This differs from patient populations in many prior large studies of mild TBI, which were retrospective and included many patients who did not warrant assessment at a Level 1 trauma center, received less intensive care in other medical settings, or did not consent to or failed to complete participation (including outpatient brain MRI and medium- or long-term outcome assessment) in a clinical trial.

The prior study of mild TBI that most closely matches the inclusion and exclusion criteria for this MDDT proposal is the TRACK-TBI pilot study, which required patients to complete both a 2-week brain MRI and 3-month outcome assessment.[11] **Figure 1** shows the distributions of 3-month GOS-E scores for the current MDDT study population (red bars, N = 517) and for the TRACK-TBI pilot study (blue bars, N = 134). The two-sided Wilcoxon rank sum test demonstrated *no statistically significant difference (p = 0.35) between 3-month GOS-E scores for the MDDT study population and for the TRACK pilot study.*

In contrast, *there was a statistically significant difference (p = 0.00011) in the 3-month GOS-E scores for the current MDDT study population and for those patients who would have been included in MDDT, but failed to complete 2-week brain MRI*. **Figure 2** shows the distributions of 3-month GOS-E scores for the current MDDT study population (red bars, N = 517) and for TRACK-TBI patients who failed to complete 2-week MRI but otherwise satisfied inclusion criteria for the current MDDT application (green bars, N = 198).

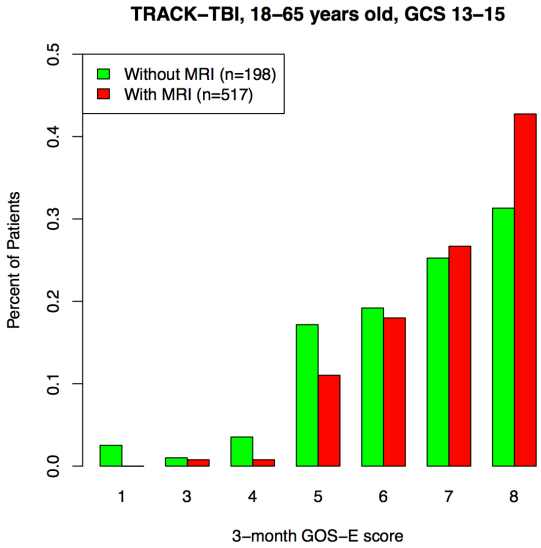

Figure 2. 3-month GOS-E scores for TRACK patients aged 18-65 years with GCS scores of 13-15 upon ED arrival who completed (red bars, N = 517) or failed (green bars, N = 198) to complete 2-week MRI. Two-sided Wilcoxon rank sum test showed a statistically significant difference in these distributions (p = 0.00011).

Appendix5_CSVfile_Demographics_BiomarkerEvals_3moGOSE.csv provides patient characteristics such as demographics, indications for radiologic test, (injury cause), and relevant medical history, for the MDDT study population (N = 517), as well as for patients who were enrolled but did not complete the MRI or 3-month GOS-E.

How the two potential MDDT biomarkers, and their cutoff values, were selected from the list of all candidate CDEs. In the TRACK-TBI pilot study,[11] we analyzed 135 mild TBI patients evaluated at 3 Level 1 trauma centers who underwent both day-of-injury head CT and early brain MRI at 12±3.9 days after injury.[1] Univariable and multivariable logistic regression were used to assess for demographic, clinical, socioeconomic, and TBI imaging Common Data Elements[15] that were predictive of 3-month global functional outcome as measured by the Extended Glasgow Outcome Scale (GOS-E). (The Imaging CDEs and their definitions are included in **Appendix 1**.) Twenty-seven percent of mild TBI patients with normal admission head CT had at least one CDE abnormality on early brain MRI. One or more brain contusions on MRI, and ≥4 foci of hemorrhagic axonal injury on MRI, were each independently associated with poorer 3-month outcome, with multivariable odds ratios of 4.5 (p = 0.01) and 3.2 (p = 0.03), respectively, even after adjusting for head CT findings and demographic, clinical, and socioeconomic factors. Although subdural and, less commonly, subarachnoid hemorrhage were also observed on early brain MRI, these were generally tiny collections that nearly always co-existed with brain contusion. Such extraaxial collections are known to resolve or redistribute such that they are no longer apparent several hours to tens of days after TBI, and their desirability as prognostic MRI biomarkers is limited because their presence on MRI is highly sensitive to the timing of the MRI exam after TBI. The utility of these as prognostic biomarkers is limited by undesirable variability based on the timing of the MRI scan, and would restrict the context of use (COU) of a MRI biomarker panel to a narrow time window following TBI.

MDDT biomarker cutoff of 1 or more brain contusions. This was chosen due to the practical difficulty of enumerating contusions when they are contiguous or nearly contiguous. In many cases, hemorrhagic contusions extend across several gyri. Exact

criteria for confluence or non-confluence would be necessary to consistently enumerate these lesions. As the TBI Imaging CDEs currently lack such criteria, enumeration of contusions would have an undesirable arbitrary component.

MDDT biomarker cutoff for number of foci of hemorrhagic shear injury. This was selected based on the TBI Imaging CDE definitions of "traumatic axonal injury (TAI)" and "diffuse axonal injury (DAI)." In the regression analyses, the TBI Imaging CDEs of TAI (1 to 3 foci) and DAI (≥4 foci) were considered as regressors. Only DAI was a statistically significant predictor of 3-month GOS-E after demographic, clinical, socioeconomic and CT findings were taken into account.

Patient sample size. Following FDA feedback on our Prequalification Package (**Appendix 2**), we had planned a sample size of 350 subjects based on a projected MRI biomarker positive rate of approximately 20%.

However, the MRI biomarker positive rates on these 350 MRI exams were 15% for contusion and 12% for diffuse axonal injury (DAI). Each of these rates is lower than the projected rates of 20% for each biomarker in our pre-qualification package. For a biomarker positive rate of 12% and our original proposed sample size of 350, the standard error for the Wilcoxon U statistic is 0.050, which would not be acceptable to FDA for providing proof that the biomarker performance is statistically different from random. We therefore increased our sample size from 350 to 517 subjects. By increasing the sample size to 517 patients, the standard error drops to 0.0408, which is again within the acceptable range. This upwardly revised patient sample size was discussed with and approved by the FDA on 6/14/2018 (**Appendix 3**).

MRI interpretation by 3 expert readers. Three neuroradiologists certified by the American Board of Radiology (ABR) with Certificate of Added Qualification (CAQ) for Neuroradiology served as readers for this study, independently reviewing the brain MRI exam for each subject.

Prior to interpretation of the MRI exams for this study, each ABR/CAQ-certified neuroradiologist reader reviewed the TBI imaging CDE definitions (most recent version, 2012).[15] Most of these CDE definitions are either identical or very similar to radiological terms that are taught in U.S. ACGME radiology residency programs and are therefore widely used in U.S. standard-of-care radiology reports.

Each reader used the OsiriX tool to assess 25 MRI training cases that illustrate the TBI Imaging CDEs based on their definitions. For each MRI exam, each reader was asked to draw a region of interest (ROI) that delineates each abnormality on at least one axial slice that demonstrates the abnormality. Each ROI has a corresponding pop-up dialog box in which the reader enters CDE information for the lesion. Readers discussed responses on discordant cases in the context of the CDE definitions, and mutually resolved any differences. The purpose of the training set was to promote consistent application of the CDE terms by all 3 readers on the validation MRI set, for which they would receive no feedback until completion of the entire set.

Once training was completed, each neuroradiologist reader evaluated the validation set of MRI exams. There was no feedback given to individual readers regarding the agreement of their interpretations relative to other readers. Individual readers had no

access to 3-month GOS-E scores until they had completed and submitted interpretation of all MRI exams in the validation set.

Description of how the imaging data were collected (make/models of imaging devices, imaging protocols). These are included in **Appendix 4**.

Study success criteria. In the initial prequalification package submission, we proposed that a TBI imaging CDE biomarker would be considered to have prognostic validity if there were a significant difference in the 3-month GOS-E between patients with and without the biomarker, using a 2-sided Wilcoxon rank sum test and a 2-sided significance level of 0.05. Following FDA feedback, we modified study success to be determined after the FDA's review of the prognostic performances of each individual reader.

Results. This study confirmed the MRI CDE, brain contusion, as measured on structural MRI scans by neuroradiologists, as a statistically significant biomarker of poorer global functional outcome as measured by the 3-month GOS-E. One or more brain contusions on 2-week MRI was associated with poorer 3-month GOS-E for Neuroradiologist 1 ($p = 0.010$), Neuroradiologist 2 ($p = 0.042$), and Neuroradiologist 3 ($p = 0.017$). **Figure 3** shows the distributions of 3-month GOS-E scores in patients with and without contusion on 2-week MRI.

The validation study did not confirm the MRI CDE, diffuse axonal injury, as measured on structural MRI scans by neuroradiologists, as a statistically significant biomarker of poorer global functional outcome as measured by the 3-month GOS-E. DAI on 2-week MRI had no significant association with poorer 3-month GOS-E for Neuroradiologist 1 ($p = 0.64$), Neuroradiologist 2 ($p = 0.94$), and Neuroradiologist 3 ($p = 1.0$). **Figure 4** shows the distributions of 3-month GOS-E scores in patients with and without DAI on 2-week MRI.

Appendix5_CSVfile_Demographics_BiomarkerEvals_3moGOSE.csv summarizes 3-month GOS-E scores in a) the subset of patients who were biomarker negative, b) the subset of patients who were biomarker positive, and c) TRACK-TBI patients who did not undergo MRI or complete the 3-month GOS-E but would have otherwise satisfied criteria for inclusion in this MDDT application. This file contains all raw data including Patient Number, Reader ID, biomarker ratings, age, gender, race, ethnicity, Injury cause, Prior TBI history, Prior psychiatric history, and 3-month GOS-E scores.

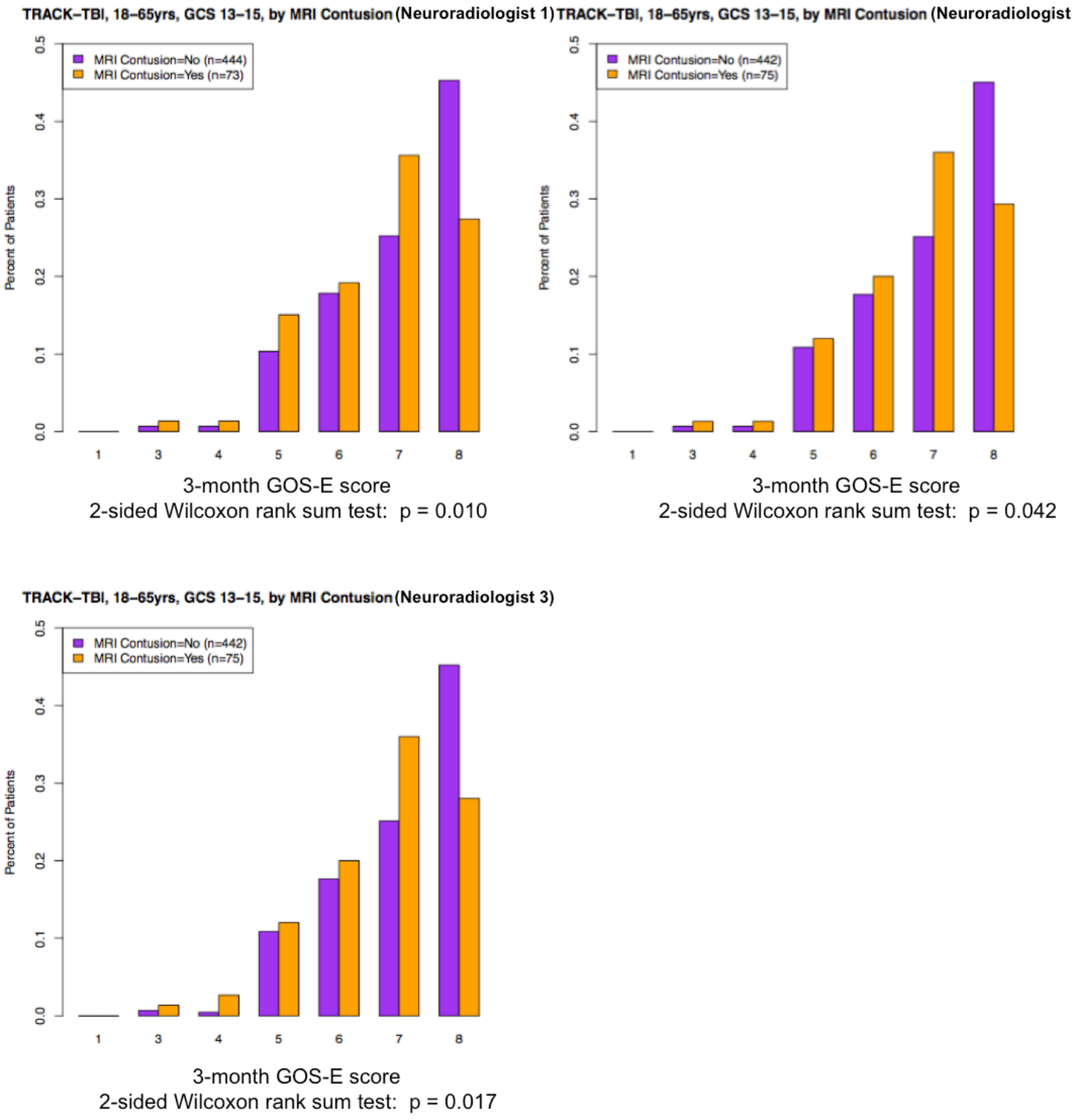

Figure 3. 3-month GOS-E scores for TRACK-TBI patients with (orange bars) or without (purple bars) MRI evidence for brain contusion on 2-week MRI. Top, middle, and bottom graphs show results based on Neuroradiologist 1's, Neuroradiologist 2's, and Neuroradiologist 3's independent interpretations. Two-sided Wilcoxon rank sum test showed a statistically significant difference in the GOS-E distributions for patients without and with contusions, for each of the 3 neuroradiologists ($p = 0.010$, $p = 0.042$, and $p = 0.017$).

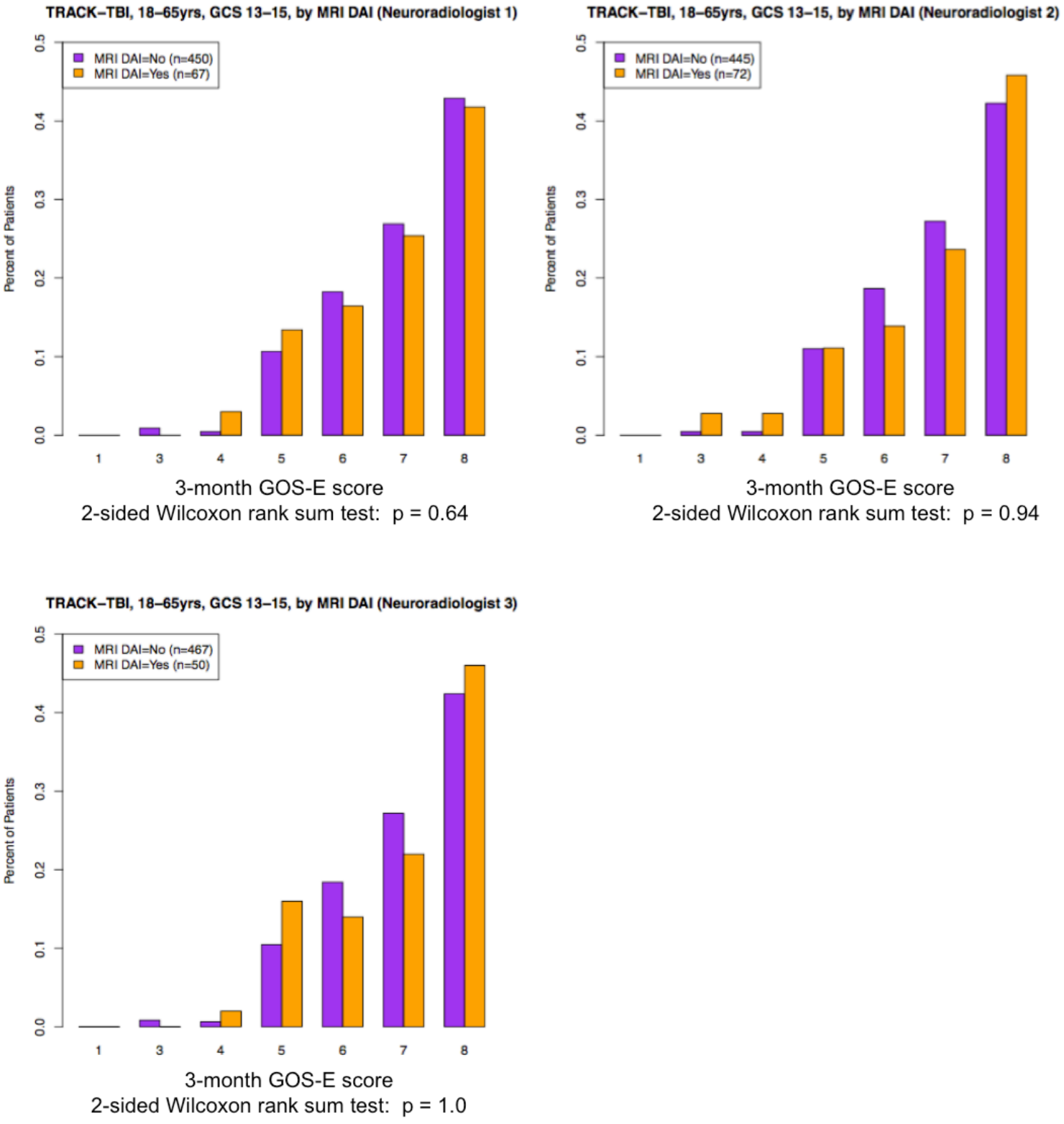

Figure 4. 3-month GOS-E scores for TRACK-TBI patients with (orange bars) or without (purple bars) MRI evidence for diffuse axonal injury (DAI) on 2-week MRI. Top, middle, and bottom graphs show results based on Neuroradiologist 1's, Neuroradiologist 2's, and Neuroradiologist 3's independent interpretations. Two-sided Wilcoxon rank sum test showed no statistically significant difference in the GOS-E distributions for patients without and with DAI, for any of the 3 neuroradiologists (p = 0.64, p = 0.94, and p = 1.0).

Part 2. Determination of interrater reliability (IRR) for evaluation of the specific MRI CDEs, brain contusion and diffuse axonal injury, with aid of the OsiriX TBI Imaging CDE software module

Approach. We determined the *percent agreement (PA)*, *positive percent agreement (PPA)*, and *negative percent agreement (NPA)* for each pair of readers and each of the MRI CDEs, brain contusion and diffuse axonal injury. We also calculated averages of the pairwise measures over the 3 readers. We calculated 95% confidence intervals for each measure using a bootstrap procedure (1000 resampled sets, each with 517 randomly selected data points from the original list of 517 data points, performed separately for each pairwise PA, PPA and NPA).

Study population, exclusion criteria, inclusion criteria, patient sample size. For Part 2, we used the same 517 patients as for Part 1.

MRI interpretation by 3 expert readers. Identical to Part 1.

Outcome measure. Not applicable for Part 2.

Study success criteria and justification of sample size for interrater reliability. In the prequalification package, we estimated 300 patients as an adequate sample size for Part 2, based on the following. We proposed to consider IRR to be adequate if the average percent agreement (PA) and the average negative percent agreement (NPA) each exceeded 80% and the average positive percent agreement (PPA) exceeded 55%. During training, PAs exceeded 86%, NPAs exceeded 91%, and PPAs exceeded 65%. Using equations in Uebersaxe (www.john-uebersax.com/stat/raw.htm, Equations 3.4 and 3.5), there is 95% confidence that, for 2 raters and 300 scans, the observed PPA will be above 55% if the true PPA exceeds 65%, as was observed in the training data. This number also ensures that, with 95% confidence, the PA and NPA would be above 80%.

Although the FDA approved the above estimate of 300 patients in our prequalification package, we ultimately performed the IRR calculations on 517 exams. This was because statistical considerations for Part 1 ultimately led to each of the 3 readers being required to interpret all 517 MRI exams.

Results. **Tables 1 and 2** summarize PA, PPA, and NPA for each pair of readers for each MRI CDE, and the averages of each of these pairwise measures over the 3 readers, along with 95% confidence intervals for each reader using bootstrap resampling (1000 resampled sets, each with 517 randomly selected data points from the original list of 517 data points, performed separately for each pairwise PA, PPA and NPA in **Tables 1D and 2D**).

Table 1A. Contusion – Neuroradiologist 1 vs. Neuroradiologist 2				
		Neuroradiologist 2		
		Yes	No	**Totals**
Neuroradiologist 1	Yes	65	8	73
	No	10	434	444
Totals		75	442	**517**

Table 1B. Contusion – Neuroradiologist 2 vs. Neuroradiologist 3				
		Neuroradiologist 3		
		Yes	No	**Totals**
Neuroradiologist 2	Yes	65	10	75
	No	10	432	442
Totals		75	442	**517**

Table 1C. Contusion – Neuroradiologist 1 vs. Neuroradiologist 3				
		Neuroradiologist 3		
		Yes	No	**Totals**
Neuroradiologist 1	Yes	66	7	73
	No	9	435	444
Totals		75	442	**517**

Table 1D. Contusion on brain MRI – Summary				
	Neuroradiologist 1 vs. Neuroradiologist 2	**Neuroradiologist 2 vs. Neuroradiologist 3**	**Neuroradiologist 1 vs. Neuroradiologist 3**	**Average pairwise**
PPA [95% CI]*	87.9 [82.5-93.2%]	86.7% [80.8-91.8%]	89.2% [84.0-94.2%]	87.9%
NPA [95% CI]**	98.0% [97.1-98.9%]	97.7% [96.7-98.6%]	98.2% [97.3-99.0%]	98.0%
PA [95% CI]***	96.5% [95.0-98.1%]	96.1% [94.4-97.7%]	96.9% [95.4-98.3%]	96.5%

* In this row, PPA for *each* reader pair was calculated from Tables 1A-1C as: $\frac{a/(a+b) + a/(a+c)}{2}$

** In this row, NPA for *each* reader pair was calculated from Tables 1A-1C as: $\frac{d/(b+d) + d/(c+d)}{2}$

*** In this row, PA for *each* pair of readers was calculated from Tables 1A-1C as: $\frac{a+d}{a+b+c+d}$

where a, b, c and d are defined here:

		Reader 2	
		Yes	No
Reader 1	Yes	a	b
	No	c	d

Table 2A. DAI – Neuroradiologist 1 vs. Neuroradiologist 2				
		Neuroradiologist 2		
		Yes	No	**Totals**
Neuroradiologist 1	Yes	57	10	67
	No	15	435	450
Totals		72	445	**517**

Table 2B. DAI – Neuroradiologist 2 vs. Neuroradiologist 3				
		Neuroradiologist 3		
		Yes	No	**Totals**
Neuroradiologist 2	Yes	44	28	72
	No	6	439	445
Totals		50	467	**517**

Table 2C. DAI – Neuroradiologist 1 vs. Neuroradiologist 3				
		Neuroradiologist 3		
		Yes	No	**Totals**
Neuroradiologist 1	Yes	44	23	67
	No	6	444	450
Totals		50	467	**517**

Table 2D. DAI on brain MRI – Summary				
	Neuroradiologist 1 vs. Neuroradiologist 2	**Neuroradiologist 2 vs. Neuroradiologist 3**	**Neuroradiologist 1 vs. Neuroradiologist 3**	**Average pairwise**
PPA [95% CI]*	82.1% [74.7-88.2%]	74.6% [66.0-81.8%]	76.8% [68.5-84.0%]	77.8%
NPA [95% CI]**	97.2% [96.1-98.2%]	96.3% [95.1-97.5%]	96.9% [95.8-98.0%]	96.8%
PA [95% CI]***	95.2% [93.2-96.9%]	93.4% [91.3-95.6%]	94.4% [92.5-96.3%]	94.3%

* In this row, PPA for *each* reader pair was calculated from Tables 2A-1C as: $\frac{a/(a+b) + a/(a+c)}{2}$

** In this row, NPA for *each* reader pair was calculated from Tables 2A-1C as: $\frac{d/(b+d) + d/(c+d)}{2}$

*** In this row, PA for *each* pair of readers was calculated from Tables 2A-1C as: $\frac{a+d}{a+b+c+d}$

where a, b, c and d are defined here:

		Reader 2	
		Yes	No
Reader 1	Yes	a	b
	No	c	d

4. STRENGTH OF EVIDENCE

a. Tool Validity

Results from our interrater reliability studies support the validity of the TBI imaging CDEs. We found average PPA, NPA and PA of 87.9%, 97.9% and 96.5% for brain contusion and 77.8%, 96.8% and 94.3% for diffuse axonal injury (average of pairwise values for all neuroradiologist pairs). One or more brain contusions on MRI was associated with poorer 3-month GOS-E for three independent U.S. board-certified neuroradiologists: Reader 1 ($p = 0.010$), Reader 2 ($p = 0.042$) and Reader 3 ($p = 0.017$).

b. Plausibility

It is scientifically plausible that mild TBI patients with evidence of traumatic intracranial injury on structural neuroimaging studies, particularly those with brain parenchymal injury such as contusion, have poorer outcomes than those with normal imaging exams.

c. Extent of Prediction

We analyzed 517 mild TBI patients evaluated at 10 Level 1 trauma centers who underwent both day-of-injury head CT and early brain MRI at 2 weeks postinjury. One or more brain contusions on MRI was associated with poorer 3-month GOS-E for three independent U.S. board-certified neuroradiologists: Reader 1 ($p = 0.010$), Reader 2 ($p = 0.042$) and Reader 3 ($p = 0.017$). This MDDT applies to the COU in which patients aged 18-65 years with acute nonpenetrating head trauma and GCS 13-15 have undergone acute head CT (e.g., as part of standard clinical care according to ACEP/CDC criteria)[10] at a U.S. Level 1 trauma center and participate in a TBI clinical trial.

d. Capture

The MDDT proposed here will allow selection of patients with poorer 3-month outcome, as defined by the GOS-E, for enrollment in clinical trials. The GOS-E is the most widely used measure for global functional outcome after mild to moderate TBI.[12-14]

5. ASSESSMENT OF ADVANTAGES AND DISADVANTAGES

Advantages of Using the MDDT. The biomarkers are intended as a prognostic enrichment tool to select patients with mild TBI at high risk for poor outcomes at 3 months postinjury (as defined by the extend Glasgow Outcome Scale, or GOS-E[12-14]) for enrollment in clinical trials of therapeutic medical devices intended to improve outcomes for mild TBI patients.

Thus, advantages of such a tool would include **allowing for smaller clinical studies** and potentially **expediting the validation of therapeutic technologies for an important public health problem**.

A hypothetical example of how the proposed MDDT would be used in the regulatory evaluation of a medical device was discussed at a joint conference call between CDRH and TED on September 27, 2016, summarized as follows:

CureForPCS designs a clinical trial using the biomarker, brain MRI evidence for contusion, to enrich the study population with patients expected to have poorer

functional outcome at 3 months. Two hundred acute TBI patients are enrolled. Of these, 100 patients have brain contusions on 2-week brain MRI, and 100 patients have no such brain contusion. These 200 patients are randomized into two groups: the treatment group has 50 participants with one or more brain contusions, and 50 who do not. Similarly, the control group has 50 participants with one or more brain contusions, and 50 who do not. Approximately 64% of the control group would be expected to have a Glasgow Outcome Scale – Extended (GOS-E) of ≤7 at 3 months after injury – an average of 55% (characteristic for mild TBI patients without brain contusion, see ***Figure 3****) and 72% (characteristic for mild patients with brain contusion, see* ***Figure 3****). The treatment group gets CureForPCS and the control group does not. It is found that 49% of the CureForPCS group has a GOS-E of ≤7 at 3 months after injury, compared to 64% of the control group. In this trial with enriched patient groups, CureForPCS demonstrates a statistically significant and clinically relevant difference between the treatment and control group. The CureForPCS is approved for mild TBI patients who satisfied ACEP/CDC criteria for noncontrast head CT upon admission. Had the two treatment groups not been enriched for those with poorer prognosis, the different treatment response rate between groups may not have attained statistical significance.*

Improved clinical trials for effective treatments for TBI are needed because almost all such trials have failed up to now, in large part due to the lack of useful biomarkers for patient selection and treatment monitoring. No imaging biomarker has been formally qualified by the FDA for neurologic emergencies. Indeed, the FDA currently recognizes only "abnormal" and "normal" head CT for patient stratification in TBI clinical trials, despite the fact that an "abnormal" head CT spans a wide spectrum of pathological lesions, anatomic locations, and numbers and sizes of lesions.[5] Imaging biomarkers could be highly beneficial for TBI clinical trials, whose 100% failure rate[2-6] has been attributed to heterogeneous pathology not accounted for by grading CT scans as "positive" or "negative."[5]

Disadvantages of Using the MDDT. It is intuitive that enriching the enrollment of subjects in clinical trials for those with poorer prognosis would improve the likelihood of demonstrating a statistically significant benefit for a therapy and/or allow for smaller clinical trials to demonstrate a statistically significant benefit. However, this is an assumption. If not the case, this MDDT could add to the cost of clinical trials through the requirement of a brain MRI and through the additional patients who would need to be screened due to some potential participants being excluded due to MRI contraindications.

6. CONSENT TO PUBLIC DISCLOSURE AND USE

We consent to public disclosure and use of the proposed MDDT.

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Appendix 1: NIH/NINDS Pathoanatomic Terms for Definitions of TBI Lesions

https://commondataelements.ninds.nih.gov/tbi.aspx#tab=Data_Standards [15]

Appendix 1: Pathoanatomic Terms for Definitions of TBI Lesions and Associated Findings

Below are the terms suggested for a starting point in creating common data elements for specific pathoanatomic entities commonly encountered in patients with traumatic brain injuries. While most of these entities are defined based on radiologic findings, specifically (for these purposes) CT and MRI, they also could be encountered as surgical or at autopsy findings. Terms are listed centripetally, from the skull inward. In addition, categories for additional pathophysiologic processes which may occur acutely or in a delayed fashion are included. As mentioned above, it is assumed that all users of the database would enter acute patient data at least at the "core" level, and this includes all the types of information currently shown in numerous studies to provide prognostic value for acute injuries, including presence or absence of various mass lesions, subarachnoid or intraventricular hemorrhage, brain shift, cisternal compression, and brain edema or swelling [3,4].

It is fully acknowledged that different centers and individuals may define many of these lesions in different fashions. As technology advances, both techniques and concepts may be altered in the future. The list below is meant to be a working and evolving document which provides *practical operational definitions* for researchers who will enter patients into databases for purposes of natural history, intervention, outcome prediction, or radiology studies.

General format

1) The following is a list of pathoanatomic lesions; each patient may have multiple lesions entered into the database. For each pathoanatomic lesion, the following index includes the precise operational definition of the lesion for purposes of this database, including how the definition differs for each applicable imaging modality, and what relevant descriptors should be used to describe its location, distribution, quantification, adjacent or remote sequelae or associations, evolution over time, timing/dating features, and pathophysiology. The intention is to format these elements in an ***interactive drop-down menu*** so that the investigator can choose and expand only those entities relevant to that patient and the particular requirements of the specific study question. For patients who have multiple lesions of a single type (for instance, multiple contusions), the interactive database will allow for repeating a specific entity type's "page" so that more than one of the same type of entity can be described and entered.

2) If an entity is NOT present, that item simply can be skipped for most studies. In other studies the organizers may request that the entity specifically be noted as "absent" in the data set. For this reason, the "absent" checkbox is listed in parentheses throughout the index.

3) For each descriptive pathoanatomic term, the specific imaging modality and/or sequence needed to optimally define the presence of the term is outlined. If the finding is seen on a different modality from the most definitive technique, additional adjectives are provided in order to connote a probability, but not a certainty, of the entity.

4) Data can be entered by levels, of complexity and detail. The "Core" tier includes descriptors as to the presence, indeterminateness, or absence of a particular lesion. "Supplementary" and "Emerging" headings include more detail about the location, extent, and other characteristics of the lesion, and some may require specific radiologic equipment or protocols. It is expected that all entries will include at least the Basic data. Additional levels of detail will depend on the particular study and level of participation of the investigator. It is also expected that this category will evolve rapidly to include newer techniques (perfusion scans, diffusion tensor imaging, functional MRI, spectroscopy, and others) which have not been addressed in this initial data set.

5) Data can be entered *for each image* obtained on the patient, or for images obtained at specific time intervals, depending on the design of the particular study. It is expected that most patients will have more than one radiologic study, and therefore, the first entry in each new imaging data set will describe the date, time, and type of radiologic study obtained. It is expected that specific radiologic protocols may be required for specific study designs, and that additional details about radiologic imaging parameters may be entered separately depending on the specific study design.

Finally, it should be noted that Appendix1 will contain links to additional resources and references to assist the user in finding more information about specific entities or normative data. The locations of the links are noted in the text and the links will be activated as the database is further developed and implemented.

Date/time of study __/__/____ ____:____ (start time)

Imaging Modality

Core: (check all that apply)

CT
- Non-contrast CT
- Contrast CT
- CT Angiography

MRI
- MRI 1.5T
- MRA 1.5T
- MRI 3.0T
- MRA 3.0T

Supplementary:

CT __(Drop-down menu: Manufacturer; Model; Software version)

MRI____(Drop-down menu: Manufacturer; Model; Software version)

Sequence name – check all that apply
- T1
- T2
- FLAIR
- DWI
- GRE
- SWI
- DTI
- Other

Were imaging parameters within CDE Appendix 2 protocol parameters?

Yes No

Emerging:

Additional imaging techniques and technical information: (free text)

Appendix 1: Pathoanatomic Terms for Definitions of TBI Lesions and Associated Findings

Pathoanatomic Lesion Types

For each lesion, define and describe as noted; if there is more than one of the same type of lesion, describe each separately.

Skull Fracture

Definition**:** A break in the normal integrity of the skull, which may be partial or full thickness, caused by presumed mechanical force.

Core:
- Present
- Indeterminate
- (Absent)

Supplementary:

Location (check all that apply; for separate fractures, list each separately; for single fractures crossing midline or region, list both sides and/or regions.)
- Frontal R L
- Parietal R L
- Temporal R L
- Occipital R L
- Skull base R L Anterior fossa Middle f. Posterior f.

Emerging:

Morphology(check all that apply)
- Linear (includes simple and branched)
- Depressed (>1 cm or full thickness of skull)
- "Ping pong" fracture (smooth depression typically seen in infants and toddlers, without a complete bony cortical disruption)
- Comminuted (involving at least one separate non-contiguous bone segment)
- Diastatic (separated more than 3 mm, or separation of a suture)
- Compound (communication with the skin, mastoid air cells, or paranasal sinuses)
- Penetrating (resulting from an indriven foreign body, such as knife or missile)
- "Probable fracture" – one in which fracture itself cannot be seen definitively, but is suspected to be present based on other findings such as adjacent subgaleal and extra-axial hemorrhage, intracranial air, or other findings
- Pneumocephalus
  - Present
  - Absent
- For children <3 years: other craniofacial fractures (of interest for relevance for inflicted injuries)

Epidural Hematoma (EDH)

Definition: A collection of blood between the skull and dura. On CT, the EDH typically (though not always) has a biconvex shape, an adjacent skull fracture/scalp injury, and classically

does not cross sutural margins. (In patients with skull fractures, especially those in children involving the sutures, this rule may not always apply.) The acute EDH is hyperdense, but may contain hypodense areas representing unclotted blood. As the EDH evolves, it gradually loses its hyperdensity and may appear iso/hypodense. On MRI, the acute EDH is hypo/isointense on T1 and very hypointense on T2, GRE, and SW-imaging. The inwardly displaced dura should be directly visualized on MR as a thin dark line on all pulse sequences.

Core:

Present
Indeterminate
(Absent)

Supplementary:

Location (check all that apply; for separate lesions, list as separate entries):

Frontal R L
Parietal R L
Temporal R L
Occipital R L
Posterior fossa R L

Size

Volume (or length, width, maximal thickness)

Emerging:

Likely arterial (due to "swirl", different densities, location near major dural artery)
Likely venous (due to association with adjacent bony injury/fracture, venous sinus, size, distribution, timing)

Extraaxial hematoma

Definition: A collection of blood between the brain surface and the skull which may be subarachnoid, subdural, or epidural, but for which the exact site cannot be determined with certainty, and is not already classified as a more specific entity elsewhere in the data set. These are typically small in volume. (This entity may be seen particularly in young children with contact injuries.)

Core:

Present
Indeterminate
(Absent)

Supplementary:

Location (check all that apply; for separate lesions, list as separate entries):

Frontal R L
Parietal R L
Temporal R L
Occipital R L
Interhemispheric supratentorial
Anterior (frontoparietal) Posterior (occip)
Tentorial R L
Posterior fossa R L

Size

Volume (or length, width, maximal thickness)

Subdural Hematoma (SDH), acute

Definition: A collection of acute blood between the arachnoid and the dura, typically (though not always) hyperdense with a crescent shape on CT. Mixed density may be seen if the collection contains unclotted blood, CSF admixture, and/or active extravasation. On MRI, the acute SDH is iso/hypointense on T1 and very hypointense on T2, GRE, and SW-imaging. Note: Please see additional categories below for subacute, chronic, and mixed collections if these better describe the lesion, or if the chronicity/timing is uncertain. (Note: For more information on neonatal birth subdurals, with examples, link to follow *here*.)

Core:

Present
Indeterminate
(Absent)

Supplementary:

Location (check all that apply; for separate lesions, list as separate entries):

Frontal R L
Parietal R L
Temporal R L
Occipital R L
Interhemispheric supratentorial
Anterior (frontoparietal) Posterior (occip)
Tentorial R L
Posterior fossa R L Interhemispheric infratentorial

Size

Volume (or length, width, maximal thickness)

Emerging: Homogeneous or Heterogeneous (i.e. mixed density)

Subdural Hematoma (SDH), subacute or chronic

Definition: A collection of non-acute blood between the arachnoid and the dura, typically (though not always) with a crescent shape. On CT, a subacute or chronic SDH will be predominantly iso- or hypodense. On MRI, a subacute SDH will be hyperintense on T1 and will have varying signal intensity on T2. The chronic SDH is slightly hyperintense compared to CSF on both T1 and T2-weighted imaging. FLAIR imaging increases the conspicuity. If rebleeding has occurred in the collection (i.e., "chronic recurrent SDH"), the signal may be a variable combination of hypo/iso/hyper-intensity/density on CT and all MR sequences. Internal loculations and septations may be seen on both CT and MRI and these are more conspicuous following intravenous contrast enhancement.

Core:

Present
Indeterminate
(Absent)

Supplementary:

Location (check all that apply: for separate lesions, list as separate entries):

Frontal R L

Parietal R L
Temporal R L
Occipital R L
Interhemispheric Anterior (frontoparietal) Posterior (occip)
Tentorial R L
Posterior fossa R L

Size

Volume (or length, width, maximal thickness)

Emerging:

Homogeneous v. Heterogeneous
Loculations/Septations

Subdural hematoma/mixed density subdural collection/CSF-like collections

Definition: A collection of inhomogeneous blood products between the arachnoid and the dura, typically (though not always) with a crescent shape, in which timing (e.g., "acute" vs. "chronic" or "subacute") is indeterminate. On CT and MRI, mixed collections may have hyper, iso, or hypodense/intense components. This classification is used for those collections in which the exact nature of the collection or its chronicity cannot be determined by the characteristics noted in the definitions of subdural hematomas in the two prior sections. In addition to mixed collections, more homogeneous CSF-density/intensity collections also may be seen *after known trauma* in which low density/intensity collections occur over time on serial images, presumably from arachnoid tears, decreased CSF absorption, increased CSF protein, or other mechanisms. This definition does NOT apply to CSF-intensity collections or prominent spaces seen on a single image, which may represent entities other than trauma. (See also section on Atrophic Changes below.)

Core:

Present
Indeterminate
(Absent)

Supplementary:

Location (check all that apply; for separate lesions, list as separate entries):

Frontal R L
Parietal R L
Temporal R L
Occipital R L
Interhemispheric Anterior (frontoparietal) Posterior (occip)
Tentorial R L
Posterior fossa R L

Size

Volume (or length, width, maximal thickness)

Emerging:

Characteristics (check all that apply)

Hypointense/dense
Hyperintense/dense
Isointense/dense

Appendix 1: Pathoanatomic Terms for Definitions of TBI Lesions and Associated Findings

Subarachnoid Hemorrhage (SAH)

Definition: Macroscopic blood located between the brain surface and the arachnoid membrane. On CT and MR, the blood in this location will follow the contour of the sulci and cisterns. Acute SAH is hyperdense on CT and hyperintense on FLAIR MR imaging. Subacute SAH may be invisible on CT, although the presence of subtle sulcal "effacement" may occasionally be seen. Chronic SAH, or "hemosiderosis" may be seen on MR as hypointense linear areas of cortical "staining" on GRE and SW-imaging.

Core:

- Present
- Indeterminate
- (Absent)

Supplementary:

Location (check all that apply):

- Frontal R L
- Parietal R L
- Temporal R L
- Occipital R L
- Interhemispheric Anterior (frontoparietal) Posterior (occip)
- Suprasellar *(Note: patients with this finding may have increased risk of diabetes insipidus.)*
- Tentorial R L
- Posterior fossa
- Perimesencephalic

Distribution/extent

- Focal (in 1-2 locations or lobes of the brain)
- Diffuse (involving *more than two* contiguous lobes or brain regions, supra- and infratentorial compartments, or multiple basal cisterns)

Emerging:

- Linear v. "mass-like" (>3mm thickness, splaying of Sylvian fissure or other cistern)
- Acute hydrocephalus present

Vascular dissection

Definition: An incomplete disruption of one or more inner layers of an artery, which may be traumatic or spontaneous. CTA and MR/MRA may show an abnormally small or irregular caliber of the injured artery. A "crescent sign" may be seen on axial MR (and less well with CTA), and is best identified on T1-weighted Fat-Saturation images. If the caliber of the lumen is unaffected, conventional catheter angiography may miss the vascular dissection, and the diagnosis may be visualized only with CTA/MR.

Note: If more than one vessel has dissection, list each separately.

Core:

- Present
- Indeterminate
- (Absent)

Supplementary:

Location (check all that apply; for separate lesions, list as separate entries):

Carotid R L
Vertebral R L
Other R L

Emerging:

Site

Cervical
Intracranial

Extent

Luminal narrowing < 50%
Luminal narrowing >50% (including "string sign")
Vessel occlusion

Associated findings

Watershed or embolic infarction in the territory of the dissected vessel
+/- SAH
Adjacent skull fracture (e.g. carotid canal)

Traumatic Aneurysm

Definition: A false aneurysmal outpouching of an artery due to mechanical disruption of the entire vessel wall with extravasation of blood into a confined soft-tissue space. CTA, MR/MRA, and catheter angiography reveal focal dilation of the vessel lumen. In contrast to non-traumatic aneurysms, the dilated wall of a pseudoaneurysm may have an irregular surface, and the lesion is not located in typical berry aneurysm locations. Intraluminal thrombus of varying ages can appear as laminated rings of varying signal intensity on MRI. Phase artifact, indicative of pulsation within the lesion, may be seen on MRI. Peripheral wall calcification may be seen in older pseudoaneurysms and is best visualized with CT or, in some cases, conventional angiography.

Core:

Present
Indeterminate
(Absent)

Supplementary:

Location (check all that apply; for separate lesions, list as separate entries):

Carotid R L
Vertebral R L
ACA R L
MCA R L
PCA R L
Basilar
Other (Describe) R L

Emerging:

Size (mm, length of involved vessel)
Intraluminal thrombus
Cavernous (intradural)
Skull fracture, +/- penetrating injury

Appendix 1: Pathoanatomic Terms for Definitions of TBI Lesions and Associated Findings

Venous sinus injury

Definition: Compression (>50%), occlusion, or laceration of a dural venous sinus due to trauma.

Core:

- Present
- Indeterminate
- (Absent)

Supplementary:

Morphology

- Compression
- Occlusion
- Laceration

Location (check all that apply; for separate lesions, list as separate entries):

Sagittal sinus Anterior (frontoparietal) Posterior (occipital)
Transverse sinus R L
Sigmoid sinus R L

Midline Shift (supratentorial)

Definition: Displacement of the supratentorial midline structures, particularly the septum pellucidum, *2 mm or more* due to mass effect of a focal traumatic lesion or brain swelling. Shift is measured at the foramen of Monro, or alternatively, where it is greatest.

Core:

- Present
- Indeterminate
- (Absent)

Supplementary:

Amount :

___mm

Emerging:

Side

- Right-to-left
- Left-to-right

Cisternal compression

Definition: Asymmetry or obliteration of the normal configuration of the perimesencephalic, suprasellar, prepontine, or superior cerebellar cistern, and/or cisterna magna due to mass effect and/or brain swelling in the setting of trauma. (Note: For children under age 3, cisternal appearance may be variable. For examples and references, link will follow *here*.)

Core:

- Present (i.e., cisternal compression is present in at least one location)
- Indeterminate
- (Absent) (i.e., cisterns normal)

Supplementary:

Amount :

- Visible but compressed
  - Asymmetric
  - Symmetric

Mixed (some cisterns open, others compressed/obliterated)
Obliterated (all cisterns)

Side of compression

Left
Right
Midline or bilateral

Emerging:

Site (check all that apply for each cistern which is abnormal)

Perimesencephalic cistern
Suprasellar cistern
Cisterna magna
Prepontine cistern
Superior cerebellar cistern

Fourth ventricle shift/effacement

Definition: Displacement or effacement of the fourth ventricle *2 mm or more* due to adjacent mass lesions or brain swelling.

Core:

Present
Indeterminate
(Absent)

Supplementary:

Amount :

___mm (maximal distance from expected location in any direction)

Emerging:

Direction

Right-to-left
Left-to-right
Anterior
Posterior

Other features

Hydrocephalus (Note: Hydrocephalus is defined operationally for database purposes as ventricles larger than seen on prior study, or, if no prior study, there is presence of periventricular spread of CSF, temporal horns are larger than frontal horns, and/or effacement of subarachnoid space is seen.)
Brainstem compression

Contusion

Definition: A focal area of brain parenchymal disruption due to acute mechanical deformation. Contusions typically occur in the cortex and may extend into subcortical region. Contusions may show grossly visible hemorrhage or minimal/absent hemorrhage. Acute contusions typically have a mottled, inhomogeneous appearance due to stippling of blood along the brain surface. As such, their size is difficult to measure. In addition, CT streak artifact limits visualization of the cortical surface, so contusions are best seen with MRI, particularly on the FLAIR sequence. For purposes of categorization, contusions are differentiated from

"intracerebral hematomas" by a containing a *mixture* of hemorrhagic and non-hemorrhagic tissue, or by having no grossly visible hemorrhage ("bland contusion"), while an "intracerebral hematoma" is predominantly a uniform collection of blood alone. The term "contusion" should not be used for hemorrhagic lesions which fit better in other categories, such as small hemorrhages associated with the pattern of diffuse axonal injury, lesions which in context are more likely to represent infarction or other primary vascular lesion, or isolated SAH. Contusions can, however, be associated with other lesions which commonly co-occur, such as brain laceration, adjacent SAH, and depressed skull fractures. Contusions which are questionable, such as those in an area of beam hardening on CT scan, should be noted as "indeterminate". Note: areas of delayed hypodensity or signal change around a traumatic lesion should not necessarily be classified as contusions. Contusions in which the hemorrhagic component enlarges over time should not be re-classified on subsequent images as "intraparenchymal hemorrhage" (next section).

Core:

- Present
- Indeterminate
- (Absent)

Supplementary:

Location (check all that apply; for separate lesions, list as separate entries):

- Frontal R L
- Parietal R L
- Temporal R L
- Occipital R L
- Internal capsule R L
- Thalamus/Basal ganglia R L
- Midbrain R L
- Pons R L
- Medulla R L
- Cerebellum R L

Size

- Volume (or length, width, maximal thickness) (Note: measurements should include *all* areas of contiguous abnormality not related to a separate lesion)

Emerging: (Check all that apply)

- Hemorrhagic
- Non-hemorrhagic
- Cortical
- Subcortical
- Deep brain structures
- Probable brain laceration (linear hemorrhagic or non-hemorrhagic pattern, often associated with overlying skull fracture)

Appendix 1: Pathoanatomic Terms for Definitions of TBI Lesions and Associated Findings

Intracerebral hemorrhage

Definition: A collection of confluent, relatively homogeneous blood within the brain parenchyma. Intracerebral hemorrhage can occur in the setting of brain laceration, diffuse axonal injury, and other brain injury types, and there is some overlap with other entities. In general, lesions characterized by mixed blood and tissue are generally classified as contusions. In most instances, the term "intracerebral hemorrhage" is used to refer to larger collections of blood (typically, more than about 5 mm). Hemorrhages can have a surrounding region of non-hemorrhagic (e.g, hypointense) signal abnormality that may represent edema or clot retraction. Very small collections more often occur in the setting of contusion or, when scattered throughout the brain, may represent diffuse axonal injury/traumatic axonal injury (sometimes called "microhemorrhages"). Note: Hemorrhages in the context of other injury types such as contusion, or small hemorrhages (e.g. < 5 mm) in the setting of DAI or TAI, should be classified in those categories only.

Core:

- Present
- Indeterminate
- (Absent)

Supplementary:

Location (check all that apply; for separate lesions, list as separate entries):

- Frontal R L
- Parietal R L
- Temporal R L
- Occipital R L
- Internal capsule R L
- Thalamus/Basal ganglia R L
- Midbrain R L
- Pons R L
- Medulla R L
- Cerebellum R L

Size

- Volume (or length, width, maximal thickness) of hemorrhagic component
- Volume (or length, width, max thickness) of entire lesion, including surrounding signal abnormalities.

Emerging: (Check all that apply)

- Layered (i.e., with fluid level)
- Surrounding ring of non-hemorrhagic signal (edema)
- Total hemorrhage volume/lesion load ___

Intraventricular hemorrhage

Definition: Acute-appearing blood within the ventricles.

Core:

- Present
- Indeterminate
- (Absent)

Supplementary:*Location* (check all that apply):
Lateral ventricle R L
Third ventricle
Fourth ventricle

Emerging:
Ventriculomegaly (acute hydrocephalus)
Hemorrhage volume_____

Diffuse Axonal Injury (DAI) and Traumatic Axonal Injury (TAI)

Related terms: Shearing injury, white matter injury, microhemorrhages

Brief history of terminology: These terms are defined differently in the clinical, radiologic, and pathologic arenas, and have evolved in the radiologic sphere concurrent with advances in detection, particularly using MRI. The term DAI was initially coined to describe the pathologic findings in primates subjected to experimental, high magnitude, non-impact angular deceleration ("inertial") forces, which resulted in prolonged unconsciousness and widespread injury to axons in the hemispheric white matter and brainstem [17]. The injury was modeled to explain prolonged coma in human patients with high-energy injury mechanisms and prolonged unconsciousness with minimal CT findings, but widespread axonal damage in a similar distribution to that seen in animal models on histopathology [18]. As CT spatial resolution improved and specialized MR sequences evolved, lesions similar to those described in autopsy studies have been identified in patients with clinically less severe injuries, in whom the length of unconsciousness is shorter and the outcome better than those for whom the term was originally employed.

Currently, there exists a spectrum of animal models of inertial white matter injuries which do not necessarily follow the specific anatomic distribution of the original descriptions. Similarly, radiologic techniques demonstrate lesions in more limited distributions in human patients. Therefore, many authors use the term "traumatic axonal injury" to refer to more limited axonal injury which appears to result from traumatic inertial forces and tissue strains in the white matter. While these injuries occur in a continuum, for purposes of classification they are operationally defined as described below.

Definition: A radiologic entity which demonstrates a pattern consistent with scattered, small hemorrhagic and/or non-hemorrhagic lesions which have been shown historically to correlate with pathologic findings of relatively widespread injury to white matter axons, typically due to mechanical strain related to rotational acceleration/deceleration forces. For current purposes, the terms "traumatic axonal injury" and "diffuse axonal injury" are defined specifically to relate to radiologic findings, and do not necessarily connote the same meaning, with respect to prognosis or extent of pathology, that may be implied when the terms are used in the clinical, experimental, or neuropathologic domains.

While detection of white matter lesions has increased with advances in techniques, axonal injury within this spectrum is scattered and occurs at the cellular level, and it is thought that current imaging techniques likely continue to underestimate the true extent of injury. "Diffuse axonal injury" refers to a widespread distribution of lesions, including the subcortical white matter in more than one lobe or hemisphere, along with lesions in the corpus callosum, and may include the dorsomedial midbrain and other brainstem and cerebellar regions. "Traumatic axonal injury" refers to similar multiple, scattered, small hemorrhagic and/or non-hemorrhagic lesions in a more confined white matter distribution. These injuries may coexist with other characteristic lesions, including intraventricular hemorrhage, small hemorrhages at the gray-

white interface, and deeper macroscopic intracerebral hematomas. *For purposes of this database, DAI includes more than three separate foci of signal abnormality, and TAI is 1-3 foci of signal abnormality.* These are described below in more detail according to their distribution and extent. DAI and TAI lesions may be hemorrhagic and are thus often identified with GRE/SW-imaging. Newer MR studies, such as diffusion tensor imaging (DTI), are able to demonstrate white matter fiber tract injury even when the standard MRI is negative. Both DAI and TAI injuries may also be found along with a wide variety other traumatic entities such as SDH, EDH, and contusions, because of the large heterogeneous forces involved in causing these lesions.

Core:

DAI (more than 3 foci of signal abnormality)
- Present
- Indeterminate
- (Absent)

TAI (1-3 foci of signal abnormality)
- Present
- Indeterminate
- (Absent)

Supplementary:

Location (check all that apply): (SEE ALSO TABLE BELOW)
- Frontal R L
- Parietal R L
- Temporal R L
- Occipital R L
- Internal capsule R L
- Thalamus/Basal ganglia R L
- Midbrain R L
- Pons R L
- Medulla R L
- Cerebellum R L

Location: (mark signal abnormalities identified by each imaging sequence in each location: e.g. DTI, CT, FLAIR, T2*, T1-Gd)

	Right	Left
Corpus Callosum: Genu		
Corpus Callosum: Body		
Corpus Callosum: Splenium		
Subcortical White matter: Frontal		
Subcortical White matter: Parietal		
Subcortical White matter: Temporal		
Subcortical White matter: Occipital		
Internal Capsule: Anterior limb		
Internal Capsule: Posterior limb		
Brainstem: Dorsolateral rostral		
Brainstem: other		

Appendix 1: Pathoanatomic Terms for Definitions of TBI Lesions and Associated Findings

	Right	Left
Cerebellar Peduncles		
Other:		

Emerging:

Overall assessment:

Operational definitions of DAI/TAI involving newer techniques including DTI will likely include "definite", "likely", and "possible" patterns or other grading schemes, and will need to be developed. In addition, software for total lesion load may be used to quantify extent of injury.

Penetrating Injuries

Definition: Injuries caused by traumatic forces which penetrate any of the normal layers of the head, including scalp, skull, dura, and brain. Examples include gunshot wounds, other missiles and projectiles, stab wounds, and other penetrating objects.

Core:

Present
Indeterminate
(Absent)

Supplementary:

Deepest extent penetrated

Scalp
Skull
Dura
Parenchyma

Location (check all that apply):

Frontal R L
Parietal R L
Temporal R L
Occipital R L
Internal capsule R L
Thalamus/Basal ganglia R L
Midbrain R L
Cerebellum R L
Pons R L
Medulla R L

Modality/mechanism

Stab wound
Gunshot wound
Caliber/type___
Other foreign body____

Emerging:

Indriven fragments (bone, foreign bodies)
Through and through trajectory (entrance and exit sites)
Transventricular trajectory
Crosses midline

Appendix 1: Pathoanatomic Terms for Definitions of TBI Lesions and Associated Findings

Cervicomedullary junction/Brainstem injury

Definition: Injuries typically occurring in the setting of crush or distraction forces which cause disruption in the brainstem and/or cervicomedullary junction. In the acute phase, these are usually areas of low density with or without blood on CT, and high signal on T2 and FLAIR with or without blood on MRI.

Core:

- Present
- Indeterminate
- (Absent)

Supplementary:

Location (check all that apply) :

- Midbrain
- Pons
- Medulla
- Cervical

Emerging:

Extent:

- Subtotal (area of abnormality involves less than the entire transverse extent of the pertinent structure)
- Total (area of abnormality involves the entire transverse extent of one or more pertinent structure)

Findings with Pathophysiologic Connotations

Edema

Definition: Edema refers to an abnormal accumulation of water in the intracellular and/or extracellular spaces of the brain. It can be divided into 4 types (recognizing that there are a number of types and schemes described by various authors): cytotoxic, vasogenic, interstitial, and osmotic. In *"cytotoxic"* edema, the blood-brain barrier (BBB) remains intact and the excess fluid is due to a derangement in cellular metabolism resulting in cellular retention of sodium and water, and the abnormal fluid is seen within the gray matter on CT and MR. In *"vasogenic"* edema, there is a breakdown of the BBB and the excess fluid is typically located in the white matter. *"Interstitial"* edema is found in obstructive hydrocephalus and the fluid is located within the extracellular space of the periventricular white matter. In *"osmotic"* cerebral edema, plasma osmolality is slightly greater than brain tissue, such as during hyponatremia or rapid drops in glucose. The abnormal pressure gradient will trigger water to flow into the brain, causing cerebral edema. In all types of edema, the abnormal fluid is hypodense on CT and hyperintense on T2-weighted and FLAIR MR.

(Note: Because of changes in myelination during development, care must be taken to interpret density/intensity in young children against age-matched norms for CT and MRI. Link to discussion and examples to follow *here*.)

Core:

- Present
- Indeterminate
- (Absent)

Supplementary:

Location (check all that apply):

Frontal
R L
Parietal
R L
Temporal
R L
Occipital
R L
Deep gray matter
R L
Cerebellum
R L
Brainstem

Extent : (check all appropriate)

Focal (involves less than half of one lobe)
Lobar (involves more than half of one lobe)
Multilobar (involves multiple lobes)
Hemispheric (involves an entire supratentorial hemisphere)
Bihemispheric (involves both hemispheres)
Posterior fossa (involves the cerebellum and/or brainstem)
Global (involves the entire brain)

Emerging: (Check all that apply)

Cytotoxic
Vasogenic
Interstitial
Osmotic
Indeterminate
Volume of edema

Brain Swelling

Definition: Brain swelling is an all-inclusive term that refers to a non-specific increase in brain tissue mass. It can result from increased water as described above in the various types of cerebral "edema", but it can also result from "hyperemia" (i.e., increased intravascular blood volume). The latter situation is typically found in venous hypertension in which the tissue is engorged due to outflow obstruction. Cerebral hyperemia can also be found in the dysautoregulated brain when the systemic blood pressure is elevated, and in some hypermetabolic states in which the tissue is hyperperfused. For radiologic purposes, cerebral hyperemia appears as focal or diffuse mass effect (i.e. sulcal/cisternal effacement) with preservation of the gray-white differentiation (GWD). Cerebral edema also appears as focal or diffuse mass effect, but the increased water results in obscuration of the GWD.

For the present purposes, *brain swelling refers to increased brain mass which does not otherwise fit into the definitions included under "Edema" in the prior section, or for which these pathophysiologies are felt to be operational in the findings noted.*

Appendix 1: Pathoanatomic Terms for Definitions of TBI Lesions and Associated Findings

Core:

Present
Indeterminate
(Absent)

Supplementary: *Location (check all that apply):*

Frontal
R L
Parietal
R L
Temporal
R L
Occipital
R L
Deep gray matter
R L
Cerebellum
R L
Brainstem

Extent :

Focal (involves less than half of one lobe)
Lobar (involves more than half of one lobe)
Multilobar (involves multiple lobes)
Hemispheric (involves an entire hemisphere)
Bihemispheric (involves both hemispheres)
Posterior fossa (involves the cerebellum and/or brainstem)
Global (involves the entire brain)

Ischemia/Infarction/Hypoxic-ischemic injury

Definition: Ischemia and other related terms above refer to findings in tissue which sustains, for a variety of reasons, a deficit between substrate demand and delivery. This may be reversible or irreversible. Examples of specific etiologies include arterial occlusion, embolic infarction, lacunar infarction, watershed infarction, venous infarction, and changes from global insults such as hypoxia, hypotension, status epilepticus, and others.

On CT, the acute *embolic* infarct is seen as an area of hypodensity which becomes more defined with time. MR features will include changes on various sequences. Petechial hemorrhage and/or overt hemorrhagic transformation may occur, and this will be best seen on GRE and SW-imaging. Unlike the bland contusion, the location of the lesion respects a specific vascular territory, and this can be a helpful radiologic clue. The *lacunar* infarct results from occlusion of one of the penetrating arteries that provides blood to the brain's deep structures. They are typically less than 1.5 cm in size, ovoid or round in shape, and located in the basal ganglia. The *watershed* infarct results from an episode of systemic hypoperfusion. The lesion is located at the junction of the ACA/MCA/PCA border zones. On diffusion-weighted MR, the acute embolic, watershed, and lacunar infarcts are seen as a focal "light-bulb" bright area. The lesion intensity will fade over time on DWI (typically gone by two weeks) but it will persist on T2 and FLAIR images. (Note: DWI may normalize sooner in neonates after ischemia.) *Venous* infarction results from reduced outflow of blood from the brain in the setting of cortical and/or

dural sinus thrombosis or occlusion. On CT, early venous hypertension is typically seen as a subcortical area of hyperemic swelling which may progress to vasogenic edema. Overt venous infarction is often hemorrhagic and multifocal. Therefore, the smaller hemorrhagic venous infarct can mimic hemorrhagic TAI . A "cord sign" or "empty delta sign" may be seen on contrast CT/MR, and CTV and MRV can often reveal the intraluminal thrombus, hypodensities in arterial distributions, or those in the pattern of venous thrombosis. Other modalities for detection of ischemic injuries include CT and MR perfusion, and arterial spin labeling (ASL).

Core:

Present
Indeterminate
(Absent)

Supplementary:

Location (check all that apply):

Frontal
R L
Parietal
R L
Temporal
R L
Occipital
R L
Deep gray matter
R L
Cerebellum
R L
Brainstem

Extent :

Focal (involves less than half of one lobe)
Lobar (involves more than half of one lobe)
Multilobar (involves multiple lobes)
Hemispheric (involves an entire supratentorial hemisphere)
Bihemispheric (involves both hemispheres)
Posterior fossa (involves the cerebellum and/or brainstem)
Global (involves the entire brain)

Acute vs. subacute

For CT: (check all that apply)

Hypodense
Isodense
Hyperdense
Mixed

For MRI: (check all that apply)

T1 hyperintense__isointense hypointense mixed
T2 hyperintense isointense hypintense mixed
FLAIR hyperintense isointense hyperintense mixed
DWI bright normal mixed

Emerging:

Pattern:

Watershed
Arterial
Lacunar
Venous
Global
Dissection
Mixed
Inderterminate

Detailed location by gyral anatomy template

Brain Atrophy/Encephalomalacia

Definition: This entity refers to loss of tissue volume over time due to cell death or shrinkage. When strictly defined, a change should be seen over serial images to confirm that the changes are due to a specific traumatic event, rather than being preexisting. In some cases, atrophy can be inferred at a single time point due to patterns of brain appearance (for example, a smaller size and increased signal of one hippocampus compared to the other). It should be noted that enlargement of the subarachnoid spaces does not in itself confirm atrophy, as it may represent primary problems with CSF hydrodynamics (for instance, in infancy or early after traumatic subarachnoid hemorrhage). (Note: For discussion of pediatric norms, head circumference, and specific considerations in infants and children, link to follow *here*.)

Core:

Present (tissue loss seen over serial images)
Likely (tissue loss in typical pattern, not seen on serial images)
Indeterminate (nonspecific tissue loss or prominence of CSF spaces, duration or cause unknown)
(Absent)

Supplementary:

Location (check all that apply):

Frontal
R L
Parietal
R L
Temporal cortex
R L
Hippocampus
R L
Occipital
R L
Deep gray matter
R L
Supratentorial white matter (corpus callosum, periventricular white matter) R L
Cerebellum

Appendix 1: Pathoanatomic Terms for Definitions of TBI Lesions and Associated Findings

R L
Brainstem Midbrain Pons Medulla

Emerging: Brain volumetric analysis

ABBREVIATIONS (used in text and Appendices)

^{99m}Tc-HMPAO - technetium-99m-labeled hexamethylpropyleneamine oxime
AC - anterior commissure
ACA - anterior cerebral artery
ADC - apparent diffusion coefficient
AF – acceleration factors
ASL – arterial spin labeling
BBB – blood-brain barrier
BOLD - blood oxygen level dependent
BW - bandwidth
CBF - capillary blood flow
CBV - capillary blood volume
CDE - common data elements
Cho - choline
CL – central line
CNS - central nervous system
COE - Defense Centers of Excellence
CPP - carbamylated plasma protein
CR - creatine
CSF - cerebrospinal fluid
CTA - computed tomography angiography
CT - computed tomography
CTP - perfusion computed tomography
CTV - computed tomographic venography
DAI - diffusion axonal injury
DRS - Disability Rating Scale
DSC - dynamic susceptibility contrast
DTI - diffusion tensor imaging
DWI - diffusion weighted imaging
EDH - epidural hematoma
EMP - employability component
EPI – echo planar imaging
F18-FDG - Fluorodeoxyglucose
FA - fractional anisotropy
fcMRI - functional connectivity magnetic resonance imaging
fMRI - functional magnetic resonance imaging
FOV - field of view
FWM - frontal white matter
GCS - Glasgow Coma Scale

Glx - glutamate
GM - gray matter
GRE - gradient-recalled echo
GWD – grey-white differentiation
ICP - intracranial pressure
IR-FSPGR - inversion recovery, fast spoiled gradient recalled echo
IV - intravenous
L - field-of-view
L/N - resolution
MAP - mean arterial pressure
MCA – middle cerebral artery
MD - mean diffusivity
MEG - magnetoencephalography
MP-RAGE - magnetization prepared-rapid gradient echo
MRA - magnetic resonance angiography
MRI - magnetic resonance imaging
MR - magnetic resonance
MRSI - MR spectroscopic imaging
MRS - Magnetic Resonance Spectroscopy
MRV – magnetic resonance venography
mTBI - mild traumatic brain injury
MTT - mean transit time
NAA - N-acetyl aspartate
Nacq - number of acquisitions
NCT - noncontrast head computed tomography
NEX - number of acquisitions
NIDR - National Institute on Disability and Rehabilitation
NINDS - National Institute of Neurological Disorders and Stroke
N - matrix size
OEF - Oxygen Extraction Fraction
PCPCS - Pediatric Cerebral Performance Category Scale
PC - posterior commissure
PCA – posterior cerebral artery
PCS - post-concussive syndrome
PET - positron emission tomography
PRESS - point resolved spectroscopy sequence
PTSD - posttraumatic stress disorder
PWI - perfusion weighted imaging
RARE - rapid acquisition with relaxation enhancement
RF - radiofrequency
SAH - subarachnoid hemorrhage
SDH - subdural hematoma
SD - standard deviation
SNR - signal-to-noise ratio
SPECT - single photon emission computed tomography
STEAM - stimulated echo acquisition mode

Appendix 1: Pathoanatomic Terms for Definitions of TBI Lesions and Associated Findings

SWI - susceptibility weighted imaging
T – Tesla (magnet strength unit)
T2* - T2 star (T2-weighted GRE)
T2 FLAIR - T2-weighted Fluid Attenuated Inversion Recovery
TAI - traumatic axonal injury
TBI - traumatic brain injury
TCD - transcranial Doppler
TE - echo delay time
TI - inversion time
TR - repeat time
VA - Veterans Administration
VESTAL - Vector-based Spatial-Temporal Analysis
WM - white matter
x - the read direction
Xe-CT - Xenon-enhanced computed tomography
y - the phase encoding direction

Appendix 2: Prequalification package written feedback from FDA and response from TED

Pre-Submission Pre-Meeting Feedback

Q161252.A002 – MDDT027 – OsiriX CDE Software Module - PQP

Date: April 14, 2017
To: Geoff Manley, M.D., Ph.D.
From: Daniel Krainak, Ph.D.

Subject: MDDT Prequalification Plan Pre-Meeting Feedback
Device Name: OsiriX CDE Software Module
Sponsor: TBI Endpoints Development (TED) Initiative

Meeting type: Teleconference
Scheduled meeting date: April 17, 2017 from 2:00 – 3:00 pm (EDT)

I. Proposed Context of Use

We are discussing the following proposed Context of Use:

> The OsiriX CDE software module may be used to collect, record and standardize data on the presence of ≥1 brain contusions and/or ≥4 foci of hemorrhagic axonal injury (biomarkers) as evaluated by a physician on magnetic resonance images collected within 2 weeks post-injury in mild TBI patients (age 18-65 years) who had presented at an emergency department within 24 hours of injury of injury and who had at that time required a head CT based on ACEP/CDC criteria. The biomarkers are intended as a prognostic enrichment tool to select patients with mild TBI at high risk for poor outcomes at 3 months postinjury (as defined by the extend Glasgow Outcome Scale, or GOS-E) for enrollment in early and pivotal clinical trials to support marketing applications of therapeutic medical devices intended to improve outcomes for mild TBI patients.

II. General comment

Some characterization of reader variability and its impact on the prognostic performance of your device is important. We believe that analysis based on a single reader evaluating all images would be insufficient to demonstrate prognostic performance. The proposed study design and number of readers included to evaluate inter-reader reliability is insufficient to fully characterize reader variability. We have reconsidered and dropped the need to fully characterize reader variability and provide error bars that account for reader variability in the assessment of the prognostic performance and inter-rater agreement results. An observation of increased variability may require future analysis with a consensus majority assessment or panel assessment to fully support the utility of this medical device development tool (MDDT) in clinical studies. We suggest including analyses that would assess inter-rater agreement of three readers (and the corresponding CIs) and the inter-rater agreement for each pair of the three readers (and the corresponding CIs). An alternative approach would be to perform a larger inter-reader reliability study to fully characterize the variability of this MDDT. If you have further questions, we are available to discuss, as needed.

III. Questions and comments for the submitter

Context of Use

1. You have provided a description of the imaging data used in the MDDT. It is unclear if the chosen imaging correlates will be used in isolation or in conjunction with one another. Please refine the COU to specify whether you are qualifying the biomarkers individually, combined with "OR", or combined with "AND". This information is needed to ensure there is a clear understanding of how the proposed tool will be used.

2. You have stated that the use of the tool may support future medical devices applications to improve outcomes. We suggest deleting the last phrase "intended to improve outcomes for mild TBI patients" from the proposed context of use. This change is requested to ensure the device description and COU may be accurately applied in the future.

3. In the context of use, you indicate that the population for the MDDT includes "mild TBI patients (age 18-65 years) who had presented at an emergency department within 24 hours of injury and who had at that time required a head CT based on ACEP/CDC criteria." In the description of the "Type of Evidence to Gather" the studies that you propose seem to be more specific about the study population. You state that, "mild TBI patients age 18-65 years with nonpenetrating head trauma and GCS 13-15 who have undergone acute head CT (e.g., as part of standard clinical care according to ACEP/CDC criteria)." Typically, the study population should be the same as the intended use population (or context of us population for MDDTs), or the differences should be discussed and justified. Please harmonize the study population across the context of use statement or discuss and justify why they are different.

Study population

4. You provide a reference for the TRACK-TBI *pilot* dataset (Ref. 15), which fully describes the collection of that data. You have planned to use 11 level-1 trauma centers to perform your clinical studies. You also provide a table showing the distribution of age, gender, race, ethnicity, and mechanism of injury in the mild TBI patients, of the TRACK-TBI *non-pilot* data. Please note this needs to be further discussed based on inclusion/exclusion criteria. If there is a reference describing the collection of the *non-pilot* data, please provide that or alternatively, please provide the full clinical protocol or summarize that data collection. In particular, please describe how patients were enrolled (i.e., were they prospectively enrolled from all-comers to the level-1 trauma center based on meeting inclusion and exclusion criteria, whether the evaluators of the final outcome blinded to the original classification of the subjects; whether there were any protocol violations and how they were addressed). Be sure to include the total screened patients, inclusion/exclusion criteria, dates and locations. Without the complete information, the current protocol is incomplete.

5. For any analysis based on a subset of subjects chosen randomly from subjects in the clinical validation study, please justify that the distribution of GOS-E scores in the sample population is roughly similar to that expected for the patient population in the context of use (patients with mild TBI). If the random sample differs from the distribution expected for the patient population in the context of use, we recommend that instead of a completely random sample, you use stratified random sampling with adequate patients across the spectrum of GOS-E scores. You may wish to refer to following CLSI document for more information, "Clinical and Laboratory Standards Institute

(CLSI). Quality Assurance for Design Control and Implementation of Immunohistochemistry Assays; Approved Guideline—Second Edition. CLSI document I/LA28-A2 (ISBN 1-56238-745-6). Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2011."

Validation of the MRI CDEs, brain contusion and hemorrhagic axonal injury, as prognostic biomarkers in mild TBI

6. In your section on type of evidence to gather, you propose to use Mann-Whitney U test statistics–-- a non-parametric test, to test whether the GOS-E score is significantly different between two marker groups-–those with DAI (>= 4 foci of diffuse axonal injury) and those without (<=3 foci) and likewise for the biomarker for brain contusion. The proposed tests appear to check whether the markers individually or combined (see comment about the Context of Use) have the ability to show a population based difference between marker positive and negative. The question is not whether there is a population difference between marker positive and negative groups, but if the inclusion of the biomarker test provides information to enrich a future patient population for poor outcomes at 3-months. When you submit your results, please provide the raw data (a data frame with a row for each observation: reader ID, case ID, biomarker evaluations, and the GOS-E scores). Also, please summarize this data with a table, figure, or other description that captures the distribution of 3-month GOS-E scores in a patient population not evaluated for the proposed markers, the distribution of GOS-E for a biomarker negative population, and the distribution of GOS-E scores for a biomarker positive population. We hope to provide future users of the tool with as much information as possible about the biomarker test performance that would allow future users flexibility in trial design.

7. You plan to evaluate the prognostic performance of one reader evaluating 671 MRI images. This study needs to show the performance of at least three readers. Given the overall study size you determined (1071 observations: Reader 1 reads 671 cases, Reader 2 reads 200 cases, and Reader 3 reads 200 cases), however, we recommend a study of similar size where each reader evaluates the same 350 cases (1050 observations). The same data can be used to evaluate prognostic performance and inter-rater agreement.

8. Please provide individual prognostic performance of each reader (and the corresponding CIs) and the inter-rater agreement for each pair of readers (and the corresponding Cis).

9. You indicated that you expect the study population will yield 20% biomarker positive patients and sized the studies accordingly. Please justify your expectation that 20% of participants will have a scan that is positive for the biomarkers. The precision of the study may be poor if there are less biomarker positive patients in the study than anticipated.

Reader qualifications

10. You indicate that the study readers will be ABR and CAQ certified neuroradiologist. You also indicate that these readers will review the TBI imaging CDE definitions (most recent version, 2012) as training before participating in the study. Finally, you indicate that each reader will use the OsiriX tool to score sets of 25 MRI training cases that illustrate the TBI Imaging CDEs based on their definitions. This training includes criteria for success that is to be achieved before participating. This would indicate that such a level of proficiency is expected from the indicated users of the MDDT (the clinicians evaluating the MRI images according to the biomarkers). This

could be a problem because it is challenging to restrict the indicated users based on training performance. A better option than requiring a level of performance is to simply provide immediate feedback on the 25 training cases. Please eliminate the training success criteria or discuss how it will be implemented in the field.

Sample size

11. Sample size justification (Prognostic performance). You provide a justification of the sample size. The justification sizes the study based on a t-statistic and then scales the size based on a stated efficiency relationship between the t-statistic and the Wilcoxon U-statistic, assuming the data is normally distributed. There is no reference for the efficiency claim and the data are not normally distributed; the data (GOS-E scale) are ordinal with 8 categories. Furthermore, the meaning of the assumed effect size used (0.28 standard deviations in average GOS-E) is unclear; this assumption raises the most concern. The justification should be based on the distribution of the Wilcoxon U-statistic, call it theta, which for reasonable sample sizes is normally distributed. So there is an expression for the standard error of theta that is a function of the sample size and the expected theta (Hanley1982_Radiology_v143p29, assuming the data is transformable to a negative exponential). Continuing, assume that the performance of the biomarker is moderately different from random, say Pr(X1>X2) = 0.55, where X1 is the GOS-E score of a positive biomarker and X2 is that of a negative biomarker. Assume also, as you assumed, that 20% of participants have a scan that is positive for the biomarker. Then you have the following:
    N0 = 0.8 * N
    N1 = 0.2 * N
    theta = 0.55
    Q1 = theta / (2 - theta)
    Q2 = 2*theta*theta / (1 + theta)
    se = sqrt((theta * (1-theta) + (N1 -1)*(Q1 - theta*theta) + (N0 - 1)*(Q2 - theta*theta))/N0/N1)
    N = 671 → se = 0.028
    N = 400 → se = 0.037
    N = 350 → se = 0.039
    N = 300 → se = 0.042
    N = 250 → se = 0.046
    N = 200 → se = 0.052

    Given that the data is ordinal with 8 categories, N=300-400 samples should be adequate for each reader, providing roughly 1 se difference from no separability, Pr(X1>X2) = 0.5.

12. Sample size justification (Inter-rater agreement). You provide a justification of the sample size. The justification begins with a justification of the size needed for a single pair of readers. The null hypothesis is that the positive percent agreement (PPA) is different from 55%. The size justification assumes the true PPA is 65%. The result is an experiment with 300 cases. The justification continues by accounting for the impact of including a third rater; the sample size is scaled by 0.67 from N=300 to 200. The scaling is derived for a kappa statistic that is an average over readers. There are two problems with this approach. We are not dealing with the kappa statistic and this scaling does not account for reader variability. If we are not accounting for reader variability, it is appropriate to size the study so that the agreement rates between each pair of readers is adequately measured. By your calculation, N should be 300.

IV. Other comments for submitter future consideration

While not necessary to be addressed in this MDDT qualification package, the review team would like to communicate the following comments to the TED Initiative.

13. The use of the GOS-E in the proposal is acknowledged but we recommend biomarker validation studies include a spectrum of TBI outcomes measures in order to assess the validity of biomarker for the condition. Moreover, a biomarker must demonstrate a meaningful relationship with the clinical condition.

14. The focus on 3-month outcomes may be useful in the acute population, but future research and development efforts may benefit from analysis of longer term outcomes and patient follow-up. A longitudinal assessment of biomarkers and a possible return to normal range should be considered for future studies. For example, resolution of such imaging features such as contusions may help to verify the utility of the measure.

15. As previously communicated, the submitter should be advised that in general FDA does not endorse use of the same data set to determine biomarker values and validate the tool. In order to validate the biomarker test on an independent data set, the independent data must be withheld from the biomarker and biomarker test development.

16. For a better understanding of prognostic versus predicative marker, please refer to “McShane L. M, et al Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) J Natl Cancer Inst 2005; 97 (16): 1180-1184. doi: 10.1093/jnci/dji237”

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University of Pittsburgh

Date: **April 20, 2017**

Subject: **Pre-Submission Feedback Call 17 April 2017: Minutes**

MDDT Type: **BIOMARKER TEST**

MDDT Tracking Record Number: **MDDT027**

Submission Type: **Amendment to Q161252.A002**

Division: **DIVISION OF RADIOLOGICAL HEALTH**

Branch: **MAGNETIC RESONANCE AND ELECTRONIC PRODUCTS BRANCH**

Lead reviewer: (in bold print) **Daniel Krainak, Ph.D.**

MDDT Name: **OsiriX CDE Software Module**

Complete submitter contact information:

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Amendment to Q161252.A002
Pre-Submission Feedback Call 17 April 2017: Minutes
Q161252.A002 – MDDT027 – OsiriX CDE Software Module - PQP

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Amy Markowitz, JD -UCSF
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CONTEXT OF USE, *AS REVISED*
The OsiriX CDE software module may be used to collect, record and standardize data on the presence of ≥1 brain contusions ~~and/~~or ≥4 foci of hemorrhagic axonal injury (biomarkers) as evaluated by a physician on magnetic resonance images collected within 2 weeks post-injury in mild TBI patients (age 18-65 years) who had presented at an emergency department within 24 hours of injury of injury and who had at that time required a head CT based on ACEP/CDC criteria. The biomarkers are each individually intended as a prognostic enrichment tool to select patients with mild TBI at high risk for poor outcomes at 3 months postinjury (as defined by the extend Glasgow Outcome Scale, or GOS-E) for enrollment in early and pivotal clinical trials to support marketing applications of therapeutic medical devices ~~intended to improve outcomes for mild TBI patients~~.

RESOLUTION: Following the MDDT team's recommendations and our discussion we have revised the COU, indicated by strikethrough of text in red font.

1. You have provided a description of the imaging data used in the MDDT. It is unclear if the chosen imaging correlates will be used in isolation or in conjunction with one another. Please refine the COU to specify whether you are qualifying the biomarkers individually, combined with "OR", or combined with "AND." This information is needed to ensure there is a clear understanding of how the proposed tool will be used.

RESOLUTION: As discussed, the two biomarkers will be evaluated individually; thus the COU is refined to: ≥1

brain contusions or ≥4 foci of hemorrhagic axonal injury. We also clarified that the intent is to validate each biomarker individually. The team will revise the numbers needed to analyze each biomarker, incorporating correction for multiple comparisons to determine the required sample size. High-level presence or absence of either biomarker on MRI would potentially enrich the target population. The COU has been revised, as set forth above.

2. You have stated that the use of the tool may support future medical devices applications to improve outcomes. We suggest deleting the last phrase "intended to improve outcomes for mild TBI patients" from the proposed context of use. This change is requested to ensure the device description and COU may be accurately applied in the future.

RESOLUTION: The phrase "intended to improve outcomes for mild TBI patients" will be deleted from the COU; the COU has been revised, as set forth above.

3. In the context of use, you indicate that the population for the MDDT includes "mild TBI patients (age 18-65 years) who had presented at an emergency department within 24 hours of injury and who had at that time required a head CT based on ACEP/CDC criteria." In the description of the "Type of Evidence to Gather" the studies that you propose seem to be more specific about the study population. You state that, "mild TBI patients age 18-65 years with nonpenetrating head trauma and GCS 13-15 who have undergone acute head CT (e.g., as part of standard clinical care according to ACEP/CDC criteria)." Typically, the study population should be the same as the intended use population (or context of us population for MDDTs), or the differences should be discussed and justified. Please harmonize the study population across the context of use statement or discuss and justify why they are different.

RESOLUTION: The inconsistency in the articulation of the inclusion criteria will be conformed to: "mild TBI patients age 18-65 years with nonpenetrating head trauma and GCS 13-15 who have undergone acute head CT (e.g., as part of standard clinical care according to ACEP/CDC criteria)" throughout the COU statement and analytic plan as well as any other reports.

Study population

4. You provide a reference for the TRACK-TBI *pilot* dataset (Ref. 15), which fully describes the collection of that data. You have planned to use 11 level-1 trauma centers to perform your clinical studies. You also provide a table showing the distribution of age, gender, race, ethnicity, and mechanism of injury in the mild TBI patients, of the TRACK-TBI *non-pilot* data. Please note this needs to be further discussed based on inclusion/exclusion criteria. If there is a reference describing the collection of the *non-pilot* data, please provide that or alternatively, please provide the full clinical protocol or summarize that data collection. In particular, please describe how patients were enrolled (i.e., were they prospectively enrolled from all-comers to the level-1 trauma center based on meeting inclusion and exclusion criteria, whether the evaluators of the final outcome blinded to the original classification of the subjects; whether there were any protocol violations and how they were addressed). Be sure to include the total screened patients, inclusion/exclusion criteria, dates and locations. Without the complete information, the current protocol is incomplete.

RESOLUTION: The complete protocol, including all criteria noted above, for the *currently enrolling* TRACK-TBI study (*non-pilot*) will be included in the qualification package submission along with the published reference for the TRACK-TBI *pilot* dataset.

5. For any analysis based on a subset of subjects chosen randomly from subjects in the clinical validation

study, please justify that the distribution of GOS-E scores in the sample population is roughly similar to that expected for the patient population in the context of use (patients with mild TBI). If the random sample differs from the distribution expected for the patient population in the context of use, we recommend that instead of a completely random sample, you use stratified random sampling with adequate patients across the spectrum of GOS-E scores. You may wish to refer to following CLSI document for more information, "Clinical and Laboratory Standards Institute (CLSI). Quality Assurance for Design Control and Implementation of Immunohistochemistry Assays; Approved Guideline—Second Edition. CLSI document I/LA28-A2 (ISBN 1-56238-745-6). Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2011."

RESOLUTION: The analytic plan will be revised to conduct stratified random sampling with adequate patients across the spectrum of GOS-E scores 8, 7, and ≤6.

Validation of the MRI CDEs, brain contusion and hemorrhagic axonal injury, as prognostic biomarkers in mild TBI

6. In your section on type of evidence to gather, you propose to use Mann-Whitney U test statistics—---a non-parametric test, to test whether the GOS-E score is significantly different between two marker groups---—those with DAI (>= 4 foci of diffuse axonal injury) and those without (<=3 foci) and likewise for the biomarker for brain contusion. The proposed tests appear to check whether the markers individually or combined (see comment about the Context of Use) have the ability to show a population based difference between marker positive and negative. The question is not whether there is a population difference between marker positive and negative groups, but if the inclusion of the biomarker test provides information to enrich a future patient population for poor outcomes at 3-months. When you submit your results, please provide the raw data (a data frame with a row for each observation: reader ID, case ID, biomarker evaluations, and the GOS-E scores). Also, please summarize this data with a table, figure, or other description that captures the distribution of 3-month GOS-E scores in a patient population not evaluated for the proposed markers, the distribution of GOS-E for a biomarker negative population, and the distribution of GOS-E scores for a biomarker positive population. We hope to provide future users of the tool with as much information as possible about the biomarker test performance that would allow future users flexibility in trial design.

RESOLUTION: The team will provide all of the raw data in the submission package for FDA's review, and FDA has confirmed that for the time being FDA will maintain all data as confidential. We will create a data frame with the raw data, as well as the requested summary figure containing the distribution of 3-month GOSE scores as outlined above.

7. You plan to evaluate the prognostic performance of one reader evaluating 671 MRI images. This study needs to show the performance of at least three readers. Given the overall study size you determined (1071 observations: Reader 1 reads 671 cases, Reader 2 reads 200 cases, and Reader 3 reads 200 cases), however, we recommend a study of similar size where each reader evaluates the same 350 cases (1050 observations). The same data can be used to evaluate prognostic performance and inter-rater agreement.

RESOLUTION: The analytic plan will utilize the same patient population for the prognostic and IRR portions of the analysis. As suggested, we will have each of three readers evaluate the same 350 cases, or the number of cases deemed sufficient after the sample size is reevaluated.

8. Please provide individual prognostic performance of each reader (and the corresponding CIs) and the inter-rater agreement for each pair of readers (and the corresponding Cis).

RESOLUTION: We will provide the individual prognostic performance of each reader (and the corresponding CIs) and the inter-rater agreement for each pair of readers (and the corresponding CIs). We will also provide overall estimates with confidence intervals obtained using bootstrapping.

9. You indicated that you expect the study population will yield 20% biomarker positive patients and sized the studies accordingly. Please justify your expectation that 20% of participants will have a scan that is positive for the biomarkers. The precision of the study may be poor if there are less biomarker positive patients in the study than anticipated.

RESOLUTION: The analytical plan will be revised pending confirmation of the percent yield in the current TRACK-TBI 'non-pilot' sample. There was agreement that this could be looked at now, to confirm it is on target. If it is lower, we will revise our power calculations accordingly.

Reader qualifications

10. You indicate that the study readers will be ABR and CAQ certified neuroradiologist. You also indicate that these readers will review the TBI imaging CDE definitions (most recent version, 2012) as training before participating in the study. Finally, you indicate that each reader will use the OsiriX tool to score sets of 25 MRI training cases that illustrate the TBI Imaging CDEs based on their definitions. This training includes criteria for success that is to be achieved before participating. This would indicate that such a level of proficiency is expected from the indicated users of the MDDT (the clinicians evaluating the MRI images according to the biomarkers). This could be a problem because it is challenging to restrict the indicated users based on training performance. A better option than requiring a level of performance is to simply provide immediate feedback on the 25 training cases. Please eliminate the training success criteria or discuss how it will be implemented in the field.

RESOLUTION: We will eliminate the training success criteria from the plan.

Sample size

11. Sample size justification (Prognostic performance). You provide a justification of the sample size. The justification sizes the study based on a t-statistic and then scales the size based on a stated efficiency relationship between the t-statistic and the Wilcoxon U-statistic, assuming the data is normally distributed. There is no reference for the efficiency claim and the data are not normally distributed; the data (GOS-E scale) are ordinal with 8 categories. Furthermore, the meaning of the assumed effect size used (0.28 standard deviations in average GOS-E) is unclear; this assumption raises the most concern. The justification should be based on the distribution of the Wilcoxon U-statistic, call it theta, which for reasonable sample sizes is normally distributed. So there is an expression for the standard error of theta that is a function of the sample size and the expected theta (Hanley1982Radiologyv143p29, assuming the data is transformable to a negative exponential). Continuing, assume that the performance of the biomarker is moderately different from random, say Pr(X1>X2) = 0.55, where X1 is the GOS-E score of a positive biomarker and X2 is that of a negative biomarker. Assume also, as you assumed, that 20% of participants have a scan that is positive for the biomarker. Then you have the following:

N0 = 0.8 * N
N1 = 0.2 * N
theta = 0.55
Q1 = theta / (2 - theta)
Q2 = 2*theta*theta / (1 + theta)

se = sqrt((theta * (1-theta) + (N1 -1)*(Q1 - theta*theta) + (N0 - 1)*(Q2 - theta*theta))/N0/N1)
N = 671 → se = 0.028
N = 400 → se = 0.037
N = 350 → se = 0.039
N = 300 → se = 0.042
N = 250 → se = 0.046
N = 200 → se = 0.052
Given that the data is ordinal with 8 categories, N=300-400 samples should be adequate for each reader, providing roughly 1 se difference from no separability, Pr(X1>X2) = 0.5.

12. Sample size justification (Inter-rater agreement). You provide a justification of the sample size. The justification begins with a justification of the size needed for a single pair of readers. The null hypothesis is that the positive percent agreement (PPA) is different from 55%. The size justification assumes the true PPA is 65%. The result is an experiment with 300 cases. The justification continues by accounting for the impact of including a third rater; the sample size is scaled by 0.67 from N=300 to 200. The scaling is derived for a kappa statistic that is an average over readers. There are two problems with this approach. We are not dealing with the kappa statistic and this scaling does not account for reader variability. If we are not accounting for reader variability, it is appropriate to size the study so that the agreement rates between each pair of readers is adequately measured. By your calculation, N should be 300.

RESOLUTION (COMBINED ITEMS 11 and 12): The analytic plan will be revised, and will not modify the number per group; we will utilize the PPA and NPA approach and average across readers (per Resolution to Items 7 and 8, which take precedence over Items 11 and 12).

While not necessary to be addressed in this MDDT qualification package, the review team would like to communicate the following comments to the TED Initiative.
13. The use of the GOS-E in the proposal is acknowledged but we recommend biomarker validation studies include a spectrum of TBI outcomes measures in order to assess the validity of biomarker for the condition. Moreover, a biomarker must demonstrate a meaningful relationship with the clinical condition.

RESOLUTION: We thank FDA for this recommendation, which will be considered for future analysis of primary and secondary outcomes using the proposed biomarkers and tool, but will not be included in the submission package.

14. The focus on 3-month outcomes may be useful in the acute population, but future research and development efforts may benefit from analysis of longer term outcomes and patient follow-up. A longitudinal assessment of biomarkers and a possible return to normal range should be considered for future studies. For example, resolution of such imaging features such as contusions may help to verify the utility of the measure.
RESOLUTION: We thank FDA for this recommendation, which will be considered for future analysis but will not be included in the submission package.

15. As previously communicated, the submitter should be advised that in general FDA does not endorse use of the same data set to determine biomarker values and validate the tool. In order to validate the biomarker test on an independent data set, the independent data must be withheld from the biomarker and biomarker test development.

RESOLUTION: This confirms that FDA deems acceptable our use of the *currently enrolling* TRACK-TBI study

data (*non-pilot*) as the independent validation set for the analyses.

16. For a better understanding of prognostic versus predicative marker, please refer to “McShane L. M, et al Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) J Natl Cancer Inst 2005; 97 (16): 1180-1184. doi: 10.1093/jnci/dji237”

We thank FDA for this recommendation.

NEXT STEPS: Following review, potential revision, and ultimate acceptance of these Minutes, the TRACK/TED team will undertake the revised analytic plan. When the analyses are completed we will communicate this and take next steps to submit a MDDT Qualification Package.

Appendix 3: Communication 6/14/2018 with FDA regarding upwardly revised sample size

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Subject: MDDT027 - OsiriX CDE Software Module
Division: Division of Radiologic Health
Branch: Magnetic Resonance and Electronic Products
Lead reviewer: Daniel Krainak, PhD

Dear Dr. Krainak:

We would like to provide you with an update on our Qualification Package submission. In March 2018, we compiled 3-month GOS-E, CT, and MR imaging data on several TRACK-TBI patient cohorts. This included the Phase 1 adult MRI cohort, which includes a total of 517 adult MRI patients with characteristics consistent with our stated context of use (patients 18-65 years old with GCS of 13-15 and head CT performed during Emergency Department evaluation) and who successfully completed both 2-week MRI and 3-month GOS-E.

Our MRI biomarker positive rate in this cohort of 517 patients was 15% for contusion and 12% for diffuse axonal injury (DAI), as determined by a single board-certified neuroradiologist. Each of these was lower than the projected approximate positive rate of 20% in our pre-qualification package. Based on the statistical analysis recommended by FDA,[1] we will increase our sample size to 517 from 350. For a biomarker positive rate of 12% and our original proposed sample size of 350, this yields a standard error for the Wilcoxon U statistic of 0.050, which by the FDA statisticians' analysis was not acceptable for providing proof that the biomarker performance is statistically different from random.[1] By increasing the sample size to 517 patients, the standard error drops to 0.0408, which is again within the acceptable range.

We will obtain the additional MRI interpretations from all neuroradiologist readers by the end of June, and submit our qualification package. If you have any concerns with this approach and wish to have a telephone call to discuss, we would be happy to do so.

Sincerely and with best regards,

Esther Yuh, MD, PhD
UCSF Department of Radiology

Amy J. Markowitz, JD
UCSF Department of Neurological Surgery

[1]Pre-Submission Feedback Call Minutes, 17 April 2017, referring to Hanley JA and McNeil BJ, *Radiology* 1982.

From: Krainak, Daniel <Daniel.Krainak@fda.hhs.gov>
Sent: Thursday, June 14, 2018 12:25 PM
To: Yuh, Esther
Cc: Markowitz, Amy; MDDT
Subject: RE: MDDT027 - OsiriX CDE Software Module

Hi Dr. Yuh,

We do not have any concerns with the proposed modifications to increase sample size based on the biomarker positive rates observed in your actual study population as described in your e-mail and attachment.

As a reminder, please submit your qualification package as an informational Q-submission supplement to Q161252 The Qualification Package should be submitted as an "informational meeting" Q-submission based on the guidance document: Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff, published on February 18, 2014. In the cover sheet of this submission please identify that is it a supplement to Q161252. The cover sheet contents should follow the enclosure: Qualification Package Cover Sheet. An example cover sheet was provided with the feedback for Q161252.A002.

The Qualification Package should contain the following information, which is also outlined in the guidance.

I. Description of the MDDT
   a. Measurement(s) provided
   b. Describe tool principle and method of measurement
II. Context of Use, including the disease and/or device area for application of MDDT
III. Evidence to Gathered to Support Qualification
IV. Discussion of the Strength of Evidence to Support
   a. Tool Validity
   b. Plausibility
   c. Extent of Prediction
   d. Capture
V. Assessment of Advantages & Disadvantages
VI. Consent to Public Disclosure and Use

Some updated information is available on the MDDT website here:https://www.fda.gov/MedicalDevices/ScienceandResearch/MedicalDeviceDevelopmentToolsMDDT/).

And here's a link to the updated guidance (August 2017) for your convenience:

Qualification of Medical Device Development Tools - Guidance for Industry, Tool Developers, and Food and Drug Administration Staff (PDF - 174KB).

Note that the guidance includes recommendations for what should be provided in a complete qualification package.

If you have any follow-up questions or otherwise, please feel free to contact me.

Regards,
Dan

From: Krainak, Daniel
Sent: Wednesday, June 13, 2018 9:43 AM
To: 'Yuh, Esther' <Esther.Yuh@ucsf.edu>
Cc: Markowitz, Amy <Amy.Markowitz@ucsf.edu>
Subject: RE: MDDT027 - OsiriX CDE Software Module

Hi Dr. Yuh,

Thanks for the e-mail and question. I'm glad to hear you're making progress with the investigation. I will discuss your proposal with my colleagues and hope to response to you within the next week.

Regards,
Dan

Daniel M. Krainak, Ph.D.
Acting Deputy Director | Division of Radiological Health

Center of Devices and Radiological Health
Office of In Vitro Diagnostics and Radiological Health
U.S. Food and Drug Administration
Tel: 301-796-0478
Daniel.Krainak@fda.hhs.gov

Appendix 4: Description of how imaging data were collected (imaging device models/protocols)

TRACK-TBI MRI SCANNERS:

Site	Vendor	Scanner model and field (Tesla)
1	Siemens	Trio 3T
2a	Siemens	Skyra 3T
2b	Siemens	Trio 3T
3	GE	MR750 3T
4	GE	Signa 3T
5	Siemens	Trio 3T
6	Siemens	Trio 3T
7a	GE	MR750 3T
7b	Siemen	Trio 3T
8	Siemens	Skyra 3T
9	GE	Signa 3T
10	Philips	Achieva 3T
11	Philips	Ingenia 3T

Siemens Trio 3T

SIEMENS MAGNETOM TrioTim syngo MR B17

\\USER\Experiments\TRACK-TBI\QA\Localizer

TA: 0:10 PAT: Off Voxel size: 1.9×1.5×8.0 mm Rel. SNR: 1.00 SIEMENS: gre

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Slice group 1	
Slices	1
Dist. factor	20 %
Position	Isocenter
Orientation	Sagittal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Slice group 2	
Slices	1
Dist. factor	20 %
Position	L6.0 P0.0 H0.0
Orientation	Coronal
Phase enc. dir.	R >> L
Rotation	0.00 deg
Slice group 3	
Slices	1
Dist. factor	20 %
Position	L6.0 P6.0 H0.0
Orientation	Transversal
Phase enc. dir.	R >> L
Rotation	90.00 deg
Phase oversampling	0 %
FoV read	280 mm
FoV phase	100.0 %
Slice thickness	8.0 mm
TR	20 ms
TE	10.00 ms
Averages	1
Concatenations	3
Filter	Raw filter, Prescan Normalize
Coil elements	HEA;HEP

Contrast

TD	0 ms
MTC	Off
Magn. preparation	None
Flip angle	40 deg
Fat suppr.	None
Water suppr.	None
Averaging mode	Short term
Reconstruction	Magnitude
Measurements	1
Multiple series	Off

Resolution

Base resolution	192
Phase resolution	75 %
Phase partial Fourier	Off
Interpolation	Off
PAT mode	None
Matrix Coil Mode	Auto (CP)
Image Filter	Off
Distortion Corr.	Off
Unfiltered images	Off
Prescan Normalize	On
Normalize	Off
B1 filter	Off
Raw filter	On
Intensity	Weak
Slope	25
Elliptical filter	Off

Geometry

Multi-slice mode	Sequential
Series	Ascending
Saturation mode	Standard
Special sat.	None
Tim CT mode	Off

System

Body	Off
HEA	On
HEP	On
Positioning mode	REF
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Adaptive Combine
Auto Coil Select	Default
Shim mode	Tune up
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
Position	Isocenter
Orientation	Transversal
Rotation	0.00 deg
R >> L	350 mm
A >> P	263 mm
F >> H	350 mm

Physio

1st Signal/Mode	None
Segments	1
Dark blood	Off
Resp. control	Off

Inline

Subtract	Off
Liver registration	Off
Std-Dev-Sag	Off
Std-Dev-Cor	Off

Std-Dev-Tra	Off
Std-Dev-Time	Off
MIP-Sag	Off
MIP-Cor	Off
MIP-Tra	Off
MIP-Time	Off
Save original images	On
Wash - In	Off
Wash - Out	Off
TTP	Off
PEI	Off
MIP - time	Off

Sequence

Introduction	On
Dimension	2D
Phase stabilisation	Off
Asymmetric echo	Off
Contrasts	1
Bandwidth	180 Hz/Px
Flow comp.	No
Allowed delay	0 s
RF pulse type	Normal
Gradient mode	Fast
Excitation	Slice-sel.
RF spoiling	On

SIEMENS MAGNETOM TrioTim syngo MR B17

\\USER\Experiments\TRACK-TBI\QA\ADNI Phantom MP-RAGE

TA: 5:12 PAT: 2 Voxel size: 1.1×1.1×1.3 mm Rel. SNR: 1.00 SIEMENS: tfl

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	Off
Wait for user to start	Off
Start measurements	single

Routine

Slab group 1	
Slabs	1
Dist. factor	50 %
Position	Isocenter
Orientation	Sagittal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Phase oversampling	0 %
Slice oversampling	0.0 %
Slices per slab	176
FoV read	270 mm
FoV phase	93.8 %
Slice thickness	1.30 mm
TR	2300 ms
TE	2.93 ms
Averages	1
Concatenations	1
Filter	Prescan Normalize
Coil elements	HEA;HEP

Contrast

Magn. preparation	Non-sel. IR
TI	900 ms
Flip angle	9 deg
Fat suppr.	None
Water suppr.	None
Averaging mode	Long term
Reconstruction	Magnitude
Measurements	1
Multiple series	Off

Resolution

Base resolution	256
Phase resolution	100 %
Slice resolution	100 %
Phase partial Fourier	Off
Slice partial Fourier	Off
Interpolation	Off
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	32
Matrix Coil Mode	Auto (CP)
Reference scan mode	Integrated
Image Filter	Off
Distortion Corr.	Off
Unfiltered images	Off
Prescan Normalize	On
Normalize	Off
B1 filter	Off
Raw filter	Off
Elliptical filter	Off

Geometry

Multi-slice mode	Single shot
Series	Interleaved

System

Body	Off
HEA	On
HEP	On
Positioning mode	REF
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Adaptive Combine
Auto Coil Select	Default
Shim mode	Standard
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
Position	Isocenter
Orientation	Sagittal
Rotation	0.00 deg
F >> H	270 mm
A >> P	254 mm
R >> L	229 mm

Physio

1st Signal/Mode	None
Dark blood	Off
Resp. control	Off

Inline

Subtract	Off
Std-Dev-Sag	Off
Std-Dev-Cor	Off
Std-Dev-Tra	Off
Std-Dev-Time	Off
MIP-Sag	Off
MIP-Cor	Off
MIP-Tra	Off
MIP-Time	Off
Save original images	On

Sequence

Introduction	On
Dimension	3D
Elliptical scanning	Off
Asymmetric echo	Off
Bandwidth	240 Hz/Px
Flow comp.	No
Echo spacing	7 ms

RF pulse type	Fast
Gradient mode	Normal
Excitation	Non-sel.
RF spoiling	On

\\USER\Experiments\TRACK-TBI\QA\Localizer

TA: 0:10 PAT: Off Voxel size: 1.9×1.5×8.0 mm Rel. SNR: 1.00 SIEMENS: gre

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Slice group 1	
Slices	1
Dist. factor	20 %
Position	Isocenter
Orientation	Sagittal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Slice group 2	
Slices	1
Dist. factor	20 %
Position	L6.0 P0.0 H0.0
Orientation	Coronal
Phase enc. dir.	R >> L
Rotation	0.00 deg
Slice group 3	
Slices	1
Dist. factor	20 %
Position	L6.0 P6.0 H0.0
Orientation	Transversal
Phase enc. dir.	R >> L
Rotation	90.00 deg
Phase oversampling	0 %
FoV read	280 mm
FoV phase	100.0 %
Slice thickness	8.0 mm
TR	20 ms
TE	10.00 ms
Averages	1
Concatenations	3
Filter	Raw filter, Prescan Normalize
Coil elements	HEA;HEP

Contrast

TD	0 ms
MTC	Off
Magn. preparation	None
Flip angle	40 deg
Fat suppr.	None
Water suppr.	None
Averaging mode	Short term
Reconstruction	Magnitude
Measurements	1
Multiple series	Off

Resolution

Base resolution	192
Phase resolution	75 %
Phase partial Fourier	Off
Interpolation	Off
PAT mode	None
Matrix Coil Mode	Auto (CP)
Image Filter	Off
Distortion Corr.	Off
Unfiltered images	Off
Prescan Normalize	On
Normalize	Off
B1 filter	Off
Raw filter	On
Intensity	Weak
Slope	25
Elliptical filter	Off

Geometry

Multi-slice mode	Sequential
Series	Ascending
Saturation mode	Standard
Special sat.	None
Tim CT mode	Off

System

Body	Off
HEA	On
HEP	On
Positioning mode	REF
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Adaptive Combine
Auto Coil Select	Default
Shim mode	Tune up
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
Position	Isocenter
Orientation	Transversal
Rotation	0.00 deg
R >> L	350 mm
A >> P	263 mm
F >> H	350 mm

Physio

1st Signal/Mode	None
Segments	1
Dark blood	Off
Resp. control	Off

Inline

Subtract	Off
Liver registration	Off
Std-Dev-Sag	Off
Std-Dev-Cor	Off

Std-Dev-Tra	Off
Std-Dev-Time	Off
MIP-Sag	Off
MIP-Cor	Off
MIP-Tra	Off
MIP-Time	Off
Save original images	On
Wash - In	Off
Wash - Out	Off
TTP	Off
PEI	Off
MIP - time	Off

Sequence

Introduction	On
Dimension	2D
Phase stabilisation	Off
Asymmetric echo	Off
Contrasts	1
Bandwidth	180 Hz/Px
Flow comp.	No
Allowed delay	0 s
RF pulse type	Normal
Gradient mode	Fast
Excitation	Slice-sel.
RF spoiling	On

\\USER\Experiments\TRACK-TBI\QA\BIRN Phantom Resting State

TA: 10:06 PAT: Off Voxel size: 3.3×3.3×3.3 mm Rel. SNR: 1.00 SIEMENS: ep2d_bold

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	Off
Wait for user to start	Off
Start measurements	single

Routine

Slice group 1	
Slices	48
Dist. factor	20 %
Position	Isocenter
Orientation	Transversal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Phase oversampling	0 %
FoV read	212 mm
FoV phase	100.0 %
Slice thickness	3.3 mm
TR	3000 ms
TE	30 ms
Averages	1
Concatenations	1
Filter	Raw filter
Coil elements	HEA;HEP

Contrast

MTC	Off
Flip angle	80 deg
Fat suppr.	Fat sat.
Averaging mode	Long term
Reconstruction	Magnitude
Measurements	200
Delay in TR	0 ms
Multiple series	Off

Resolution

Base resolution	64
Phase resolution	100 %
Phase partial Fourier	Off
Interpolation	Off
PAT mode	None
Matrix Coil Mode	Auto (CP)
Distortion Corr.	Off
Prescan Normalize	Off
Raw filter	On
Intensity	Weak
Slope	25
Elliptical filter	Off
Hamming	Off

Geometry

Multi-slice mode	Interleaved
Series	Interleaved
Special sat.	None

System

Body	Off
HEA	On
HEP	On
Positioning mode	FIX
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Coil Combine Mode	Sum of Squares
Auto Coil Select	Default
Shim mode	Standard
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
Position	Isocenter
Orientation	Transversal
Rotation	0.00 deg
R >> L	212 mm
A >> P	212 mm
F >> H	190 mm

Physio

1st Signal/Mode	None

BOLD

GLM Statistics	Off
Dynamic t-maps	Off
Starting ignore meas	0
Ignore after transition	0
Model transition states	On
Temp. highpass filter	On
Threshold	4.00
Paradigm size	20
Meas[1]	Baseline
Meas[2]	Baseline
Meas[3]	Baseline
Meas[4]	Baseline
Meas[5]	Baseline
Meas[6]	Baseline
Meas[7]	Baseline
Meas[8]	Baseline
Meas[9]	Baseline
Meas[10]	Baseline
Meas[11]	Active
Meas[12]	Active
Meas[13]	Active
Meas[14]	Active
Meas[15]	Active
Meas[16]	Active
Meas[17]	Active
Meas[18]	Active
Meas[19]	Active
Meas[20]	Active
Motion correction	On
Interpolation	3D-K-space
Spatial filter	Off

Sequence

Introduction	Off
Bandwidth	2004 Hz/Px
Free echo spacing	Off
Echo spacing	0.56 ms
EPI factor	64
RF pulse type	Normal
Gradient mode	Fast

\\USER\Experiments\TRACK-TBI\QA\Localizer

TA: 0:10 PAT: Off Voxel size: 1.9×1.5×8.0 mm Rel. SNR: 1.00 SIEMENS: gre

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Slice group 1	
Slices	1
Dist. factor	20 %
Position	Isocenter
Orientation	Sagittal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Slice group 2	
Slices	1
Dist. factor	20 %
Position	L6.0 P0.0 H0.0
Orientation	Coronal
Phase enc. dir.	R >> L
Rotation	0.00 deg
Slice group 3	
Slices	1
Dist. factor	20 %
Position	L6.0 P6.0 H0.0
Orientation	Transversal
Phase enc. dir.	R >> L
Rotation	90.00 deg
Phase oversampling	0 %
FoV read	280 mm
FoV phase	100.0 %
Slice thickness	8.0 mm
TR	20 ms
TE	10.00 ms
Averages	1
Concatenations	3
Filter	Raw filter, Prescan Normalize
Coil elements	HEA;HEP

Contrast

TD	0 ms
MTC	Off
Magn. preparation	None
Flip angle	40 deg
Fat suppr.	None
Water suppr.	None
Averaging mode	Short term
Reconstruction	Magnitude
Measurements	1
Multiple series	Off

Resolution

Base resolution	192
Phase resolution	75 %
Phase partial Fourier	Off
Interpolation	Off
PAT mode	None
Matrix Coil Mode	Auto (CP)
Image Filter	Off
Distortion Corr.	Off
Unfiltered images	Off
Prescan Normalize	On
Normalize	Off
B1 filter	Off
Raw filter	On
Intensity	Weak
Slope	25
Elliptical filter	Off

Geometry

Multi-slice mode	Sequential
Series	Ascending
Saturation mode	Standard
Special sat.	None
Tim CT mode	Off

System

Body	Off
HEA	On
HEP	On
Positioning mode	REF
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Adaptive Combine
Auto Coil Select	Default
Shim mode	Tune up
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
Position	Isocenter
Orientation	Transversal
Rotation	0.00 deg
R >> L	350 mm
A >> P	263 mm
F >> H	350 mm

Physio

1st Signal/Mode	None
Segments	1
Dark blood	Off
Resp. control	Off

Inline

Subtract	Off
Liver registration	Off
Std-Dev-Sag	Off
Std-Dev-Cor	Off

Std-Dev-Tra	Off
Std-Dev-Time	Off
MIP-Sag	Off
MIP-Cor	Off
MIP-Tra	Off
MIP-Time	Off
Save original images	On
Wash - In	Off
Wash - Out	Off
TTP	Off
PEI	Off
MIP - time	Off

Sequence

Introduction	On
Dimension	2D
Phase stabilisation	Off
Asymmetric echo	Off
Contrasts	1
Bandwidth	180 Hz/Px
Flow comp.	No
Allowed delay	0 s
RF pulse type	Normal
Gradient mode	Fast
Excitation	Slice-sel.
RF spoiling	On

\\USER\Experiments\TRACK-TBI\QA\NIST Ice Water Phantom

TA: 5:10 PAT: 2 Voxel size: 1.1×1.1×5.0 mm Rel. SNR: 1.00 SIEMENS: ep2d_diff

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	On
Start measurements	single

Routine

Slice group 1	
Slices	11
Dist. factor	30 %
Position	Isocenter
Orientation	Transversal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Phase oversampling	0 %
FoV read	210 mm
FoV phase	100.0 %
Slice thickness	5.0 mm
TR	10000 ms
TE	98 ms
Averages	4
Concatenations	1
Filter	Elliptical filter
Coil elements	HEA;HEP

Contrast

MTC	Off
Magn. preparation	None
Fat suppr.	Fat sat.
Averaging mode	Long term
Reconstruction	Magnitude
Delay in TR	0 ms

Resolution

Base resolution	188
Phase resolution	100 %
Phase partial Fourier	6/8
Interpolation	Off
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	16
Matrix Coil Mode	Auto (CP)
Reference scan mode	Separate
Distortion Corr.	Off
Prescan Normalize	Off
Raw filter	Off
Elliptical filter	On
Mode	Inplane
Hamming	Off

Geometry

Multi-slice mode	Interleaved
Series	Interleaved
Special sat.	None

System

Body	Off
HEA	On
HEP	On
Positioning mode	REF
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	P >> A
Transversal	F >> H
Coil Combine Mode	Adaptive Combine
Auto Coil Select	Default
Shim mode	Standard
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
Position	Isocenter
Orientation	Transversal
Rotation	0.00 deg
R >> L	210 mm
A >> P	210 mm
F >> H	70 mm

Physio

1st Signal/Mode	None
Resp. control	Off

Diff

Diffusion mode	3-Scan Trace
Diff. weightings	3
b-value 1	0 s/mm²
b-value 2	500 s/mm²
b-value 3	900 s/mm²
Diff. weighted images	Off
Trace weighted images	On
Average ADC maps	On
Individual ADC maps	Off
FA maps	Off
Mosaic	Off
Tensor	Off
Noise level	40
Diff. directions	3

Sequence

Introduction	Off
Bandwidth	1330 Hz/Px
Free echo spacing	Off
Echo spacing	1.09 ms
EPI factor	188
RF pulse type	Normal
Gradient mode	Fast

\\USER\Experiments\TRACK-TBI\QA\NIST Ice Water Phantom lowres

TA: 5:10 PAT: 2 Voxel size: 1.6×1.6×4.0 mm Rel. SNR: 1.00 SIEMENS: ep2d_diff

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	Off
Wait for user to start	Off
Start measurements	single

Routine

Slice group 1	
Slices	11
Dist. factor	0 %
Position	Isocenter
Orientation	Transversal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Phase oversampling	0 %
FoV read	210 mm
FoV phase	100.0 %
Slice thickness	4.0 mm
TR	10000 ms
TE	98 ms
Averages	4
Concatenations	1
Filter	Elliptical filter
Coil elements	HEA;HEP

Contrast

MTC	Off
Magn. preparation	None
Fat suppr.	Fat sat.
Averaging mode	Long term
Reconstruction	Magnitude
Delay in TR	0 ms

Resolution

Base resolution	128
Phase resolution	100 %
Phase partial Fourier	6/8
Interpolation	Off
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	16
Matrix Coil Mode	Auto (CP)
Reference scan mode	Separate
Distortion Corr.	Off
Prescan Normalize	Off
Raw filter	Off
Elliptical filter	On
Mode	Inplane
Hamming	Off

Geometry

Multi-slice mode	Interleaved
Series	Interleaved
Special sat.	None

System

Body	Off
HEA	On
HEP	On
Positioning mode	REF
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	P >> A
Transversal	F >> H
Coil Combine Mode	Adaptive Combine
Auto Coil Select	Default
Shim mode	Standard
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
Position	Isocenter
Orientation	Transversal
Rotation	0.00 deg
R >> L	210 mm
A >> P	210 mm
F >> H	44 mm

Physio

1st Signal/Mode	None
Resp. control	Off

Diff

Diffusion mode	3-Scan Trace
Diff. weightings	3
b-value 1	0 s/mm²
b-value 2	500 s/mm²
b-value 3	900 s/mm²
Diff. weighted images	Off
Trace weighted images	On
Average ADC maps	On
Individual ADC maps	Off
FA maps	Off
Mosaic	Off
Tensor	Off
Noise level	40
Diff. directions	3

Sequence

Introduction	Off
Bandwidth	1302 Hz/Px
Free echo spacing	Off
Echo spacing	0.85 ms
EPI factor	128
RF pulse type	Normal
Gradient mode	Fast

\\USER\Experiments\TRACK-TBI\TBI Patient\Localizer (NO ANGULATIONS FOR STUDY)

TA: 0:10 PAT: Off Voxel size: 1.9×1.5×8.0 mm Rel. SNR: 1.00 SIEMENS: gre

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Slice group 1	
Slices	1
Dist. factor	20 %
Position	Isocenter
Orientation	Sagittal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Slice group 2	
Slices	1
Dist. factor	20 %
Position	L6.0 P0.0 H0.0
Orientation	Coronal
Phase enc. dir.	R >> L
Rotation	0.00 deg
Slice group 3	
Slices	1
Dist. factor	20 %
Position	L6.0 P6.0 H0.0
Orientation	Transversal
Phase enc. dir.	R >> L
Rotation	90.00 deg
Phase oversampling	0 %
FoV read	280 mm
FoV phase	100.0 %
Slice thickness	8.0 mm
TR	20 ms
TE	10.00 ms
Averages	1
Concatenations	3
Filter	Raw filter, Prescan Normalize
Coil elements	HEA;HEP

Contrast

TD	0 ms
MTC	Off
Magn. preparation	None
Flip angle	40 deg
Fat suppr.	None
Water suppr.	None
Averaging mode	Short term
Reconstruction	Magnitude
Measurements	1
Multiple series	Off

Resolution

Base resolution	192
Phase resolution	75 %
Phase partial Fourier	Off
Interpolation	Off
PAT mode	None
Matrix Coil Mode	Auto (CP)
Image Filter	Off
Distortion Corr.	Off
Unfiltered images	Off
Prescan Normalize	On
Normalize	Off
B1 filter	Off
Raw filter	On
Intensity	Weak
Slope	25
Elliptical filter	Off

Geometry

Multi-slice mode	Sequential
Series	Ascending
Saturation mode	Standard
Special sat.	None
Tim CT mode	Off

System

Body	Off
HEA	On
HEP	On
Positioning mode	REF
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Adaptive Combine
Auto Coil Select	Default
Shim mode	Tune up
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
Position	Isocenter
Orientation	Transversal
Rotation	0.00 deg
R >> L	350 mm
A >> P	263 mm
F >> H	350 mm

Physio

1st Signal/Mode	None
Segments	1
Dark blood	Off
Resp. control	Off

Inline

Subtract	Off
Liver registration	Off
Std-Dev-Sag	Off
Std-Dev-Cor	Off

Std-Dev-Tra	Off
Std-Dev-Time	Off
MIP-Sag	Off
MIP-Cor	Off
MIP-Tra	Off
MIP-Time	Off
Save original images	On
Wash - In	Off
Wash - Out	Off
TTP	Off
PEI	Off
MIP - time	Off

Sequence

Introduction	On
Dimension	2D
Phase stabilisation	Off
Asymmetric echo	Off
Contrasts	1
Bandwidth	180 Hz/Px
Flow comp.	No
Allowed delay	0 s
RF pulse type	Normal
Gradient mode	Fast
Excitation	Slice-sel.
RF spoiling	On

SIEMENS MAGNETOM TrioTim syngo MR B17

\\USER\Experiments\TRACK-TBI\TBI Patient\MP-RAGE

TA: 9:14 PAT: Off Voxel size: 1.0×1.0×1.2 mm Rel. SNR: 1.00 SIEMENS: tfl

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Slab group 1	
Slabs	1
Dist. factor	50 %
Position	Isocenter
Orientation	Sagittal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Phase oversampling	0 %
Slice oversampling	0.0 %
Slices per slab	176
FoV read	256 mm
FoV phase	93.8 %
Slice thickness	1.20 mm
TR	2300 ms
TE	2.96 ms
Averages	1
Concatenations	1
Filter	Prescan Normalize
Coil elements	HEA;HEP

Contrast

Magn. preparation	Non-sel. IR
TI	900 ms
Flip angle	9 deg
Fat suppr.	None
Water suppr.	None
Averaging mode	Long term
Reconstruction	Magnitude
Measurements	1
Multiple series	Off

Resolution

Base resolution	256
Phase resolution	100 %
Slice resolution	100 %
Phase partial Fourier	Off
Slice partial Fourier	Off
Interpolation	Off
PAT mode	None
Matrix Coil Mode	Auto (CP)
Image Filter	Off
Distortion Corr.	Off
Unfiltered images	Off
Prescan Normalize	On
Normalize	Off
B1 filter	Off
Raw filter	Off
Elliptical filter	Off

Geometry

Multi-slice mode	Single shot
Series	Interleaved

System

Body	Off
HEA	On
HEP	On
Positioning mode	REF
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Adaptive Combine
Auto Coil Select	Default
Shim mode	Standard
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
Position	Isocenter
Orientation	Sagittal
Rotation	0.00 deg
F >> H	256 mm
A >> P	240 mm
R >> L	212 mm

Physio

1st Signal/Mode	None
Dark blood	Off
Resp. control	Off

Inline

Subtract	Off
Std-Dev-Sag	Off
Std-Dev-Cor	Off
Std-Dev-Tra	Off
Std-Dev-Time	Off
MIP-Sag	Off
MIP-Cor	Off
MIP-Tra	Off
MIP-Time	Off
Save original images	On

Sequence

Introduction	On
Dimension	3D
Elliptical scanning	Off
Asymmetric echo	Off
Bandwidth	240 Hz/Px
Flow comp.	No
Echo spacing	7.1 ms
RF pulse type	Fast
Gradient mode	Normal
Excitation	Non-sel.

RF spoiling	On

\\USER\Experiments\TRACK-TBI\TBI Patient\3D T2star GRE

TA: 7:18 PAT: 2 Voxel size: 1.3×1.3×1.6 mm Rel. SNR: 1.00 SIEMENS: gre

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Slab group 1	
Slabs	1
Dist. factor	20 %
Position	Isocenter
Orientation	Sagittal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Phase oversampling	0 %
Slice oversampling	0.0 %
Slices per slab	128
FoV read	256 mm
FoV phase	93.8 %
Slice thickness	1.60 mm
TR	45 ms
TE	25.00 ms
Averages	1
Concatenations	1
Filter	Distortion Corr.(3D), Prescan Normalize
Coil elements	HEA;HEP

Contrast

MTC	Off
Magn. preparation	None
Flip angle	10 deg
Fat suppr.	Fat sat.
Water suppr.	None
Averaging mode	Short term
Reconstruction	Magn./Phase
Measurements	1
Multiple series	Each measurement

Resolution

Base resolution	192
Phase resolution	100 %
Slice resolution	100 %
Phase partial Fourier	Off
Slice partial Fourier	6/8
Interpolation	Off
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	24
Matrix Coil Mode	Auto (CP)
Reference scan mode	Integrated
Image Filter	Off
Distortion Corr.	On
Mode	3D
Unfiltered images	On
Unfiltered images	Off
Prescan Normalize	On
Normalize	Off
B1 filter	Off
Raw filter	Off
Elliptical filter	Off

Geometry

Multi-slice mode	Interleaved
Series	Interleaved
Saturation mode	Standard
Special sat.	None
Tim CT mode	Off

System

Body	Off
HEA	On
HEP	On
Positioning mode	FIX
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Adaptive Combine
Auto Coil Select	Default
Shim mode	Standard
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
Position	Isocenter
Orientation	Sagittal
Rotation	0.00 deg
F >> H	256 mm
A >> P	240 mm
R >> L	205 mm

Physio

1st Signal/Mode	None
Segments	1
Dark blood	Off
Resp. control	Off

Inline

Subtract	Off
Liver registration	Off
Std-Dev-Sag	Off
Std-Dev-Cor	Off
Std-Dev-Tra	Off
Std-Dev-Time	Off
MIP-Sag	Off
MIP-Cor	Off
MIP-Tra	Off
MIP-Time	Off
Save original images	On

Wash - In	Off
Wash - Out	Off
TTP	Off
PEI	Off
MIP - time	Off

Sequence

Introduction	On
Dimension	3D
Elliptical scanning	Off
Phase stabilisation	Off
Asymmetric echo	Allowed
Contrasts	1
Bandwidth	160 Hz/Px
Flow comp.	Yes
Allowed delay	0 s
RF pulse type	Normal
Gradient mode	Fast
Excitation	Slab-sel.
RF spoiling	On

\\USER\Experiments\TRACK-TBI\TBI Patient\DTI 64 dir, b=1300

TA: 10:14 PAT: 2 Voxel size: 2.7×2.7×2.7 mm Rel. SNR: 1.00 SIEMENS: ep2d_diff

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Slice group 1	
Slices	59
Dist. factor	0 %
Position	Isocenter
Orientation	Transversal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Phase oversampling	0 %
FoV read	350 mm
FoV phase	65.6 %
Slice thickness	2.7 mm
TR	9000 ms
TE	94 ms
Averages	1
Concatenations	1
Filter	Prescan Normalize
Coil elements	HEA;HEP

Contrast

MTC	Off
Magn. preparation	None
Fat suppr.	Fat sat.
Averaging mode	Long term
Reconstruction	Magnitude
Delay in TR	0 ms
Multiple series	Off

Resolution

Base resolution	128
Phase resolution	100 %
Phase partial Fourier	Off
Interpolation	Off
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	38
Matrix Coil Mode	Auto (CP)
Reference scan mode	Separate
Distortion Corr.	Off
Prescan Normalize	On
Raw filter	On
Elliptical filter	Off
Hamming	Off

Geometry

Multi-slice mode	Interleaved
Series	Interleaved
Special sat.	None

System

Body	Off
HEP	On
HEA	On
SP4	Off
SP2	Off
SP8	Off
SP6	Off
SP3	Off
SP1	Off
SP7	Off
SP5	Off
Positioning mode	REF
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Coil Combine Mode	Adaptive Combine
Auto Coil Select	Default
Shim mode	Standard
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
Position	Isocenter
Orientation	Transversal
Rotation	0.00 deg
R >> L	350 mm
A >> P	230 mm
F >> H	160 mm

Physio

1st Signal/Mode	None
Resp. control	Off

Diff

Diffusion mode	MDDW
Diff. weightings	2
b-value 1	0 s/mm²
b-value 2	1300 s/mm²
Diff. weighted images	On
Trace weighted images	On
Average ADC maps	On
Individual ADC maps	Off
FA maps	On
Mosaic	On
Tensor	Off
Noise level	30
Diff. directions	64

Sequence

Introduction	On
Bandwidth	1346 Hz/Px
Free echo spacing	Off
Echo spacing	0.83 ms
EPI factor	84
RF pulse type	Normal

Gradient mode	Fast

\\USER\Experiments\TRACK-TBI\TBI Patient\DTI 64 dir, b=0, 8 averages

TA: 1:41 PAT: 2 Voxel size: 2.7×2.7×2.7 mm Rel. SNR: 1.00 SIEMENS: ep2d_diff

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	Off
Wait for user to start	Off
Start measurements	single

Routine

Slice group 1	
Slices	59
Dist. factor	0 %
Position	Isocenter
Orientation	Transversal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Phase oversampling	0 %
FoV read	350 mm
FoV phase	65.6 %
Slice thickness	2.7 mm
TR	9000 ms
TE	94 ms
Averages	8
Concatenations	1
Filter	Prescan Normalize
Coil elements	HEA;HEP

Contrast

MTC	Off
Magn. preparation	None
Fat suppr.	Fat sat.
Averaging mode	Long term
Reconstruction	Magnitude
Delay in TR	0 ms
Multiple series	Off

Resolution

Base resolution	128
Phase resolution	100 %
Phase partial Fourier	Off
Interpolation	Off
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	38
Matrix Coil Mode	Auto (CP)
Reference scan mode	Separate
Distortion Corr.	Off
Prescan Normalize	On
Raw filter	On
Elliptical filter	Off
Hamming	Off

Geometry

Multi-slice mode	Interleaved
Series	Interleaved
Special sat.	None

System

Body	Off
HEP	On
HEA	On
SP4	Off
SP2	Off
SP8	Off
SP6	Off
SP3	Off
SP1	Off
SP7	Off
SP5	Off
Positioning mode	FIX
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Coil Combine Mode	Adaptive Combine
Auto Coil Select	Default
Shim mode	Standard
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
Position	Isocenter
Orientation	Transversal
Rotation	0.00 deg
R >> L	350 mm
A >> P	230 mm
F >> H	160 mm

Physio

1st Signal/Mode	None
Resp. control	Off

Diff

Diffusion mode	MDDW
Diff. weightings	1
b-value	0 s/mm²
Diff. weighted images	On
Trace weighted images	Off
Average ADC maps	Off
Individual ADC maps	Off
FA maps	Off
Mosaic	Off
Tensor	Off
Noise level	30
Diff. directions	64

Sequence

Introduction	On
Bandwidth	1346 Hz/Px
Free echo spacing	Off
Echo spacing	0.83 ms
EPI factor	84
RF pulse type	Normal
Gradient mode	Fast

\\USER\Experiments\TRACK-TBI\TBI Patient\Resting State fMRI

TA: 10:06 PAT: Off Voxel size: 3.3×3.3×3.3 mm Rel. SNR: 1.00 SIEMENS: ep2d_bold

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Slice group 1	
Slices	48
Dist. factor	20 %
Position	Isocenter
Orientation	Transversal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Phase oversampling	0 %
FoV read	212 mm
FoV phase	100.0 %
Slice thickness	3.3 mm
TR	3000 ms
TE	30 ms
Averages	1
Concatenations	1
Filter	Raw filter
Coil elements	HEA;HEP

Contrast

MTC	Off
Flip angle	80 deg
Fat suppr.	Fat sat.
Averaging mode	Long term
Reconstruction	Magnitude
Measurements	200
Delay in TR	0 ms
Multiple series	Off

Resolution

Base resolution	64
Phase resolution	100 %
Phase partial Fourier	Off
Interpolation	Off
PAT mode	None
Matrix Coil Mode	Auto (CP)
Distortion Corr.	Off
Prescan Normalize	Off
Raw filter	On
Intensity	Weak
Slope	25
Elliptical filter	Off
Hamming	Off

Geometry

Multi-slice mode	Interleaved
Series	Interleaved
Special sat.	None

System

Body	Off
HEA	On
HEP	On
Positioning mode	FIX
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Coil Combine Mode	Sum of Squares
Auto Coil Select	Default
Shim mode	Standard
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
Position	Isocenter
Orientation	Transversal
Rotation	0.00 deg
R >> L	212 mm
A >> P	212 mm
F >> H	190 mm

Physio

1st Signal/Mode	None

BOLD

GLM Statistics	Off
Dynamic t-maps	Off
Starting ignore meas	0
Ignore after transition	0
Model transition states	On
Temp. highpass filter	On
Threshold	4.00
Paradigm size	20
Meas[1]	Baseline
Meas[2]	Baseline
Meas[3]	Baseline
Meas[4]	Baseline
Meas[5]	Baseline
Meas[6]	Baseline
Meas[7]	Baseline
Meas[8]	Baseline
Meas[9]	Baseline
Meas[10]	Baseline
Meas[11]	Active
Meas[12]	Active
Meas[13]	Active
Meas[14]	Active
Meas[15]	Active
Meas[16]	Active
Meas[17]	Active
Meas[18]	Active
Meas[19]	Active
Meas[20]	Active
Motion correction	On
Interpolation	3D-K-space
Spatial filter	Off

Sequence

Introduction	Off
Bandwidth	2004 Hz/Px
Free echo spacing	Off
Echo spacing	0.56 ms
EPI factor	64
RF pulse type	Normal
Gradient mode	Fast

\\USER\Experiments\TRACK-TBI\TBI Patient\3D TFLR

TA: 7:50 PAT: 2 Voxel size: 1.0×1.0×1.2 mm Rel. SNR: 1.00 SIEMENS: tse_vfl

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Slab group 1	
Slabs	1
Position	Isocenter
Orientation	Sagittal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Phase oversampling	0 %
Slice oversampling	18.2 %
Slices per slab	176
FoV read	256 mm
FoV phase	93.8 %
Slice thickness	1.20 mm
TR	6000 ms
TE	390 ms
Averages	1.0
Concatenations	1
Filter	Raw filter, Prescan Normalize
Coil elements	HEA;HEP

Contrast

MTC	Off
Magn. preparation	Non-sel. IR
TI	2100 ms
Fat suppr.	None
Water suppr.	None
Restore magn.	Off
Reconstruction	Magnitude
Measurements	1
Multiple series	Each measurement

Resolution

Base resolution	256
Phase resolution	101 %
Slice resolution	100 %
Phase partial Fourier	Allowed
Slice partial Fourier	6/8
Interpolation	On
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	24
Matrix Coil Mode	Auto (CP)
Reference scan mode	Integrated
Image Filter	Off
Distortion Corr.	Off
Unfiltered images	Off
Prescan Normalize	On
Normalize	Off
B1 filter	Off
Raw filter	On
Intensity	Weak
Slope	25
Elliptical filter	Off

Geometry

Special sat.	None

System

Body	Off
HEA	On
HEP	On
Positioning mode	FIX
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Adaptive Combine
Auto Coil Select	Default
Shim mode	Standard
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
Position	Isocenter
Orientation	Sagittal
Rotation	0.00 deg
F >> H	256 mm
A >> P	240 mm
R >> L	212 mm

Physio

1st Signal/Mode	None
Dark blood	Off
Resp. control	Off

Inline

Subtract	Off
Std-Dev-Sag	Off
Std-Dev-Cor	Off
Std-Dev-Tra	Off
Std-Dev-Time	Off
MIP-Sag	Off
MIP-Cor	Off
MIP-Tra	Off
MIP-Time	Off
Save original images	On

Sequence

Introduction	On
Dimension	3D
Bandwidth	781 Hz/Px
Flow comp.	No
Allowed delay	30 s
Echo spacing	3.26 ms
Adiabatic-mode	Off

Define	Echo trains
Turbo factor	133
Slice turbo factor	2
Echo trains per slice	1
Echo train duration	818
RF pulse type	Normal
Gradient mode	Fast
Excitation	Non-sel.
Flip angle mode	T2 var

\\USER\Experiments\TRACK-TBI\TBI Patient\3D T2 TSE

TA: 4:26 PAT: 2 Voxel size: 1.0×1.0×1.2 mm Rel. SNR: 1.00 SIEMENS: tse_vfl

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	Off
Wait for user to start	Off
Start measurements	single

Routine

Slab group 1	
Slabs	1
Position	Isocenter
Orientation	Sagittal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Phase oversampling	0 %
Slice oversampling	0.0 %
Slices per slab	176
FoV read	256 mm
FoV phase	93.8 %
Slice thickness	1.20 mm
TR	3000 ms
TE	224 ms
Averages	1.0
Concatenations	1
Filter	Raw filter, Prescan Normalize
Coil elements	HEA;HEP

Contrast

MTC	Off
Magn. preparation	None
Fat suppr.	None
Water suppr.	None
Restore magn.	Off
Reconstruction	Magnitude
Measurements	1
Multiple series	Each measurement

Resolution

Base resolution	256
Phase resolution	101 %
Slice resolution	100 %
Phase partial Fourier	Allowed
Slice partial Fourier	Off
Interpolation	On
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	24
Matrix Coil Mode	Auto (CP)
Reference scan mode	Integrated
Image Filter	Off
Distortion Corr.	Off
Unfiltered images	Off
Prescan Normalize	On
Normalize	Off
B1 filter	Off
Raw filter	On
Intensity	Weak
Slope	25
Elliptical filter	Off

Geometry

Special sat.	None

System

Body	Off
HEA	On
HEP	On
Positioning mode	FIX
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Adaptive Combine
Auto Coil Select	Default
Shim mode	Tune up
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
Position	Isocenter
Orientation	Transversal
Rotation	0.00 deg
R >> L	350 mm
A >> P	263 mm
F >> H	350 mm

Physio

1st Signal/Mode	None
Dark blood	Off
Resp. control	Off

Inline

Subtract	Off
Std-Dev-Sag	Off
Std-Dev-Cor	Off
Std-Dev-Tra	Off
Std-Dev-Time	Off
MIP-Sag	Off
MIP-Cor	Off
MIP-Tra	Off
MIP-Time	Off
Save original images	On

Sequence

Introduction	On
Dimension	3D
Bandwidth	751 Hz/Px
Flow comp.	No
Allowed delay	30 s
Echo spacing	3.32 ms
Adiabatic-mode	Off

Define	Echo trains
Turbo factor	133
Slice turbo factor	2
Echo trains per slice	1
Echo train duration	661
RF pulse type	Normal
Gradient mode	Fast
Excitation	Non-sel.
Flip angle mode	T2 var

Siemens Skyra 3T

SIEMENS MAGNETOM Skyra syngo MR D13

\\USER\Schnyer\TRACK-TBI SKYRA\TRACK TBI SUBJECT\localizer
TA:0:10 PAT:Off Voxel size:1.5×1.5×8.0 mm Rel. SNR:1.00 :fl

Properties

Prio Recon	Off
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Wait for user to start	Off
Start measurements	single

Routine

Nr. of slice groups	3
Slices	1
Dist. factor	20 %
Position	Isocenter
Orientation	Sagittal
Phase enc. dir.	A >> P
AutoAlign	---
Phase oversampling	0 %
FoV read	280 mm
FoV phase	100.0 %
Slice thickness	8.0 mm
TR	20.0 ms
TE	5.00 ms
Averages	1
Concatenations	3
Filter	Raw filter, Prescan Normalize
Coil elements	HE1-4

Contrast	
TD	0 ms
MTC	Off
Magn. preparation	None
Flip angle	40 deg
Fat suppr.	None
Water suppr.	None
SWI	Off
Averaging mode	Short term
Measurements	1
Reconstruction	Magnitude
Multiple series	Off

Resolution	
Base resolution	192
Phase resolution	75 %
Phase partial Fourier	Off
Interpolation	Off
PAT mode	None
Image Filter	Off
Distortion Corr.	Off
TD	0 ms
Unfiltered images	Off
Prescan Normalize	On
Normalize	Off
B1 filter	Off
Raw filter	On
Intensity	Weak
Slope	25
Elliptical filter	Off

Geometry

Nr. of slice groups	3
Slices	1
Dist. factor	20 %
Position	Isocenter
Phase enc. dir.	A >> P
Phase oversampling	0 %
Multi-slice mode	Sequential
Series	Ascending
Saturation mode	Standard
Nr. of sat. regions	0
Position mode	L-P-H
Fat suppr.	None
Water suppr.	None
Special sat.	None
Special sat.	None
Table position	P

System

Body	Off
HE1	On
HE3	On
NE1	Off
HE2	On
HE4	On
NE2	Off
Position mode	L-P-H
Positioning mode	REF
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Adaptive Combine
AutoAlign	---
Coil Select Mode	Default
Shim mode	Tune up
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Dominant Fat	Off
Assume Silicone	Off
Adjustment Tolerance	Auto
? Ref. amplitude 1H	0.000 V
Position	Isocenter
Rotation	0.00 deg
R >> L	350 mm
A >> P	263 mm
F >> H	350 mm
Frequency 1H	123.191272 MHz
Correction factor	1
SRFExcit 1H	129.382 V
Gain	High
Table position	0 mm
Img. Scale. Cor.	1.000

Physio

1st Signal/Mode	None
Segments	1
Magn. preparation	None
Dark blood	Off
Resp. control	Off

Inline

Distortion correction	Off

Sequence

Introduction	On
Dimension	2D
Averaging mode	Short term
Multi-slice mode	Sequential
Asymmetric echo	Off
Contrasts	1
Bandwidth	180 Hz/Px
Flow comp.	No
Allowed delay	0 s
RF pulse type	Normal
Gradient mode	Fast
Excitation	Slice-sel.
RF spoiling	On
TX/RX delta frequency	0 Hz
TX Nucleus	None
TX delta frequency	0 Hz
Coil elements	HE1-4
Acquisition duration	0 ms
Mode	Off

BOLD

Subtract	Off
Liver registration	Off
StdDev	Off
MIP-Sag	Off
MIP-Cor	Off
MIP-Tra	Off
MIP-Time	Off
Save original images	On
Distortion Corr.	Off
Contrasts	1
Save original images	On
Wash - In	Off
Wash - Out	Off
TTP	Off
PEI	Off
MIP - time	Off

SIEMENS MAGNETOM Skyra syngo MR D13

\\USER\Schnyer\TRACK-TBI SKYRA\TRACK TBI SUBJECT\SAG MPRAGE
TA:9:14 PAT:Off Voxel size:1.0×1.0×1.2 mm Rel. SNR:1.00 :tfl

Properties

Prio Recon	Off
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Wait for user to start	Off
Start measurements	single

Routine

Nr. of slab groups	1
Slabs	1
Dist. factor	50 %
Position	Isocenter
Orientation	Sagittal
Phase enc. dir.	A >> P
AutoAlign	---
Phase oversampling	0 %
Slice oversampling	0.0 %
FoV read	256 mm
FoV phase	93.8 %
Slice thickness	1.20 mm
TR	2300.0 ms
TE	2.98 ms
Averages	1
Concatenations	1
Filter	Prescan Normalize
Coil elements	HE1-4

Contrast

Magn. preparation	Non-sel. IR
TI	900 ms
Flip angle	9 deg
Fat suppr.	None
Water suppr.	None
Averaging mode	Long term
Measurements	1
Reconstruction	Magnitude
Multiple series	Off

Resolution

Base resolution	256
Phase resolution	100 %
Phase partial Fourier	Off
Interpolation	Off
PAT mode	None
Image Filter	Off
Distortion Corr.	Off
Unfiltered images	Off
Prescan Normalize	On
Normalize	Off
B1 filter	Off
Raw filter	Off
Elliptical filter	Off
Slice resolution	100 %
Slice partial Fourier	Off

Geometry

Nr. of slab groups	1
Slabs	1
Dist. factor	50 %
Position	Isocenter
Phase enc. dir.	A >> P
Phase oversampling	0 %
Slice oversampling	0.0 %
Slices per slab	176
Multi-slice mode	Single shot
Series	Interleaved
Nr. of sat. regions	0
Position mode	L-P-H
Fat suppr.	None
Water suppr.	None
Special sat.	None
Table position	P

System

Body	Off
HE1	On
HE3	On
NE1	Off
HE2	On
HE4	On
NE2	Off
Position mode	L-P-H
Positioning mode	REF
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Adaptive Combine
AutoAlign	---
Coil Select Mode	Default
Shim mode	Standard
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Dominant Fat	Off
Assume Silicone	Off
Adjustment Tolerance	Auto
? Ref. amplitude 1H	0.000 V
Position	Isocenter
Rotation	0.00 deg
F >> H	256 mm
A >> P	240 mm
R >> L	212 mm
Frequency 1H	123.191272 MHz
Correction factor	1
SLoopIRns1 1H	611.244 V
Gain	Low
Table position	0 mm
Img. Scale. Cor.	1.000

Physio	
1st Signal/Mode	None
Magn. preparation	Non-sel. IR
TI	900 ms
Dark blood	Off
Resp. control	Off

Inline	
Distortion correction	Off

Sequence	
Introduction	On
Dimension	3D
Elliptical scanning	Off
Averaging mode	Long term
Multi-slice mode	Single shot
Reordering	Linear
Asymmetric echo	Off
Bandwidth	240 Hz/Px
Flow comp.	No
Echo spacing	7.1 ms
Turbo factor	176
RF pulse type	Fast
Gradient mode	Normal
Excitation	Non-sel.
RF spoiling	On
TX/RX delta frequency	0 Hz
TX Nucleus	None
TX delta frequency	0 Hz
Coil elements	HE1-4
Acquisition duration	0 ms
Mode	Off

BOLD	
Subtract	Off
StdDev	Off
MIP-Sag	Off
MIP-Cor	Off
MIP-Tra	Off
MIP-Time	Off
Save original images	On
Distortion Corr.	Off
Save original images	On

SIEMENS MAGNETOM Skyra syngo MR D13

\\USER\Schnyer\TRACK-TBI SKYRA\TRACK TBI SUBJECT\SAG SWI 3D
TA:7:02 PAT:2 Voxel size:1.3×1.3×1.6 mm Rel. SNR:1.00 :fl_r

Properties

Prio Recon	Off
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Wait for user to start	Off
Start measurements	single

Routine

Nr. of slab groups	1
Slabs	1
Dist. factor	20 %
Position	Isocenter
Orientation	Sagittal
Phase enc. dir.	A >> P
AutoAlign	---
Phase oversampling	0 %
Slice oversampling	0.0 %
FoV read	256 mm
FoV phase	100.0 %
Slice thickness	1.60 mm
TR	47.0 ms
TE	25.00 ms
Averages	1
Concatenations	1
Filter	Distortion Corr.(2D), Prescan Normalize
Coil elements	HE1-4

Contrast

MTC	Off
Magn. preparation	None
Flip angle	10 deg
Fat suppr.	Fat sat.
Water suppr.	None
SWI	Off
Averaging mode	Short term
Measurements	1
Reconstruction	Magn./Phase
Multiple series	Each measurement

Resolution

Base resolution	192
Phase resolution	100 %
Phase partial Fourier	Off
Interpolation	Off
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	24
Reference scan mode	Integrated
Image Filter	Off
Distortion Corr.	On
Accel. factor 3D	1
Mode	2D
Unfiltered images	Off
Unfiltered images	Off
Prescan Normalize	On
Normalize	Off
B1 filter	Off
Raw filter	Off
Elliptical filter	Off
Slice resolution	100 %
Slice partial Fourier	6/8

Geometry

Nr. of slab groups	1
Slabs	1
Dist. factor	20 %
Position	Isocenter
Phase enc. dir.	A >> P
Phase oversampling	0 %
Slice oversampling	0.0 %
Slices per slab	128
Multi-slice mode	Interleaved
Series	Interleaved
Saturation mode	Standard
Nr. of sat. regions	0
Position mode	L-P-H
Fat suppr.	Fat sat.
Water suppr.	None
Special sat.	None
Special sat.	None
Table position	P

System

Body	Off
HE1	On
HE3	On
NE1	Off
HE2	On
HE4	On
NE2	Off
Position mode	L-P-H
Positioning mode	FIX
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Adaptive Combine
AutoAlign	---
Coil Select Mode	Default
Shim mode	Standard
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Dominant Fat	Off
Assume Silicone	Off
Adjustment Tolerance	Auto
? Ref. amplitude 1H	0.000 V
Position	Isocenter
Rotation	0.00 deg
F >> H	256 mm
A >> P	256 mm
R >> L	205 mm
Frequency 1H	123.191272 MHz
Correction factor	1
greFSCSatNS 1H	100.576 V
Gain	Low
Table position	0 mm
Img. Scale. Cor.	1.000

Physio	
1st Signal/Mode	None
Segments	1
Magn. preparation	None
Dark blood	Off
Resp. control	Off

Inline	
Distortion correction	Off

Sequence	
Introduction	On
Dimension	3D
Elliptical scanning	On
Averaging mode	Short term
Multi-slice mode	Interleaved
Asymmetric echo	Off
Contrasts	1
Bandwidth	150 Hz/Px
Flow comp.	Yes
Allowed delay	0 s
RF pulse type	Normal
Gradient mode	Fast
Excitation	Slab-sel.
RF spoiling	On
TX/RX delta frequency	0 Hz
TX Nucleus	None
TX delta frequency	0 Hz
Coil elements	HE1-4
Acquisition duration	0 ms
Mode	Off

BOLD

Subtract	Off
Liver registration	Off
StdDev	Off
MIP-Sag	Off
MIP-Cor	Off
MIP-Tra	Off
MIP-Time	Off
Save original images	On
Distortion Corr.	On
Mode	2D
Unfiltered images	Off
Contrasts	1
Save original images	On
Wash - In	Off
Wash - Out	Off
TTP	Off
PEI	Off
MIP - time	Off

SIEMENS MAGNETOM Skyra syngo MR D13

\\USER\Schnyer\TRACK-TBI SKYRA\TRACK TBI SUBJECT\DTI 64, dir b=1300, 8 b=0
TA:11:15 PAT:2 Voxel size:2.7×2.7×2.7 mm Rel. SNR:1.00 :epse

Properties

Prio Recon	Off
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Wait for user to start	Off
Start measurements	single

Routine

Nr. of slice groups	1
Slices	59
Dist. factor	0 %
Position	R5.3 A9.1 H9.1 mm
Orientation	Transversal
Phase enc. dir.	A >> P
AutoAlign	---
Phase oversampling	0 %
FoV read	350 mm
FoV phase	65.6 %
Slice thickness	2.7 mm
TR	9000 ms
TE	92.0 ms
Concatenations	1
Filter	None
Coil elements	HE1-4

Contrast

MTC	Off
Magn. preparation	None
Fat suppr.	Fat sat.
Fat sat. mode	Weak
Averaging mode	Long term
Measurements	1
Delay in TR	0 ms
Reconstruction	Magnitude
Multiple series	Off

Resolution

Base resolution	128
Phase resolution	100 %
Phase partial Fourier	Off
Interpolation	Off
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	24
Reference scan mode	Separate
Distortion Corr.	Off
Prescan Normalize	Off
Normalize	Off
Raw filter	Off
Elliptical filter	Off
Dynamic Field Corr.	Off

Geometry

Nr. of slice groups	1
Slices	59
Dist. factor	0 %
Position	R5.3 A9.1 H9.1 mm
Phase enc. dir.	A >> P
Phase oversampling	0 %
Multi-slice mode	Interleaved
Series	Interleaved
Nr. of sat. regions	0
Position mode	L-P-H
Fat suppr.	Fat sat.
Special sat.	None
Fat sat. mode	Weak
Special sat.	None
Table position	P

System

Body	Off
HE1	On
HE3	On
NE1	Off
HE2	On
HE4	On
NE2	Off
Position mode	L-P-H
Positioning mode	FIX
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Coil Combine Mode	Adaptive Combine
AutoAlign	---
Coil Select Mode	Default
Shim mode	Standard
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Dominant Fat	Off
Assume Silicone	Off
Adjustment Tolerance	Auto
? Ref. amplitude 1H	0.000 V
Position	R5.3 A9.1 H9.1 mm
Rotation	0.00 deg
R >> L	350 mm
A >> P	230 mm
F >> H	160 mm
Frequency 1H	123.191272 MHz
Correction factor	1
AddCSaCSatNS 1H	100.576 V
Gain	High
Table position	0 mm
Img. Scale. Cor.	1.000

Physio

1st Signal/Mode	None
Magn. preparation	None
Resp. control	Off

Inline

Distortion correction	Off

Sequence

Introduction	Off
Averaging mode	Long term
Multi-slice mode	Interleaved
Bandwidth	1346 Hz/Px
Optimization	None
Free echo spacing	Off
Echo spacing	0.94 ms
EPI factor	84
RF pulse type	Normal
Gradient mode	Fast
TX/RX delta frequency	0 Hz
TX Nucleus	None
TX delta frequency	0 Hz
Coil elements	HE1-4
Acquisition duration	0 ms

BOLD

Delay in TR	0 ms
Diffusion mode	MDDW
Diff. weightings	2
b-value 1	0 s/mm²
Diff. weighted images	On
Trace weighted images	On
ADC maps	On
FA maps	On
Mosaic	On
Tensor	Off
Distortion Corr.	Off
b-Value >=	0 s/mm²
Exponential ADC Maps	Off
Invert Gray Scale	Off
Calculated Image	Off

SIEMENS MAGNETOM Skyra syngo MR D13

\\USER\Schnyer\TRACK-TBI SKYRA\TRACK TBI SUBJECT\Field_mapping
TA:1:44 Voxel size:2.7×2.7×3.0 mm Rel. SNR:1.00 :fm_r

Properties	
Prio Recon	Off
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Wait for user to start	Off
Start measurements	single

Routine	
Nr. of slice groups	1
Slices	48
Dist. factor	25 %
Position	Isocenter
Orientation	Transversal
Phase enc. dir.	R >> L
AutoAlign	---
Phase oversampling	0 %
FoV read	350 mm
FoV phase	65.6 %
Slice thickness	3.0 mm
TR	300.0 ms
TE 1	5.19 ms
Averages	1
Concatenations	2
Filter	None
Coil elements	HE1-4

Contrast	
MTC	Off
Flip angle	60 deg
Fat suppr.	None
Averaging mode	Long term
Measurements	1
Reconstruction	Phase
Multiple series	Off

Resolution

Base resolution	128
Phase resolution	100 %
Phase partial Fourier	Off
Interpolation	Off
Image Filter	Off
Distortion Corr.	Off
Prescan Normalize	Off
Normalize	Off
B1 filter	Off
Raw filter	Off
Elliptical filter	Off

Geometry

Nr. of slice groups	1
Slices	48
Dist. factor	25 %
Position	Isocenter
Phase enc. dir.	R >> L
Phase oversampling	0 %
Multi-slice mode	Interleaved
Series	Interleaved
Nr. of sat. regions	0
Position mode	L-P-H
Fat suppr.	None
Special sat.	None
Special sat.	None
Table position	P

System

Body	Off
HE1	On
HE3	On
NE1	Off
HE2	On
HE4	On
NE2	Off
Position mode	L-P-H
Positioning mode	FIX
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Sum of Squares
AutoAlign	---
Coil Select Mode	Default
Shim mode	Standard
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Dominant Fat	Off
Assume Silicone	Off
Adjustment Tolerance	Auto
? Ref. amplitude 1H	0.000 V
Position	Isocenter
Rotation	90.00 deg
A >> P	350 mm
R >> L	230 mm
F >> H	180 mm
Frequency 1H	123.191272 MHz
Correction factor	1
01GreFCE 1H	194.073 V
Gain	High
Table position	0 mm
Img. Scale. Cor.	1.000

Physio

Inline

Distortion correction	Off

Sequence

Introduction	On
Dimension	2D
Averaging mode	Long term
Multi-slice mode	Interleaved
Asymmetric echo	Off
Contrasts	2
Bandwidth	260 Hz/Px
Flow comp.	Yes
RF pulse type	Normal
Gradient mode	Normal
RF spoiling	On
TX/RX delta frequency	0 Hz
TX Nucleus	None
TX delta frequency	0 Hz
Coil elements	HE1-4
Acquisition duration	0 ms
Mode	Off

BOLD

Distortion Corr.	Off
Contrasts	2

SIEMENS MAGNETOM Skyra syngo MR D13

\\USER\Schnyer\TRACK-TBI SKYRA\TRACK TBI SUBJECT\Resting State fMRI extended ADNI

TA:10:06 PAT:Off Voxel size:3.3×3.3×3.3 mm Rel. SNR:1.00 :epfid

Properties

Prio Recon	Off
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Wait for user to start	On
Start measurements	single

Routine

Nr. of slice groups	1
Slices	48
Dist. factor	20 %
Position	R0.6 P3.5 H14.3 mm
Orientation	Transversal
Phase enc. dir.	A >> P
AutoAlign	---
Phase oversampling	0 %
FoV read	212 mm
FoV phase	93.8 %
Slice thickness	3.3 mm
TR	3000 ms
TE	30.0 ms
Averages	1
Concatenations	1
Filter	Raw filter
Coil elements	HE1-4

Contrast

MTC	Off
Flip angle	80 deg
Fat suppr.	Fat sat.
Averaging mode	Long term
Measurements	200
Delay in TR	0 ms
Reconstruction	Magnitude
Multiple series	Off

Resolution

Base resolution	64
Phase resolution	100 %
Phase partial Fourier	Off
Interpolation	Off
PAT mode	None
Distortion Corr.	Off
Hamming	Off
Prescan Normalize	Off
Raw filter	On
Intensity	Weak
Slope	25
Elliptical filter	Off

Geometry

Nr. of slice groups	1
Slices	48
Dist. factor	20 %
Position	R0.6 P3.5 H14.3 mm
Phase enc. dir.	A >> P
Phase oversampling	0 %
Multi-slice mode	Interleaved
Series	Interleaved
Nr. of sat. regions	0
Position mode	L-P-H
Fat suppr.	Fat sat.
Special sat.	None
Special sat.	None
Table position	P

System

Body	Off
HE1	On
HE3	On
NE1	Off
HE2	On
HE4	On
NE2	Off
Position mode	L-P-H
Positioning mode	FIX
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Coil Combine Mode	Sum of Squares
AutoAlign	---
Coil Select Mode	Default
Shim mode	Standard
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Dominant Fat	Off
Assume Silicone	Off
Adjustment Tolerance	Auto
? Ref. amplitude 1H	0.000 V
Position	R0.6 P3.5 H14.3 mm
Rotation	-0.70 deg
R >> L	212 mm
A >> P	199 mm
F >> H	190 mm
Frequency 1H	123.191272 MHz
Correction factor	1
SincRFPulse 1H	368.244 V
Gain	High
Table position	0 mm
Img. Scale. Cor.	1.000

Physio

1st Signal/Mode	None

Inline

Distortion correction	Off

Sequence

Introduction	Off
Averaging mode	Long term
Multi-slice mode	Interleaved
Bandwidth	1906 Hz/Px
Free echo spacing	Off
Echo spacing	0.59 ms
EPI factor	60
RF pulse type	Normal
Gradient mode	Fast
TX/RX delta frequency	0 Hz
TX Nucleus	None
TX delta frequency	0 Hz
Coil elements	HE1-4
Acquisition duration	0 ms

BOLD

GLM Statistics	Off
Dynamic t-maps	Off
Ignore meas. at start	0
Ignore after transition	0
Model transition states	On
Temp. highpass filter	On
Threshold	4.00
Paradigm size	20
Motion correction	On
Spatial filter	Off
Delay in TR	0 ms
Distortion Corr.	Off

SIEMENS MAGNETOM Skyra syngo MR D13

\\USER\Schnyer\TRACK-TBI SKYRA\TRACK TBI SUBJECT\3D T2 Turbo FLAIR TA:9:50 PAT:4 Voxel size:0.5×0.5×1.2 mm Rel. SNR:1.00 :spcir

Properties	
Prio Recon	Off
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Wait for user to start	Off
Start measurements	single

Routine	
Nr. of slab groups	1
Slabs	1
Position	Isocenter
Orientation	Sagittal
Phase enc. dir.	A >> P
AutoAlign	---
Phase oversampling	0 %
Slice oversampling	18.2 %
FoV read	256 mm
FoV phase	93.8 %
Slice thickness	1.20 mm
TR	6000 ms
TE	272.0 ms
Concatenations	1
Filter	Raw filter, Prescan Normalize
Coil elements	HE1-4

Contrast	
MTC	Off
Magn. preparation	Non-sel. IR
TI 1	2100 ms
Fat suppr.	None
Restore magn.	Off
Measurements	1
Reconstruction	Magnitude
Multiple series	Each measurement

Resolution

Base resolution	256
Phase resolution	100 %
Phase partial Fourier	Allowed
Interpolation	On
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	24
Reference scan mode	Integrated
Image Filter	Off
Distortion Corr.	Off
Accel. factor 3D	2
Ref. lines 3D	24
Unfiltered images	Off
Prescan Normalize	On
Normalize	Off
B1 filter	Off
Raw filter	On
Intensity	Weak
Slope	25
Elliptical filter	Off
Slice resolution	100 %
Slice partial Fourier	Off

Geometry

Nr. of slab groups	1
Slabs	1
Position	Isocenter
Phase enc. dir.	A >> P
Phase oversampling	0 %
Slice oversampling	18.2 %
Slices per slab	176
Series	Interleaved
Nr. of sat. regions	0
Position mode	L-P-H
Fat suppr.	None
Special sat.	None
Special sat.	None
Table position	P
Restore magn.	Off

System

Body	Off
HE1	On
HE3	On
NE1	Off
HE2	On
HE4	On
NE2	Off
Position mode	L-P-H
Positioning mode	FIX
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Sum of Squares
AutoAlign	---
Coil Select Mode	Default
Shim mode	Standard
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Dominant Fat	Off
Assume Silicone	Off
Adjustment Tolerance	Auto
? Ref. amplitude 1H	0.000 V
Position	Isocenter
Rotation	0.00 deg
F >> H	256 mm
A >> P	240 mm
R >> L	212 mm
Frequency 1H	123.191272 MHz
Correction factor	1
SLoopIRns1 1H	611.244 V
Gain	High
Table position	0 mm
Img. Scale. Cor.	1.000

Physio

1st Signal/Mode	None
Trigger delay	0 ms
Magn. preparation	Non-sel. IR
TI 1	2100 ms
Dark blood	Off
Resp. control	Off

Inline

Distortion correction	Off

Sequence

Introduction	On
Dimension	3D
Elliptical scanning	Off
Reordering	Linear
Bandwidth	781 Hz/Px
Flow comp.	No
Allowed delay	30 s
Echo spacing	3.53 ms
Adiabatic-mode	Off
Turbo factor	133
Echo train duration	466
RF pulse type	Normal
Gradient mode	Fast
Excitation	Non-sel.
Flip angle mode	T2 var
TX/RX delta frequency	0 Hz
TX Nucleus	None
TX delta frequency	0 Hz
Coil elements	HE1-4
Acquisition duration	0 ms
Organ under exam.	Standard
Tissue T1	940 ms
Tissue T2	100 ms

BOLD

Subtract	Off
StdDev	Off
MIP-Sag	Off
MIP-Cor	Off
MIP-Tra	Off
MIP-Time	Off
Save original images	On
Distortion Corr.	Off
Save original images	On

SIEMENS MAGNETOM Skyra syngo MR D13

\\USER\Schnyer\TRACK-TBI SKYRA\TRACK TBI SUBJECT\3D T2 TSE TA:5:15 PAT:4 Voxel size:1.0×1.0×1.2 mm Rel. SNR:1.00 :spc

Properties

Prio Recon	Off
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Wait for user to start	Off
Start measurements	single

Routine

Nr. of slab groups	1
Slabs	1
Position	Isocenter
Orientation	Sagittal
Phase enc. dir.	A >> P
AutoAlign	---
Phase oversampling	0 %
Slice oversampling	18.2 %
FoV read	256 mm
FoV phase	93.8 %
Slice thickness	1.20 mm
TR	3200 ms
TE	222.0 ms
Concatenations	1
Filter	Raw filter, Prescan Normalize
Coil elements	HE1-4

Contrast

MTC	Off
Magn. preparation	None
Fat suppr.	None
Restore magn.	Off
Measurements	1
Reconstruction	Magnitude
Multiple series	Each measurement

Resolution

Base resolution	256
Phase resolution	100 %
Phase partial Fourier	Allowed
Interpolation	Off
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	24
Reference scan mode	Integrated
Image Filter	Off
Distortion Corr.	Off
Accel. factor 3D	2
Ref. lines 3D	24
Unfiltered images	Off
Prescan Normalize	On
Normalize	Off
B1 filter	Off
Raw filter	On
Intensity	Weak
Slope	25
Elliptical filter	Off
Slice resolution	100 %
Slice partial Fourier	Off

Geometry

Nr. of slab groups	1
Slabs	1
Position	Isocenter
Phase enc. dir.	A >> P
Phase oversampling	0 %
Slice oversampling	18.2 %
Slices per slab	176
Series	Interleaved
Nr. of sat. regions	0
Position mode	L-P-H
Fat suppr.	None
Special sat.	None
Special sat.	None
Table position	P
Restore magn.	Off

System

Body	Off
HE1	On
HE3	On
NE1	Off
HE2	On
HE4	On
NE2	Off
Position mode	L-P-H
Positioning mode	FIX
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Sum of Squares
AutoAlign	---
Coil Select Mode	Default
Shim mode	Standard
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Dominant Fat	Off
Assume Silicone	Off
Adjustment Tolerance	Auto
? Ref. amplitude 1H	0.000 V
Position	Isocenter
Rotation	0.00 deg
F >> H	256 mm
A >> P	240 mm
R >> L	212 mm
Frequency 1H	123.191272 MHz
Correction factor	1
SRFExcit 1H	340.000 V
Gain	High
Table position	0 mm
Img. Scale. Cor.	1.000

Physio	
1st Signal/Mode	None
Trigger delay	0 ms
Magn. preparation	None
Dark blood	Off
Resp. control	Off

Inline	
Distortion correction	Off

Sequence	
Introduction	On
Dimension	3D
Elliptical scanning	Off
Reordering	Linear
Bandwidth	751 Hz/Px
Flow comp.	No
Allowed delay	0 s
Echo spacing	3.53 ms
Adiabatic-mode	Off
Turbo factor	133
Echo train duration	452
RF pulse type	Normal
Gradient mode	Fast
Excitation	Non-sel.
Flip angle mode	T2 var
TX/RX delta frequency	0 Hz
TX Nucleus	None
TX delta frequency	0 Hz
Coil elements	HE1-4
Acquisition duration	0 ms
Organ under exam.	Standard
Tissue T1	940 ms
Tissue T2	100 ms

BOLD	
Subtract	Off
StdDev	Off
MIP-Sag	Off
MIP-Cor	Off
MIP-Tra	Off
MIP-Time	Off
Save original images	On
Distortion Corr.	Off
Save original images	On

GE MR750 3T
GE Signa 3T

Protocol: adult_other_TRACKTBI2014-02-12_20140213163854642_1

3 PL LOC

PATIENT POSITION		IMAGING PARAMETERS	
Patient Entry	*Head First*	**Gradient Mode**	*ZOOM*
Patient Position	*Supine*	**Imaging Mode**	*2D*
Coil Configuration	*0*	**Pulse Sequence**	*Spin Echo*
Plane	*3-PLANE*	**Imaging Options**	*Seq, Fast, SS*
Series Description	*3 PL LOC*	**n/a**	*12*
SCAN TIMING		**SCAN RANGE**	
TE	*Minimum*	**FOV**	*24.0*
TR	*Minimum*	**Slice Thickness**	*8.0*
Receiver Bandwidth	*31.25*	**Slice Spacing**	*2.0*
		Center Location 1	*0.0*
		Center Location 2	*A30.0*
		Center Location 3	*0.0*
		Slice for 3 Plane Localizaion	*0*
		Slice for 3 Plane Localizaion	*5*
		Slice for 3 Plane Localizaion	*5*
		Slice for 3 Plane Localizaion	*5*
		Space per Plane 1	*2.0*
		Space per Plane 2	*2.0*
		Table Delta	*0.00*
IMAGE ENHANCE		**ACQ TIMING**	
Filter Choice	*None*	**Freq**	*256*
		Phase	*128*
		Freq DIR	*Unswap*
		# of Acq. Before Pause	*0*
		Phase FOV	*1.00*
		Auto Shim	*Auto*
		Phase Correction	*No*
GATING/TRIGGER		**USER CVS**	
Heart Beat per Minute Mode	*0*	**User CV2**	*240.00*
Auto Trigger Type	*Off*	**User CV13**	*1.00*
Auto Trigger Window	*Off*	**User CV Mask**	*70*
FMRI		**MULTI-PHASE**	
PSD Trigger	*Internal*	**# of Acquisition**	*0*
Slice Order	*Interleaved*	**Seperate Series**	*0*
View Order	*Bottom/Up*	**Mask Phase**	*0*
# of Repetitions REST	*0*	**Mask Pause**	*0*
# of Repetitions ACTIVE	*0*		
SAT		**DIFFUSION**	

3 PL LOC

Protocol: adult_other_TRACKTBI2014-02-12_20140213163854642_1

Tag Type	*None*	**Recon All Images**	*On*
TRICKS		**CONTRAST**	
Pause On/Off	*On*	**Contrast Yes/No**	*No*
Auto Subtract	*0*	**Contrast Amount**	*Yes*
Auto SCIC	*Off*		

ASSET cal

PATIENT POSITION	
Patient Entry	*Head First*
Patient Position	*Supine*
Coil Configuration	*8HRBRAIN*
Plane	*AXIAL*
Series Description	*ASSET cal*

SCAN TIMING	
Number of Echoes	*1*

IMAGE ENHANCE	
Filter Choice	*None*

GATING/TRIGGER	
Heart Beat per Minute Mode	*0*
Auto Trigger Type	*Off*
Auto Trigger Window	*Off*

FMRI	
PSD Trigger	*Internal*
Slice Order	*Interleaved*
View Order	*Bottom/Up*
# of Repetitions REST	*0*

IMAGING PARAMETERS	
Gradient Mode	*WHOLE*
Imaging Mode	*2D*
Pulse Sequence	*Gradient Echo*
Imaging Options	*Fast, Calib*
n/a	*5*
Acceleration Factor	*1.00*

SCAN RANGE	
FOV	*30.0*
Slice Thickness	*9.0*
Slice Spacing	*0.0*
GRXOPT	*0*
Start Location 1	*I70.9*
End Location 1	*S118.1*
End Location 2	*0.0*
End Location 3	*A50.6*
Center of Location Start	*0.0*
Center of Location End	*A50.6*
Number of Slices	*22*
Slice for 3 Plane Localizaion	*0*
Slice for 3 Plane Localizaion	*0*
Slice for 3 Plane Localizaion	*0*
Slice for 3 Plane Localizaion	*0*
Space per Plane 1	*0.0*
Space per Plane 2	*0.0*
Table Delta	*0.00*

ACQ TIMING	
Freq DIR	*R/L*
Auto Shim	*Auto*
Phase Correction	*No*

USER CVS	
User CV Mask	*0*

MULTI-PHASE	
# of Acquisition	*0*
Seperate Series	*0*
Mask Phase	*0*
Mask Pause	*0*

ASSET cal

Protocol: adult_other_TRACKTBI2014-02-12_20140213163854642_1

# of Repetitions ACTIVE	*0*

SAT		**ASSET**	
Tag Type	*None*	**Slice Acceleration Factor**	*1.00*
		Phase Acceleration Factor	*1.00*

TRICKS		**CONTRAST**	
Pause On/Off	*On*	**Contrast Yes/No**	*No*
Auto Subtract	*0*	**Contrast Amount**	*Yes*
Auto SCIC	*Off*		

OTHERS	
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	0.000000
Auto Voice	*Off*
Preset Delay	*0.0*

SAG IR-FSPGR (ADNI)

PATIENT POSITION	
Patient Entry	*Head First*
Patient Position	*Supine*
Coil Configuration	*0*
Plane	*SAGITTAL*
Series Description	*SAG IR-FSPGR (ADNI)*

SCAN TIMING	
Flip Angle	*11*
TI	*400*
Receiver Bandwidth	*31.25*

IMAGE ENHANCE	
Filter Choice	*None*

GATING/TRIGGER	
Heart Beat per Minute Mode	*0*
Auto Trigger Type	*Off*
Auto Trigger Window	*Off*

FMRI	
Initial State	*Control*
PSD Trigger	*Internal*
Slice Order	*Interleaved*

IMAGING PARAMETERS	
Gradient Mode	*ZOOM*
Imaging Mode	*3D*
Pulse Sequence	*BRAVO*
Imaging Options	*EDR, Fast, IrP, ARC*
n/a	*41*

SCAN RANGE	
FOV	*25.6*
Slice Thickness	*1.2*
Location per Slab	*200*
Overlap Locations	*0*
End Location 2	*0.0*
End Location 3	*0.0*
Center of Location Start	*0.0*
Center of Location End	*0.0*
Number of Slices	*1*
Slice for 3 Plane Localizaion	*0*
Slice for 3 Plane Localizaion	*0*
Slice for 3 Plane Localizaion	*0*
Slice for 3 Plane Localizaion	*0*
Space per Plane 1	*0.0*
Space per Plane 2	*0.0*
Table Delta	*0.00*

ACQ TIMING	
Freq	*256*
Phase	*256*
Freq DIR	*S/I*
NEX	*1.00*
Phase FOV	*1.00*
Auto Shim	*Auto*
Phase Correction	*No*

USER CVS	
User CV5	*1.00*
User CV Mask	*48*

MULTI-PHASE	
# of Acquisition	*0*
Seperate Series	*0*
Mask Phase	*0*

SAG IR-FSPGR (ADNI)

Protocol: adult_other_TRACKTBI2014-02-12_20140213163854642_1

View Order	*Bottom/Up*	**Mask Pause**	*0*
# of Repetitions REST	*0*		
# of Repetitions ACTIVE	*0*		
SAT		**DIFFUSION**	
Tag Type	*None*	**Recon All Images**	*On*
TRICKS		**CONTRAST**	
Pause On/Off	*On*	**Contrast Yes/No**	*No*
Auto Subtract	*0*	**Contrast Amount**	*Yes*
Auto SCIC	*Off*		

SAG 3D SWAN

PATIENT POSITION	
Patient Entry	*Head First*
Patient Position	*Supine*
Coil Configuration	*0*
Plane	*SAGITTAL*
Series Description	*SAG 3D SWAN*

SCAN TIMING	
Flip Angle	*10*
TE	*25.0*
TR	*45.0*
Receiver Bandwidth	*62.50*

IMAGE ENHANCE	
Filter Choice	*None*

GATING/TRIGGER	
Heart Beat per Minute Mode	*0*
Auto Trigger Type	*Off*
Auto Trigger Window	*Off*

FMRI	
Initial State	*Control*
PSD Trigger	*Internal*
Slice Order	*Interleaved*
View Order	*Bottom/Up*

IMAGING PARAMETERS	
Gradient Mode	*ZOOM*
Imaging Mode	*3D*
Pulse Sequence	*SWAN*
Imaging Options	*FC, EDR, Fast, ZIP2, Asset*
n/a	*60*

SCAN RANGE	
FOV	*25.6*
Slice Thickness	*1.6*
Location per Slab	*130*
Overlap Locations	*0*
End Location 2	*0.0*
End Location 3	*0.0*
Center of Location Start	*0.0*
Center of Location End	*0.0*
Number of Slices	*1*
Slice for 3 Plane Localizaion	*0*
Slice for 3 Plane Localizaion	*0*
Slice for 3 Plane Localizaion	*0*
Slice for 3 Plane Localizaion	*0*
Space per Plane 1	*0.0*
Space per Plane 2	*0.0*
Table Delta	*0.00*

ACQ TIMING	
Freq	*192*
Phase	*192*
Freq DIR	*S/I*
Phase FOV	*1.00*
Auto Shim	*Auto*
Phase Correction	*No*

USER CVS	
User CV Mask	*65568*

MULTI-PHASE	
# of Acquisition	*0*
Seperate Series	*0*
Mask Phase	*0*
Mask Pause	*0*

SAG 3D SWAN

Protocol: adult_other_TRACKTBI2014-02-12_20140213163854642_1

# of Repetitions REST	*0*		
# of Repetitions ACTIVE	*0*		
SAT		**DIFFUSION**	
Tag Type	*None*	**Recon All Images**	*On*
TRICKS		**CONTRAST**	
Pause On/Off	*On*	**Contrast Yes/No**	*Yes*
Auto Subtract	*0*	**Contrast Amount**	*Yes*
Auto SCIC	*Off*		

Ax DTI 60 DIR, b=1300

PATIENT POSITION	
Patient Entry	*Head First*
Patient Position	*Supine*
Coil Configuration	*0*
Plane	*AXIAL*
Series Description	*Ax DTI 60 DIR, b=1300*

SCAN TIMING	
TE	*Minimum*
TR	*14000.0*
Number of Shots	*1*

IMAGE ENHANCE	
Filter Choice	*None*

GATING/TRIGGER	
Heart Beat per Minute Mode	*0*
Auto Trigger Type	*Off*
Auto Trigger Window	*Off*

FMRI	
PSD Trigger	*Internal*
Slice Order	*Interleaved*
View Order	*Bottom/Up*
# of Repetitions REST	*0*
# of Repetitions ACTIVE	*0*

IMAGING PARAMETERS	
Gradient Mode	*ZOOM*
Imaging Mode	*2D*
Pulse Sequence	*Spin Echo*
Imaging Options	*EPI, DIFF, Asset*
n/a	*8*

SCAN RANGE	
FOV	*34.0*
Slice Thickness	*2.7*
Slice Spacing	*0.0*
End Location 2	*0.0*
End Location 3	*0.0*
Center of Location Start	*0.0*
Center of Location End	*0.0*
Number of Slices	*54*
Slice for 3 Plane Localizaion	*0*
Slice for 3 Plane Localizaion	*0*
Slice for 3 Plane Localizaion	*0*
Slice for 3 Plane Localizaion	*0*
Space per Plane 1	*0.0*
Space per Plane 2	*0.0*
Table Delta	*0.00*

ACQ TIMING	
Freq	*128*
Phase	*128*
Freq DIR	*R/L*
Phase FOV	*0.66*
Auto Shim	*Auto*
Phase Correction	*Yes*

USER CVS	
User CV Mask	*263712*

MULTI-PHASE	
# of Acquisition	*0*
Seperate Series	*0*
Mask Phase	*0*
Mask Pause	*0*

Ax DTI 60 DIR, b=1300

Protocol: adult_other_TRACKTBI2014-02-12_20140213163854642_1

SAT		DIFFUSION	
Tag Type	*None*	**Optimized TE**	*Yes*
Fat/Water Saturation	*Fat*	**Diffusion Directions**	*Tensor*
		Number of Diffusion Directions	*60*
		Number of T2 Images	*8*
		Dual Spin Echo	*On*
		Diffusion Tenser Processing Output	*No Selection*
		Recon All Images	*Off*
TRICKS		**CONTRAST**	
Pause On/Off	*On*	**Contrast Yes/No**	*No*
Auto Subtract	*0*	**Contrast Amount**	*Yes*
Auto SCIC	*Off*		

Resting State fMRI

PATIENT POSITION	
Patient Entry	*Head First*
Patient Position	*Supine*
Coil Configuration	*0*
Plane	*AXIAL*
Series Description	*Resting State fMRI*

SCAN TIMING	
Flip Angle	*80*
TE	*30.0*
TR	*3000.0*
Number of Shots	*1*

IMAGE ENHANCE	
Filter Choice	*None*

GATING/TRIGGER	
Heart Beat per Minute Mode	*0*
Auto Trigger Type	*Off*
Auto Trigger Window	*Off*

FMRI	
Brain Wave Real Time	*1*
Paradigm String	*Resting State fMRI*
Paradigm UID	*1.2.840.113819.3.6034207302*

IMAGING PARAMETERS	
Gradient Mode	*ZOOM*
Imaging Mode	*2D*
Pulse Sequence	*Gradient Echo*
Imaging Options	*EPI, FMRI*
n/a	*9*

SCAN RANGE	
FOV	*21.2*
Slice Thickness	*3.3*
Slice Spacing	*0.0*
Start Location 1	*S79.3*
End Location 1	*I64.7*
End Location 2	*L7.5*
End Location 3	*A40.9*
Center of Location Start	*L7.5*
Center of Location End	*A40.9*
Slice for 3 Plane Localizaion	*0*
Slice for 3 Plane Localizaion	*0*
Slice for 3 Plane Localizaion	*0*
Slice for 3 Plane Localizaion	*0*
Space per Plane 1	*0.0*
Space per Plane 2	*0.0*
Table Delta	*0.00*

ACQ TIMING	
Freq	*64*
Phase	*64*
Freq DIR	*R/L*
NEX	*1.00*
Phase FOV	*1.00*
Auto Shim	*Auto*
Phase Correction	*Yes*

USER CVS	
User CV0	*1.00*
User CV Mask	*1*

MULTI-PHASE	
Slice per Location	*200*
Delay after Acquisition	*0*
# of Acquisition	*0*

Resting State fMRI

Protocol: adult_other_TRACKTBI2014-02-12_20140213163854642_1

	8.1321382205.441		
Initial State	*Control*	**Seperate Series**	*0*
PSD Trigger	*Internal*	**Delay after Acquisition without AV**	*0*
Slice Order	*Interleaved*	**Mask Phase**	*0*
View Order	*Bottom/Up*	**Mask Pause**	*0*
# of Repetitions REST	*10*		
# of Repetitions ACTIVE	*10*		
# of Dummy Acquisition	*3*		
SAT		**DIFFUSION**	
Tag Type	*None*	**Recon All Images**	*On*
Fat/Water Saturation	*Fat*		
TRICKS		**TRACKER**	
Pause On/Off	*On*	**Tracker Length**	*200.0*
Auto Subtract	*0*	**Tracker Thickness**	*20.0*
Auto SCIC	*Off*		
CONTRAST			
Contrast Yes/No	*No*		
Contrast Amount	*Yes*		

Sag CUBE FLAIR

PATIENT POSITION	
Patient Entry	*Head First*
Patient Position	*Supine*
Coil Configuration	*HD 8Ch High Res Brain Array by Invivo*
Plane	*SAGITTAL*
Series Description	*Sag CUBE FLAIR*

SCAN TIMING	
TR	*6000.0*
Echo Train Length	*142*
Receiver Bandwidth	*31.25*

IMAGE ENHANCE	
Filter Choice	*None*

GATING/TRIGGER	
Auto Trigger Type	*Off*
Auto Trigger Window	*Off*

FMRI	
PSD Trigger	*Internal*
Slice Order	*Interleaved*

IMAGING PARAMETERS	
Gradient Mode	*ZOOM*
Imaging Mode	*3D*
Pulse Sequence	*Cube T2 FLAIR*
Imaging Options	*EDR, Fast, IrP, ZIP512, ZIP2, ARC*
n/a	*56*

SCAN RANGE	
FOV	*25.6*
Slice Thickness	*1.2*
Location per Slab	*176*
Overlap Locations	*0*
End Location 2	*0.0*
End Location 3	*0.0*
Center of Location Start	*0.0*
Center of Location End	*0.0*
Number of Slices	*1*
Slice for 3 Plane Localizaion	*0*
Slice for 3 Plane Localizaion	*0*
Slice for 3 Plane Localizaion	*0*
Slice for 3 Plane Localizaion	*0*
Space per Plane 1	*0.0*
Space per Plane 2	*0.0*
Table Delta	*0.00*

ACQ TIMING	
Freq	*256*
Phase	*256*
Freq DIR	*S/I*
NEX	*1.00*
Phase FOV	*1.00*
Auto Shim	*Auto*
Phase Correction	*No*

USER CVS	
User CV23	*1.00*
User CV Mask	*8388608*

MULTI-PHASE	
# of Acquisition	*0*
Seperate Series	*0*

Sag CUBE FLAIR

Protocol: adult_other_TRACKTBI2014-02-12_20140213163854642_1

View Order	*Bottom/Up*	**Mask Phase**	*0*
# of Repetitions REST	*0*	**Mask Pause**	*0*
# of Repetitions ACTIVE	*0*		
SAT		**DIFFUSION**	
Tag Type	*None*	**Recon All Images**	*On*
TRICKS		**CONTRAST**	
Pause On/Off	*On*	**Contrast Yes/No**	*No*
Auto Subtract	*0*	**Contrast Amount**	*Yes*
Auto SCIC	*Off*		

SAG 3D T2

PATIENT POSITION	
Patient Entry	*Head First*
Patient Position	*Supine*
Coil Configuration	*MRI Devices 8ch high res brain array*
Plane	*SAGITTAL*
Series Description	*SAG 3D T2*

SCAN TIMING	
TR	*2000.0*
Echo Train Length	*123*
Receiver Bandwidth	*83.33*

IMAGE ENHANCE	
Filter Choice	*None*

GATING/TRIGGER	
Heart Beat per Minute Mode	*0*
Auto Trigger Type	*Off*
Auto Trigger Window	*Off*

FMRI	
PSD Trigger	*Internal*
Slice Order	*Interleaved*

IMAGING PARAMETERS	
Gradient Mode	*WHOLE*
Imaging Mode	*3D*
Pulse Sequence	*Cube T2*
Imaging Options	*EDR, Fast, ZIP512, FR, ARC*
n/a	*53*

SCAN RANGE	
FOV	*25.6*
Slice Thickness	*1.2*
Location per Slab	*176*
Overlap Locations	*0*
End Location 2	*0.0*
End Location 3	*0.0*
Center of Location Start	*0.0*
Center of Location End	*0.0*
Number of Slices	*1*
Slice for 3 Plane Localizaion	*0*
Slice for 3 Plane Localizaion	*0*
Slice for 3 Plane Localizaion	*0*
Slice for 3 Plane Localizaion	*0*
Space per Plane 1	*0.0*
Space per Plane 2	*0.0*
Table Delta	*0.00*

ACQ TIMING	
Freq	*256*
Phase	*256*
Freq DIR	*S/I*
NEX	*2.00*
Phase FOV	*1.00*
Auto Shim	*Auto*
Phase Correction	*No*

USER CVS	
User CV22	*2.00*
User CV23	*1.00*
User CV Mask	*12582912*

MULTI-PHASE	
# of Acquisition	*0*
Seperate Series	*0*

SAG 3D T2

Protocol: adult_other_TRACKTBI2014-02-12_20140213163854642_1

View Order	*Bottom/Up*	**Mask Phase**	*0*
# of Repetitions REST	*0*	**Mask Pause**	*0*
# of Repetitions ACTIVE	*0*		
SAT		**DIFFUSION**	
Tag Type	*None*	**Recon All Images**	*On*
TRICKS		**CONTRAST**	
Pause On/Off	*On*	**Contrast Yes/No**	*No*
Auto Subtract	*0*	**Contrast Amount**	*Yes*
Auto SCIC	*Off*		

Philips Achieva 3T
Philips Ingenia 3T

3D_FLAIR SENSE

ScanningSequence	Inversion Recovery
SequenceVariant:	SK
ScanOptions:	FS
MRAcquisitionType:	3D
SliceThickness:	1.200000
RepetitionTime:	4800
EchoTime:	323.495
InversionTime:	1650
EchoNumbers:	1
MagneticFieldStrength:	3
SpacingBetweenSlices:	1.2
NumberOfPhaseEncodingSteps:	254
EchoTrainLength:	182
PercentSampling:	78.2330169677734
PercentPhaseFieldOfView:	100
PixelBandwidth:	957
SoftwareVersions:	5.1.2\5.1.2.0
ProtocolName:	3D_FLAIR SENSE
LowRRValue:	0
HighRRValue:	0
IntervalsAcquired:	0
IntervalsRejected:	0
ReconstructionDiameter:	256
ReceiveCoilName:	MULTI COIL
AcquisitionMatrix:	0\256\254\0
InPlanePhaseEncodingDirection:	ROW
FlipAngle:	90

T1 MPRAGE CLEAR

ScanningSequence	Gradient echo
SequenceVariant:	MP
ScanOptions:	OTHER
MRAcquisitionType:	3D
SliceThickness:	1.200000
RepetitionTime:	6.78009986877441
EchoTime:	3.157
EchoNumbers:	1
MagneticFieldStrength:	3
SpacingBetweenSlices:	1.2
NumberOfPhaseEncodingSteps:	256
EchoTrainLength:	240
PercentSampling:	100
PercentPhaseFieldOfView:	93.75
PixelBandwidth:	241
SoftwareVersions:	5.1.2\5.1.2.0
ProtocolName:	MPRAGE CLEA
LowRRValue:	0
HighRRValue:	0
IntervalsAcquired:	0
IntervalsRejected:	0
ReconstructionDiameter:	256
ReceiveCoilName:	MULTI COIL
AcquisitionMatrix:	0\256\254\0
InPlanePhaseEncodingDirection:	ROW
FlipAngle:	9

3D_T2 SENSE

ScanningSequence	Spin echo
SequenceVariant:	SK
ScanOptions:	FS
MRAcquisitionType:	3D
SliceThickness:	1.200000
RepetitionTime:	2500
EchoTime:	245.409
EchoNumbers:	1
MagneticFieldStrength:	3
SpacingBetweenSlices:	1.2
NumberOfPhaseEncodingSteps:	256
EchoTrainLength:	133
PercentSampling:	78.5398178100586
PercentPhaseFieldOfView:	100
PixelBandwidth:	957
SoftwareVersions:	5.1.2\5.1.2.0
ProtocolName:	3D_T2 SENSE
LowRRValue:	0
HighRRValue:	0
IntervalsAcquired:	0
IntervalsRejected:	0
ReconstructionDiameter:	256
ReceiveCoilName:	MULTI COIL
AcquisitionMatrix:	0\256\256\0
InPlanePhaseEncodingDirection:	ROW
FlipAngle:	90

3D T2-Star SENSE

ScanningSequence	Gradient echo
SequenceVariant:	SP
ScanOptions:	FS
MRAcquisitionType:	3D
SliceThickness:	1.000000
RepetitionTime:	45
EchoTime:	25
EchoNumbers:	1
MagneticFieldStrength:	3
SpacingBetweenSlices:	1.6
NumberOfPhaseEncodingSteps:	198
EchoTrainLength:	1
PercentSampling:	78.9666595458984
PercentPhaseFieldOfView:	93.8775539398193
PixelBandwidth:	145
SoftwareVersions:	5.1.2\5.1.2.0
ProtocolName:	3D T2-Star SENSE
LowRRValue:	0
HighRRValue:	0
IntervalsAcquired:	0
IntervalsRejected:	0
ReconstructionDiameter:	256
ReceiveCoilName:	MULTI COIL
AcquisitionMatrix:	0\196\198\0
InPlanePhaseEncodingDirection:	ROW
FlipAngle:	10

Appendix 2

TBI Endpoints Development Initiative

A collaborative for advancing diagnosis and treatment of TBI

Principal Investigators

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Date: **October 6, 2018**

Subject: **MDDT QUALIFICATION PACKAGE**

MDDT Type: **BIOMARKER TEST**

MDDT Tracking Record Number: **MDDT027**

Submission Type: **Q-SUBMISSION: INFORMATIONAL MEETING REQUEST**

A supplement to Q-SUBMISSION Number: **Q161252 (responding to 9/26/18 correspondence and 10/2/18 teleconference)**

Division: **DIVISION OF RADIOLOGICAL HEALTH**

Branch: **MAGNETIC RESONANCE AND ELECTRONIC PRODUCTS BRANCH**

Lead reviewers: **Eriko Yoshimaru, Ph.D. and Daniel Krainak, Ph.D.**

MDDT Name: **OsiriX CDE Software Module**

(Revised) Context of Use: Contusions, as assessed by an expert rater from MRI using this MDDT, may be used for prognostic enrichment of clinical trials for therapeutic medical devices intended to improve outcomes at 3-months for patients aged 18-65 years with acute nonpenetrating head trauma and GCS 13-15 that have undergone acute head CT (e.g., as part of standard clinical care) at a U.S. Level 1 trauma center.

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RESPONSE TO SEPTEMBER 26, 2018 QUERIES Re: Q161252/S001
Incorporating minutes of OCTOBER 2, 2018 telecon:
Attendees: FDA: Eriko Yoshimaru, Ph.D., Daniel Krainak, Ph.D.
Submitting team: Esther Yuh, MD, Geoffrey T. Manley, MD, Ph.D., Sonia Jain, Ph.D., Nancy Temkin, Ph.D., Shelly Sun, Ph.D., Allison Kumar

1. REVISED CONTEXT OF USE STATEMENT

The first question is related to the proposed Context of Use. In the current submission, the proposed COU is as follows:

This MDDT applies to the COU in which the patients aged 18-65 years with acute nonpenetrating head trauma and GCS 1315 have undergone acute head CT (e.g., as part of standard clinical care according to ACEP/CDC criteria) at a U.S. Level 1 trauma center and participate in a TBI clinical trial.

In general, the review team concluded that the COU lacked several key elements and did not adequately describe the conditions and boundaries within which the MDDT is to be qualified for use. As described on the FDA's Medical Device Development Tools (MDDT) website (and also in our MDDT guidance document *Qualification of Medical Device Development Tools*), the COU should include details on 1) the tool or product area in which the MDDT is proposed to be qualified, 2) the specific output or measure from the MDDT, 3) the role of the MDDT, and 4) the phases of medical device development during which the MDDT or tool measurements can be used. The review team feels that these four criteria are not adequately described in the current proposed COU. The COU statement provided in Q161252/A002 includes the information as described in our guidance document. We suggest that the final COU include similar level of information. Alternatively, wording such as the one provided below could also be considered.

Contusions as assessed by an expert rater from MRI using this MDDT may be used for prognostic enrichment of clinical trials for therapeutic medical devices intended to improve outcomes at 3-months for patients aged 18-65 years with acute nonpenetrating head trauma and GCS 13-15 have undergone acute head CT (e.g., as part of standard clinical care according to ACEP/CDC criteria) at a U.S. Level 1 trauma center.

Resolution:

We thank the FDA for suggesting the above changes and we are in agreement that this will greatly clarify the Context of Use. Based on the FDA's suggested rewording, in addition to suggestions during the teleconference on 10/2/2018 that the COU need not be tied to a specific named practice guideline (ACEP/CDC), we would like to revise the COU to the following:

Contusions, as assessed by an expert rater from MRI using this MDDT, may be used for prognostic enrichment of clinical trials for therapeutic medical devices intended to improve outcomes at 3-months for patients aged 18-65 years with acute nonpenetrating head trauma and GCS 13-15 that have undergone acute head CT (e.g., as part of standard clinical care) at a U.S. Level 1 trauma center.

2. CLARIFICATION OF "INTENT TO DIAGNOSE" POPULATION

Please address how your current analysis on 517 patients ignoring 198 patients who met inclusion and exclusion criteria but were missing 2-week MRI data represents your intent to diagnose (ITD) population. Based on your analysis of the GOS-E scores, the patients groups with and without 2-week MRI have significantly different distributions, and thus please provide imputations for missing data. Please refer to Gregory Campbell, Gene Pennello & Lilly Yue (2011) Missing Data in the Regulation of Medical Devices, Journal of Biopharmaceutical Statistics, 21:2, 180-195, DOI: 10.1080/10543406.2011.550094.

Resolution:

We thank the FDA for helping us to clarify this point, both here and during the teleconference on 10/2/2018. We would like to propose that based on the central role that MRI plays in the proposed MDDT, that the "Intent to Diagnose" population consists of those patients who successfully complete 2-week MRI. The follow-up rate for patients in TRACK-TBI to complete a planned 2-week MRI was 75%. This compares favorably to follow-up rates in prior studies.

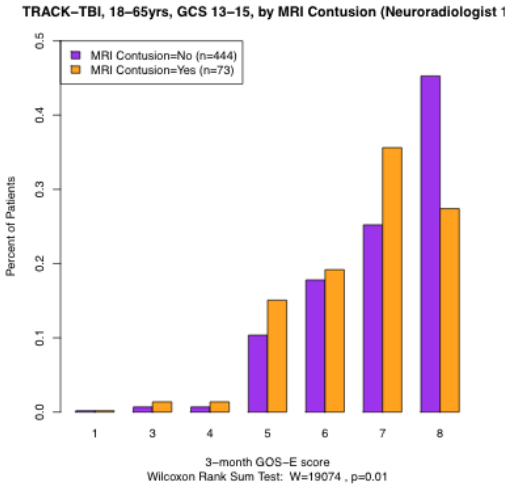
3. WILCOXON RANK SUM TEST STATISTICS

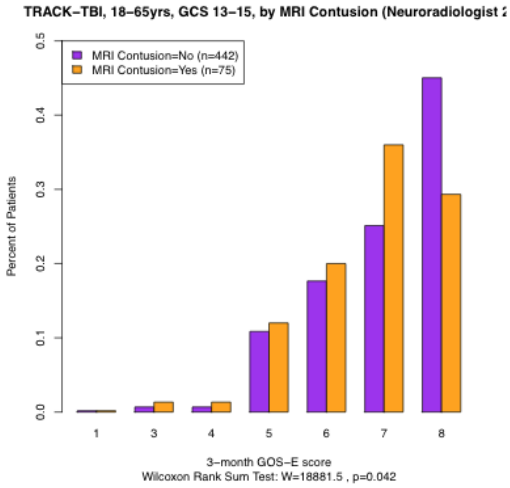
You provided the p-values for the prognostic validation study results. These results indicate the probability that the results could have come from the null hypothesis that there is no relationship between the biomarker and the GOS-E result. These p-values do not provide a practical sense of how strong the relationship is. The actual performance results can provide a practical sense of how strong the relationship is. Please provide the actual Wilcoxon rank sum test statistics.

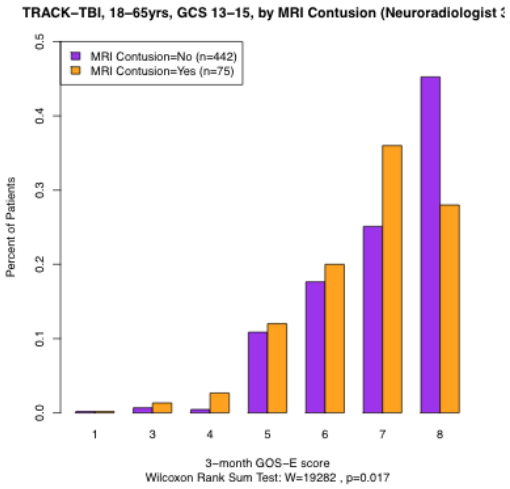
Resolution:

We have revised the qualification package to include the Wilcoxon rank sum test statistics:

2 Comparison of 3-month GOS-E scores between subjects with MRI Contusion Yes vs No







4. RECALCULATION OF AVERAGE PPA AND NNA AND CONFIDENCE INTERVALS

You have provided the inter-rater reliability study results on pages 14 and 15. Your currently reported statistics PPA and NPA are incorrect. In addition, please provide APA and ANA. Please revise your analyses and provide the following estimates from your 2 by 2 table for each reader pairs ((i,j) :

		Reader j	
		Yes	No
Reader i	Yes	a	b
	No	c	d

For PPA between reader 1 vs 2=a/(a+c)
For PPA between Reader 2 vs 1 = a/(a+b)
APA= 2a/(2a+b+c)
For NPA between reader 1 vs 2=d/(b+d)
For NPA between Reader 2 vs 1 = d/(c+d)
ANA= 2d/(2d+b+c)

You may use bootstrap sampling method to estimate the confidence intervals for point estimate values different from 100% and may address the cases with 100% percent agreements with Clopper-Pearson method.

Resolution:

We have revised the APA and NPA calculations in the qualification package using the formulas provided by the FDA above. We have also provided the corresponding 95% confidence intervals using the Clopper-Pearson, method as suggested. (See replacement tables of Section 4.1 of our analyses, following.)

4.1 Contusion on brain MRI

	Reader 2		
	0	1	Total
Reader 1			
0	434	10	444
1	8	65	73
Total	442	75	517

Cohen's Kappa: 0.858, 95% CI: (0.794, 0.922)

	Estimate	95CI.lower	95CI.upper
PPA 1 vs 2	0.867	0.768	0.934
PPA 2 vs 1	0.890	0.795	0.951
APA	0.878	0.815	0.926
NPA 1 vs 2	0.982	0.965	0.992
NPA 2 vs 1	0.977	0.959	0.989
ANA	0.980	0.968	0.988

Confidence intervals calculated by Clopper-Pearson method

	Reader 3		
	0	1	Total
Reader 1			
0	435	9	444
1	7	66	73
Total	442	75	517

Cohen's Kappa: 0.874, 95% CI: (0.813, 0.934)

	Estimate	95CI.lower	95CI.upper
PPA 1 vs 2	0.880	0.784	0.944
PPA 2 vs 1	0.904	0.812	0.961
APA	0.892	0.830	0.937
NPA 1 vs 2	0.984	0.968	0.994
NPA 2 vs 1	0.980	0.962	0.991
ANA	0.982	0.971	0.990

	Reader 3		
	0	1	Total
Reader 2			
0	432	10	442
1	10	65	75
Total	442	75	517

Cohen's Kappa: 0.844, 95% CI: (0.777, 0.911)

	Estimate	95CI.lower	95CI.upper
PPA 1 vs 2	0.867	0.768	0.934
PPA 2 vs 1	0.867	0.768	0.934
APA	0.867	0.802	0.917
NPA 1 vs 2	0.977	0.959	0.989
NPA 2 vs 1	0.977	0.959	0.989
ANA	0.977	0.965	0.986

Center for Drug Evaluation and Research Food and Drug Administration

Date: January 10, 2018

ATTN: Geoffrey T. Manley, M.D., Ph.D.
Principal Investigator, TBI Endpoints Development (TED) Initiative and TRACK-TBI Study
University of California, San Francisco
1001 Potrero Avenue
Bldg. 1, Room 101
San Francisco, CA 94110

SUBJECT: Biomarker Letter of Support

Dear Dr. Manley:

We are issuing this Letter of Support to the TBI Endpoints Development (TED) Initiative and the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) investigators to encourage the further study of blood levels of glial fibrillary acidic protein (GFAP), a possible biomarker of astrocytic injury, and ubiquitin carboxyl-terminal hydrolase-L1 (UCH-L1), a possible biomarker of neuronal injury, as exploratory prognostic enrichment biomarkers to identify patients who are likely to develop persistent disability during the course of mild traumatic brain injury (TBI) clinical trials.

Although most patients with mild TBI have no abnormalities on non-contrast head computed tomography (NCCT), a typical imaging modality used for evaluation of mild TBI, some of these patients develop persistent disabling symptoms despite having a normal NCCT. There is no current standard technique to identify which of these mild TBI patients will experience unfavorable long-term outcomes. Identifying patients with mild TBI who are likely to develop persistent disability within the time frame of a clinical trial could lead to the development of therapies for this condition.

We support the TED Initiative and TRACK-TBI's proposed plan to study GFAP and UCH-L1 as prognostic enrichment biomarkers. Inclusion of patients expected to develop clinically relevant disability over the course of a clinical trial of reasonable duration may enhance the potential to observe clinically meaningful effects of novel therapeutic agents. Such application is consistent with the FDA's draft guidance "Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products."[1] Greater experience with the use of these biomarkers in clinical trials may be useful to more accurately determine their clinical utility for prognostic enrichment, drug development decisions, and study design considerations.

[1] https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm332181.pdf

We support the TED Initiative and TRACK-TBI's plan to leverage blood-based biomarker data from multi-center studies, allowing within-study and between-study comparisons to elucidate the prognostic accuracy of blood-based biomarkers. Additionally, we recommend further studies to improve the current understanding of the biological and analytical variations in biomarker levels and to determine optimal biomarker cut points for informing TBI outcome prognostication. Because blood-based biomarkers of TBI may be elevated irrespective of the underlying cause of brain injury and may also be elevated in injuries to the peripheral nervous system, we encourage the conduct of additional studies that will elucidate the role of confounding factors, such as age, polytrauma, gender, and various comorbidities, on blood levels of proposed biomarkers of brain injury. Strong emphasis on applying good scientific and laboratory practices for quality control and validation of the proposed biomarkers is imperative.

We encourage exploration of blood levels of GFAP and UCH-L1 to identify patients with mild TBI who may be more likely to develop persistent disability from their injuries for the purpose of clinical trial enrichment. We will consider data collection on these biomarkers to be exploratory in nature. When including biomarkers in clinical trials, sponsors are encouraged to employ consensus TBI Clinical Data Interchange Consortium (CDISC)[2] standards for data harmonization. We believe data sharing and integration across trials can foster an accelerated path for TBI drug development programs. If sponsors intend to include analyses of these biomarkers to support regulatory decision making for a given Investigational New Drug (IND) development program, they should prospectively discuss the approach to these analyses with the Division of Neurology Products in CDER.

Any groups (academia, industry, and government) that would like to join in this effort or have information or data that may be useful can contact Dr. Geoff Manley (manleyg@ucsf.edu), the TED Initiative and TRACK-TBI point of contact for this project, or view the TED Initiative and TRACK-TBI websites.

Signed:

Christopher Leptak, MD/PhD
Director, CDER Biomarker Qualification Program

Billy Dunn, M.D.
Director, OND Division of Neurology Products

[2] https://www.cdisc.org/standards

Appendix 4

TRACK-TBI
Transforming Research and Clinical Knowledge in Traumatic Brain Injury
International Traumatic Brain Injury Research Initiative

TBI Endpoints Development Initiative
A collaborative for advancing diagnosis and treatment of TBI

TRACK-TBI/TED Initiative Strategic Planning Meeting Agenda

Day 1 | January 31, 2018 Mission Hall Room 2103

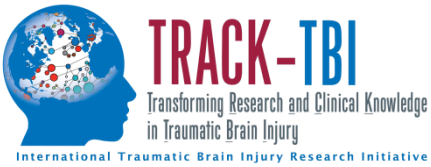
8:00am – 8:30am	**Continental Breakfast**
8:30am – 9:00am	**Meeting Overview and High-Level Objectives for TRACK and TED** Timeline and Review of Current Grants | Manley • U01, U01 NCE, TED, HDFT, SDII, Precision Trauma Review of pending/potential grants | Manley & Markowitz • TRACK-TBI Long; DoD/MTEC Phase 2 Clinical Trial Network; NINDS U01 Validation of Biomarkers • Update on Public-Private Partnerships • Goals for the Meeting
9:00am – 10:00am	**AIMs Completion: Status Report by Core** • COAs | Giacino & Team • Imaging biomarkers | Mukherjee • Biofluid biomarkers | Diaz-Arrastia, Wang, & Korley • Clinical | Robertson & Okonkwo, Duhaime, Gardner • Biostatistical/CER | Temkin, Jain & Seabury
10:00am – 10:30am	**Review of SWOT Analyses |** Manley & Markowitz
10:30am – 10:40am	**Coffee Break**
10:40am – 12:00pm	**Core Breakouts: Clinical, Imaging & Blood-based Biomarkers, Outcomes** • Research priorities, plans for 2018, continuing and new resource requirements, 2018 abstract cycle titles (MHSRS/INTS), plans for new grants/sustainability, 5-year plan **Clinical MH-2103, Outcomes MH-2107, Biomarkers MH-2108**
12:00 pm – 12:45pm	**Group Lunch Main Conference Room**
12:45pm – 1:15pm	**Core Breakouts Report Back**
1:15pm – 2:35pm	**Interactive Discussion Among All Cores Toward Way Forward** • Biomarker and COA Validation • Characterizing acute phenotypes and outcome phenotypes • Tracking TBI natural history • Translation toward optimizing clinical trials
2:35pm – 2:40pm	**Data Acquisition and Quality Committee/Task Force** | Manley
2:40pm – 3:00pm	**TRACK-TBI Network: Different Models** | Markowitz & Diaz-Arrastia
3:00pm – 4:00pm	**New Ideas / Directions** | Okonkwo, Gardner, Korley, Stein, Manley
4:00pm – 5:15pm	Free
5:30pm	Shuttle pick up at Hyatt Regency Embarcadero for dinner at the Manley's Southside of hotel on Market Street in 'white zone' - Look for Brian

TRACK-TBI/TED Initiative Strategic Planning Meeting Agenda

Day 2 – February 1, 2018 | Mission Hall Room 2103

8:00am – 8:30am	**Continental Breakfast**
8:30am – 8:50am	**Introduction of external Scientific Advisors and Guests** **Overview: Grants and Timelines (Manley)**
8:50am – 9:10am	**Report Back of Day 1 (Markowitz)**
9:10am – 10:20am	**Core Action Plans** • COAs | Giacino & Team • Imaging Biomarkers | Mukherjee • Biofluid Biomarkers | Diaz-Arrastia, Wang, & Korley • Clinical | Robertson & Okonkwo, Duhaime, Gardner • Biostatistical/CER | Temkin, Jain & Seabury
10:20am – 10:30am	**Coffee Break**
10:30am - 11:30am	**Interactive discussion with Scientific Advisors and Key Personnel**
11:30am - 12:00pm	**Wrap Up** • Plans for completion of TRACK, TED, HDFT, SDII • Plans for launch of TRACK-TBI Precision Medicine
12:00pm	**Strategic Planning Meeting Adjourned**
12:15pm – 4:00pm	**Data Curation Breakout Meeting | MH-2107**

Appendix 5



TRACK-TBI/TED Investigators Meeting

August 11-12, 2018 | Toronto, ON

Pier 2 | Westin Harbour Castle

Saturday, August 11

12:00pm – 12:15pm | Welcome/Objectives of Meeting

12:15pm – 12:30pm | TRACK-TBI + add on study enrollment status/timelines

- TRACK-TBI, Abbott, i-STAT, HDFT, SDII, TED Friend Controls

12:30pm – 2:00pm | Update on follow-on grants/collaborations/pending grants

- TRACK-TBI Precision Medicine, TRACK-TBI LONG, TRACK-TBI NET, DOE/National Laboratories
- Potential Abbott pivotal trial

2:00pm – 3:00pm | AIMs Completion Status & Synergies by Core / TRACK-TBI & TED Initiative / Review Data request pipeline

3:00pm – 3:15pm | Coffee Break

3:15pm – 5:30 pm | Core Breakout Sessions / Priorities by Study

❖ TRACK-TBI U01 closeout procedures; TED; TRACK-TBI Precision Medicine, LONG, & NET Start-up Plans

- COAs | Giacino & Team
- Imaging Biomarkers | Mukherjee
- Biofluid Biomarkers | Diaz-Arrastia, Wang, & Korley
- Clinical | Robertson & Okonkwo
- Data Management & Curation | Vassar & Brinck

5:30 pm – 6:00pm | Wrap up, Goals for InTBIR, September DOE meeting, Writing retreat

6:00pm – 8:00pm | Cocktails & Hors d'oeuvres | The Goodman Pub & Kitchen

Sunday, August 12

8:00am – 8:30am | Continental Breakfast

8:30am – 9:30am | Core Readouts / Summary Reports

9:30am – 10:45am | All Hands discussion

10:45am – 11:00am | Coffee Break – Private Partners, Funders will join

11:00am – 12:00pm | Welcome to Private Partners / Targeted Action Plan for TRACK-TBI NET

Appendix 6

2018 MHSRS Abstracts Submitted

1 ***Point-of-Care GFAP versus core lab S100B Biomarker Testing for CT Abnormalities in Traumatic Brain Injury: a prospective TRACK-TBI study***
Okonkwo D, Puffer R, Puccio A, Yue J, Diaz-Arrastia R, Korley F, Wang K, Mukherjee P, Yuh E, Temkin N, Robertson C, Manley G and the TRACK-TBI Investigators

2 ***Acute blood levels of two neuronal biomarkers (UCH-L and NSE): Correlation to injury cranial CT abnormality – A TRACK-TBI Phase 1 study***
Wang K, Lautenslager L, Munoz-Pareja J, Diaz-Arrastia R, Korley F, Puccio A, Yue J, Mukherjee P, Yuh E, Temkin N, Robertson C, Sun X, Jain S, Manley G and the TRACK-TBI Investigators and TED Investigators

3 ***Diagnostic utility of plasma glial fibrillary acidic protein (GFAP) for identification of traumatic brain injury patients with MRI abnormalities despite a normal head CT: A TRACK-TBI study***
Yue, Korley, Choy W, Puffer R, Winkler E, Deng H, Taylor S, Ferguson A, Huie J, Sun X, Jain S, Yuh E, Mukherjee P, Puccio A, Wang K, Diaz-Arrastia R, Okonkwo D, Manley G, and the TRACK-TBI Investigators

4 ***CT and MRI prognostic biomarkers for -month outcome in mild traumatic brain injury: A TRACK-TBI study***
Yuh E, Levin H, Taylor S, Sun X, Mac Donald C, Temkin N, Giacino J, Markowitz A, Mukherjee P, Dikmen S, Jain S, Manley G, and the TRACK-TBI Investigators

5 ***Characteristics and course of clinical recovery in civilian patients with mild traumatic brain injury (GCS 13-15)***
Nelson L, Temkin N, Dikmen S, Manley G, and the TRACK-TBI Investigators

6 ***Glasgow Outcome Scale Extended—Differences counting disability from only brain injury versus including peripheral injuries in those with Glasgow Coma Scale 13-15: A TRACK-TBI study***
Temkin N, Zahniser E, Morrissey M, Barber J, Machamer J, Manley G, Dikmen S

7 ***Glasgow Outcome Scale Extended—Differences counting disability from only brain injury versus including peripheral injuries in those with GCS Scale 3-12***
Temkin N, Satris G, Machamer J, Manley G, Dikmen S

8 ***The Functional Status Examination as a measure of functional status following mild traumatic brain injury***
Zahniser E, Temkin N, Machamer J, Manley G, Nelson L, Dikmen S

9 ***Functional Status Examination in patients with moderate-to-severe traumatic brain injuries***
Machamer J, Temkin N, Manley G, Dikmen S

10 ***Prevalence and predictors of suicidality following mild TBI***
Fisher L, Agtarap S, Jain S, Sun X, Manley G, Giacino J, Stein M, on behalf of the TRACK-TBI Investigators

11 ***An evidentiary review of the Glasgow Outcome Scale – Extended: Is it appropriate for use in TBI clinical trials***
Christoforou A, Bergin M, Armstrong M, Robbins A, Merillat S, Erwin P, Getchius T, McCrea M, Giacino J

12 ***The validity of the Rivermead Post-Concussion Questionnaire in detection and monitoring of post-concussive symptoms***
Christoforou A, Agtarap S, Merillat S, Erwin P, Stein M, Giacino J

13 ***Feasibility assessment of a flexible outcome assessment battery for use in longitudinal TBI Research***
Bodien Y, Sherer M, Taylor S, Dikemen S, Yue J, Murray S, Corrigan J, Levin H, Temkin N, Machamer J, Boase K, Vasser M, McCrea M, McAllister T, Whyte J, Kramer J, Ngwnenya L, Manley G, Giacino J, and the TRACK-TBI Investigators

14 ***Location of brain contusions and outcome of GCS 9-15 TBI patients in the TRACK-TBI pilot study***
Levin H, Robertson C, Mukherjee P, Yuh E, Giacino J, Temkin N, Yan F, Manley G and the TRACK-TBI Pilot Investigators

Point-of-Care GFAP versus core lab S100B Biomarker Testing for CT Abnormalities in Traumatic Brain Injury: a prospective TRACK-TBI study

Author List: David Okonkwo, Ross Puffer, Sonia Jain , Ava Puccio, John Yue, Xiaoying Sun, Ramon Diaz-Arrastia, Fred Korley, Kevin Wang, Pratik Mukherjee, Esther Yuh, Nancy Temkin, Claudia Robertson, Geoffrey T. Manley and the TRACK-TBI Investigators

Introduction

Glial fibrillary acidic protein (GFAP) is one of the strongest candidate diagnostic biomarkers in traumatic brain injury (TBI), demonstrating high sensitivity to detect lesions on head CT when measured in the acute phase (detectable 1 hour after injury and peak concentrations reached at 16-20 hours). The clinical utility of serum GFAP as a TBI biomarker is most frequently compared with S100B, a small protein involved in calcium homeostasis also released after trauma. To date, in clinical practice, limitations of the utility of S100B and GFAP include the need to measure them within 6 and 12 hours of injury, respectively, and the impact of extracranial injuries (polytrauma) on test specificity. This study leverages the prospective, multicenter, observational Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study to analyze the point-of-care i-STAT test (in development, Abbott Laboratories, Abbott Park, IL) that returns results within 15 minutes for GFAP versus a core lab S100B test for potential detection of CT abnormalities.

Methods

TRACK-TBI enrolls participants with presenting TBI across the injury (GCS 3-15) and demographic spectra and controls, at 11 U.S. Level 1 trauma centers. To be eligible, TBI subjects had to have undergone non-contrast head CT upon arrival in the emergency department as a part of their clinical TBI evaluation. Blood samples were collected from subjects who consented to genetic and proteomic analysis within 24h of injury. Sample analyses for GFAP were carried out by a single laboratory (i-STAT, Abbott Laboratories) in blinded fashion, and analyses for S100b occurred at a single laboratory (University college of Dublin) in blinded fashion. CT scans were graded according to published recommendations by the neuroimaging working group of the TBI-CDEs. We performed area under the receiver operating characteristic curve (AUC) analyses to determine the ability of GFAP to discriminate among patients with varying CT findings, and compare this AUC curve to one generated by the analysis of S100B from the same samples.

Results

A total of 1359 TBI subjects and 122 orthopedic controls had EDTA plasma drawn for GFAP analysis. All TBI subjects underwent a CT scan, while only 16 orthopedic controls had a CT scan performed (all negative). A total of 1285 TBI subjects underwent a CT and had serum S100B analyzed. Injury mechanisms included 815 (60.1%) road traffic accidents, 336 (24.8%) incidental falls, 97 (7.2%) episodes of violence or assault, and 108 (7.9%) classified as “other” injuries. Ninety-three (7.3%) subjects presented with severe TBI (GCS 3-8), 48 (3.8%) presented with moderate TBI (GCS 9-12), and 1137 (88.9%) presented with mild TBI (GCS 13-15). In the GFAP cohort, 810 (59.6%) subjects had a negative head CT, while 549 (40.4%) had a positive

CT. GFAP levels were significantly increased in subjects with a positive head CT (mean 3974.3 pg/ml, SD 7820.2 pg/ml) compared to those with a negative head CT (mean 363.8 pg/ml, SD 706.3 pg/ml) and orthopedic controls (mean 23.8 pg/ml, SD 37.3 pg/ml), $p<0.001$. The AUC for GFAP was significantly higher than S100B in the same patient cohort (GFAP AUC – 0.853 95% CI 0.833-0.874, S100B AUC – 0.666 95% CI 0.636-0.696), $p<0.001$.

Conclusion:

In the prospective TRACK-TBI study, GFAP substantially outperformed S100B as a TBI blood biomarker indicative of positive head CT. The AUC of GFAP was 0.853, falling in the "very good" category, as compared with the AUC of S100B (0.666 – poor) in the same cohort. Further, GFAP can potentially be used in a broader cohort of TBI patients in the ED, namely patients further than 6 hours from time of injury, as well as patients with concomitant polytrauma. In addition, with a point-of-care platform, blood values of GFAP can be ascertained in <15 minutes. Taken together, the results of this analysis strongly suggest that GFAP will supplant S100B as the most common diagnostic biomarker for CT scan abnormalities after TBI. The point-of-care platform opens the door to forward deployment of biomarker technology for use in military settings.

Acute blood levels of two neuronal biomarkers (UCH-L1 and NSE): Correlation to cranial CT abnormality: a TRACK-TBI Phase 1 study

Kevin K. Wang1, Lauren Lautenslager1, Jennifer C. Munoz-Pareja1, Ramon Diaz-Arrastia2, Fred Korley3, Ava Puccio4, John Yue5, Pratik Mukherjee5, Esther Yuh5, Nancy Temkin6, Claudia Robertson7, Xiaoying Sun8, Sonia Jain8, Geoffrey T. Manley5 and the TRACK-TBI Investigators5 and TED Investigators5

1. University of Florida, Gainesville, FL
2. University of Pennsylvania, Philadelphia. PA
3. University of Michigan, Ann Arbor, MI
4. University of Pittsburgh, Pittsburgh, PA
5. University of California, San Francisco, CA
6. University of Washington, Seattle, WA
7. Baylor College of Medicine, Houston, TX
8. University of California, San Diego, La Jolla, CA
9. Brain Rehabilitation Research Center, Malcom Randall VA Medical Center, Gainesville, FL

Background

Traumatic brain injury (TBI) is a major cause of death and disability in the United States and it is particularly pervasive in populations of service men and women. Healthcare costs associated with managing and mediating the effects of TBI are astronomical and hampered by scant appropriate diagnostic and treatment guidelines. Currently, there are no FDA-approved treatments for acute TBI and diagnostic approaches rely heavily on the Glasgow Coma Scale (GCS) and CT pathology. In addition to these diagnostic approaches, emerging data support the use of biofluid-based TBI biomarker tests to diagnose TBI of varying severity, and also to predict outcomes. Two biomarkers of particular interest for TBI are two neuronal proteins - NSE (neuron-specific enolase) and UCH-L1 (ubiquitin C-terminal hydrolase-L1). NSE is a protein present in neurons in high concentration, but also present in neuroendocrine cells and red blood cells. UCH-L1 is a protein present in neuronal soma cytoplasm with recent research suggesting it to be a promising new TBI biomarker. Upon brain injury, UCH-L1 and NSE are released from injured neurons into the extracellular fluid and cerebrospinal fluid and then permeate the blood brain barrier or the glymphatic system to reach the circulating blood. Collective research results thus far have demonstrated blood NSE and UCH-L1 levels correlate with TBI severity/long-term prognosis; releases of these neuronal proteins are observed even in "mild" TBI (GCS 13-15). Using the large, and well-characterized Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) observational study, we systemically determined and contrasted the acute profiles of these two neuronal biomarkers in blood within the 24-hour period after TBI.

Methods:

The multisite TRACK-TBI study enrolls participants with presenting TBI across the injury (GCS 3-15) and demographic spectra, along with controls, at . Level 1 trauma centers. To be eligible, TBI subjects had to have undergone non-contrast head CT upon arrival in the emergency

department as a part of their clinical TBI evaluation. Blood samples were collected from subjects who consented to genetic and proteomic analysis within 24h of injury. At its interim analysis point, the study has enrolled 1,375 TBI subjects and 69 orthopedic injury subjects from whom serial blood sample biomarker measurements were collected. For this study, the serum and matching plasma samples collected within 24h post-injury were assayed with 2 clinical platforms: the Roche Cobas NSE assay and the Abbott i-STAT prototype UCH-L1 assay, respectively. The biosample biomarker analyses were correlated with cranial CT results, which is indicative of presence or absence of pathoanatomical abnormality (positive (+) vs negative (-) CT). Additionally, demographic and clinical characteristics of study participants and 2-week post-injury MRI data were also subjected to biomarker correlation analysis.

Results:
The TBI Cohort has 810 CT- subjects and 549 CT+ subjects. Plasma UCH-L1 levels had a median of 305 pg/mL (first and third quartile intervals (1Q-3Q) of 158 – 692 pg/mL) for CT+ subjects, which is significantly higher than the CT- counterpart (median 163 pg/mL; 1Q-3Q 85 – 306 pg/mL) ($p < 0.001$). Similarly, plasma NSE levels had a median of 26,055 pg/mL (1Q-3Q 15,683 – 44,965 pg/mL) for CT+ subjects, which is also significantly higher than the CT- cohort (median 17,510 pg/mL (1Q-3Q 13,150 – 26,810 pg/mL) ($p < 0.001$). Overall, Receiver Operating Characteristics (ROC) curve analysis shows an Area Under the Curve (AUC) of 0.683 (95% Confidence Interval (CI) 0.654 – 0.712) for UCH-L1, and an AUC of 0.635 (CI 0.604 – 0.666) for NSE. We also observed that plasma UCH-L1 levels declined over time within the first 24 h post-injury period (from median of 269.5 pg/mL in the 0-8 h interval to 167 pg/mL in the 17-24 h interval). NSE did not show such a decline (median of 18,390 pg/mL in 0-8 h vs. 19,130 pg/mL in 17-24 h interval). Further examination shows that UCH-L1 provides the best diagnostic discriminatory properties for CT abnormality when measured in the earliest interval (0-8 h), with an ROC AUC of 0.779. In contrast, NSE has a ROC AUC of 0.695 in the same time interval.

Conclusion:
Comparing these TBI neuronal biomarkers examined, UCH-L1 outperformed NSE as an acute (≤24 h) diagnostic biomarker for CT abnormality in the TRACK-TBI cohort. Importantly, plasma UCH-L1 alone is found to be a fair early (0-8 h) biomarker for the identification of subjects who will have a CT-detectable pathoanatomical abnormality.

Diagnostic utility of plasma glial fibrillary acidic protein (GFAP) for identification of traumatic brain injury patients with MRI abnormalities despite a normal head CT: A TRACK-TBI study

John K. Yue,[1,2,*] Frederick K. Korley,[3,*] Winward Choy,[1,2] Ross C. Puffer,[4,5] Ethan A. Winkler,[1,2] Hansen Deng, [1,2] Sabrina R. Taylor,[1,2] Adam R. Ferguson,[1,2] J. Russell Huie,[1,2] Xiaoying Sun,[6] Sonia Jain,[6] Esther L. Yuh,[2,7] Pratik Mukherjee,[2,7] Ava M. Puccio,[5] Kevin K. W. Wang,[8] Ramon Diaz-Arrastia,[9] David O. Okonkwo,[5] Geoffrey T. Manley,[1,2] and the TRACK-TBI Investigators

[1] Department of Neurological Surgery, University of California San Francisco, San Francisco, CA
[2] Brain and Spinal Injury Center, Zuckerberg San Francisco General Hospital, San Francisco, CA
[3] Department of Emergency Medicine, University of Michigan, Ann Arbor, MI
[4] Department of Neurological Surgery, Mayo Clinic, Rochester, MN
[5] Department of Neurological Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA
[6] Division of Biostatistics and Bioinformatics, University of California San Diego, San Diego, CA
[7] Department of Radiology, University of California San Francisco, San Francisco, CA
[8] Department of Psychiatry and Neurosciences, McKnight Brain Institute, University of Florida, Gainesville, FL
[9] Department of Neurology, Center for Neurodegeneration and Repair, University of Pennsylvania, Philadelphia, PA

[*]Authors contributed to this work equally

Background: Traumatic brain injury (TBI) comprises a spectrum of intracranial pathologies, some of which remain diagnostic challenges. Glial fibrillary acidic protein (GFAP), a marker of astroglial injury, is released into the systemic circulation following TBI and correlates with acute intracranial pathology on computed tomography (CT). However, up to 27% of TBI patients suffer injuries not readily detectable on CT (e.g., gliding contusions, diffuse axonal injury) but which are present on magnetic resonance imaging (MRI). These injuries can cause chronic sequelae and impairment, and pose unique challenges to TBI diagnosis, severity stratification, and triage. A blood-based biomarker capable of identifying patients with these CT-occult injuries that are present on MRI will enable better diagnosis, inform treatment and surveillance strategies, and improve clinical trials.

Methods: The NIH-funded, prospective, 18-center Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) enrolled patients with TBI and controls who were triaged to a participating U.S. level 1 trauma center. The study enrolls participants with presenting TBI across the injury spectrum (Glasgow Coma Scale (GCS) score 3-15) and demographic spectra and who have received a clinically-indicated head CT within 24 hours of injury. For the current analysis, we included participants who had no acute intracranial pathology on the clinical head CT; and who had consented to analyses of blood samples drawn within 24 hours of injury, and who received a TRACK-TBI research MRI within two weeks following injury. Acute traumatic intracranial pathology on CT and MRI were evaluated by one central board-certified neuroradiologist according to the NIH/NINDS Neuroimaging Common Data Elements (https://www.commondataelements.ninds.nih.gov/TBI.aspx). Patients were grouped by CT-negative/MRI-negative (CT-/MRI-) and CT-negative/MRI-positive (CT-/MRI+). GFAP plasma concentrations (pg/mL) were analyzed by Abbott Laboratories. Blood samples from participants who suffered extracranial trauma (orthopedic controls (OC)) but no TBI were analyzed using the same assay. Median and interquartile ranges (IQR) are reported for biomarkers. The Wilcoxon Rank Sum test was performed for continuous variables, and Fisher's exact test for categorical variables. Area under the receiver-operating characteristic curve (AUC) was calculated to evaluate the discriminative ability of GFAP for intracranial abnormality on MRI in CT- TBI patients, with 95% confidence intervals reported. To evaluate the influence of time from injury on the discriminative values, GFAP was analyzed in 6 hour

time intervals (0-6h, 7-12h, 13-18h, 19-24h from injury). Analyses were performed using the statistical software R version 3.3.2 (http://www.r-project.org). Statistical significance was assessed at $p<0.05$.

Results: Data from 454 participants with TBI (CT-/MRI-: n=320, CT-/MRI+: n=134) and 122 OC were evaluated; 29.5% of CT- participants were MRI+. TBI patients were 63.2% male and 73.6% Caucasian. Injury mechanism was 67.0% road traffic accident, 20.0% incidental fall, 4.6% violence/assault, and 8.4% other. From the ED, 52.4% were discharged home, 38.1% were admitted to hospital ward, and 9.5% were admitted to intensive care unit. GFAP ranges by participant group were: OC: 0-217, CT-/MRI-: 0-1865, CT-/MRI+: 5-4095, and GFAP values were associated with likelihood of intracranial injury (OC: 13 IQR [7-20], CT-/MRI-: 74 [17-213.5], CT-/MRI+ 368.5 [122.75-796]; $p<0.001$), with the highest values seen in the CT-/MRI+ group.

Overall, GFAP showed fair discriminative ability for CT-/MRI+ vs. CT-/MRI- (AUC 0.76, 95% CI [0.71-0.81], $p<0.001$). When considering time between injury and blood draw, GFAP's discriminative ability for CT-/MRI+ vs. CT-/MRI- was (AUC 0.74 at 0-6h, AUC 0.68 at 7-12h, AUC 0.84 at 13-18h, AUC 0.79 at 19-24h), with the highest AUC obtained at 13-18 hours from injury.

Conclusion: To our knowledge, this is the first study to evaluate the discriminatory ability of plasma GFAP for evidence of traumatic intracranial pathology on MRI and indicates that the GFAP biomarker is more sensitive than CT. With nearly 30% of CT- participants showing intracranial injury on MRI, the burden of undetected TBI by our current standard of care is significant. GFAP shows evidence for detecting CT-occult injuries with an AUC of 0.70-0.80, which with optimal cutoff levels should capture the bulk of the 30% MRI+ patients in the population, and identify those who need an MRI. Analyzing blood GFAP levels within 24 hours of injury could improve TBI diagnosis, acute management, and follow up. Our findings also suggest that there may be a role for serial measurements of serum GFAP in order to maximize its sensitivity and specificity.

CT and MRI prognostic biomarkers for 3-month outcome in mild traumatic brain injury: A TRACK-TBI Study

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BACKGROUND: Prior studies have demonstrated conflicting results regarding the relationship between acute and subacute brain imaging studies and medium- to long-term outcome after mild traumatic brain injury (TBI). In addition, there have been very few studies that demonstrate the relative clinical significance of different subtypes of intracranial pathology on admission head CT and early brain MRI to outcome.
METHODS: We studied 567 patients (≥17 years of age), who underwent head CT for suspicion of acute traumatic brain injury, and who had Glasgow Coma Scores (GCS) of 13-15 upon Emergency Department (ED) arrival. These patients were enrolled prospectively in the multicenter Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study. TRACK-TBI enrolls participants with presenting TBI across the injury (GCS 3-15) and demographic spectra, along with controls, at 18 Level 1 trauma centers across the US. . A neuroradiologist assigned NIH-NINDS Common Data Element (CDE) descriptors to each pathoanatomic abnormality on the initial head CT, performed within 24 hours of ED arrival, and post-acute brain MRI, performed 2 weeks after injury. For head CT, these CDEs included subarachnoid hemorrhage, subdural hematoma, brain contusion, hemorrhagic axonal injury, epidural hematoma, and skull fracture on admission head CT. For brain MRI, the CDEs included brain contusion and traumatic/diffuse axonal injury. Glasgow Outcome Scale–Extended (GOSE) was assessed at 3 months after injury. The Wilcoxon Rank Sum test (Mann-Whitney U test) and Kruskal-Wallis test were performed to assess for relationships between CT and MRI features and 3-month GOSE outcome.
RESULTS: Study patients (365 male, 202 female) were 17 to 90 yrs of age (mean 39 yrs, SD 16.7 yrs, median 34 yrs, interquartile range 25-51 yrs), with 0 to 20 years of formal education (mean 14 yrs, SD 2.7 years, median 14 yrs, interquartile range 12-16 yrs). The 3-month GOSE distribution (3-8) was as follows: 3-Lower severe disability (1% subjects),

4-Upper severe disability (1% of subjects), 5-Lower moderate disability (10% of subjects), 6-Upper moderate disability (17% of subjects), 7-Lower good recovery (28% of subjects), and 8-Upper good recovery (43% of subjects). Regarding head CT, 30% of all subjects had at least one type of acute intracranial pathology on initial head CT, most often subarachnoid hemorrhage (19% of subjects), followed by subdural hematoma (13% of subjects), brain contusion (9% of subjects), epidural hematoma (5% of subjects), and hemorrhagic axonal injury (4% of subjects). The Wilcoxon Rank Sum test indicated statistically significant relationships at $p<0.05$ for unfavorable outcome (lower GOSE) at 3 months with the following head CT features: any acute traumatic intracranial injury ($p = 0.004$), acute subarachnoid hemorrhage ($p = 0.02$), and brain contusion ($p < 0.001$). Kruskal-Wallis test for a relationship between 3-month GOSE and Rotterdam CT score did not reach statistical significance ($p = 0.18$). Regarding subacute brain MRI, 47% of subjects had traumatic intracranial pathology, including brain contusion (15% of subjects) and traumatic (14% of subjects) and diffuse axonal injury (12% of subjects). Wilcoxon Rank Sum test showed a statistically significant relationship of 3-month GOSE to brain contusion ($p = 0.008$) but not to traumatic axonal injury or diffuse axonal injury ($p = 0.99$).

CONCLUSION: We demonstrate the clinical relevance of subtypes of acute intracranial pathology on admission head CT and subacute brain MRI in 567 subjects with GCS 13-15 in the prospective multicenter TRACK-TBI study. Less favorable 3-month GOSE was significantly associated with acute subarachnoid hemorrhage and brain contusion on admission head CT, and with brain contusion on subacute brain MRI.

Characteristics and Course of Clinical Recovery in Civilian Patients with Mild Traumatic Brain Injury (GCS 13-15)

Lindsay D. Nelson, Nancy R. Temkin, Sureyya S. Dikmen, Jason Barber, Geoffrey T. Manley, and the TRACK-TBI Investigators

Background. Traumatic brain injury (TBI) is a highly prevalent injury, and the vast majority (> 80%) of TBIs have been historically classified as "mild" (mTBI) based on acute injury characteristics (i.e., admission Glasgow Coma Scale, or GCS, score of 13–15). Although mTBI is commonly thought to rapidly resolve with no long-term sequelae, the prevalence and time course of functional limitations for civilian patients with mTBI is unclear owing to variable study methodology in prior research. Furthermore, there is evidence that the historical definition of mTBI based on GCS score alone results in aggregating patients with diverse injuries and prognoses into a single group. Our goal was to characterize the nature and time course of recovery in major domains of day-to-day functioning following civilian mTBI (those with admission GCS 13-15) from 2 weeks to 12 months postinjury using data from the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study, the largest prospective study of civilian mTBI patients to date. We characterized outcomes separately by the presence versus absence of acute intracranial findings on clinical head CT in order to provide separate prognostic information for patients with complicated (CT+) versus uncomplicated (CT-), respectively.

Methods. The multisite TRACK-TBI study enrolls participants with presenting TBI across the injury (GCS 3-15) and demographic spectra, along with controls, at 18 Level 1 trauma centers across the US. To be eligible, TBI subjects must have undergone non-contrast head CT upon arrival in the emergency department as a part of their clinical TBI evaluation. This study included TBI patients in the current TRACK-TBI sample who had an admission GCS score of 13–15 (N = 1,155, 343 CT+, 781 CT-). All participants were enrolled within 24 hours of injury and provided clinical outcome data at 2 weeks and 3, 6, and 12 months postinjury. The primary outcome was return to normal functioning in broad life domains (e.g., independence in home, travel, work, and social activities) as measured with the Glasgow Outcome Scale—Extended (GOSE).

Results. At 2 weeks postinjury, only 16% of CT- and 9% of CT+ ($p < .001$) reported being back to normal functioning in all major life areas (GOSE 8). At 12 months, 51% of mTBI patients whose acute CTs were negative reported having returned to their normal pre-injury levels of functioning (i.e., were back to work or other preinjury activities and without disabling mTBI symptoms). Having a positive acute head CT was associated with significantly more long-term impairment ($p < .001$); only 37% of CT+ patients reported being back to normal pre-injury levels of functioning in all major life areas at 12 months postinjury.

Conclusions. The findings imply that civilian patients with mTBI, as defined by admission GCS 13-15, have substantial rates of disability at 12 months postinjury. Furthermore, the presence of acute intracranial injury on head CT is associated with poorer functional outcome. These findings suggest that the more favorable prognoses seen in other head injury populations (i.e., athletes treated in the community) do not translate to civilian patients treated in level 1 trauma centers. Further work is needed to explicate the mechanisms underlying persistent difficulties faced by these patients and to develop effective treatment strategies to reduce morbidity in this population.

Glasgow Outcome Scale Extended—Differences counting disability from only brain injury versus including peripheral injuries in those with Glasgow Coma Scale 13-15: A TRACK-TBI study

Temkin N, Zahniser E, Morrissey M, Barber J, Machamer J, Manley G, Dikmen S

Background: The Glasgow Outcome Scale-Extended (GOSE) is the most common outcome measure utilized in acute clinical treatment trials of traumatic brain injury (TBI) enrolling those with moderate-to-severe injury (i.e., Glasgow Coma Scale [GCS] scores of ≤12). As potential therapies for mild TBI (i.e., GCS 13-15) are developed and evaluated, the GOSE may also be used in these trials. The GOSE may be administered 2 possible ways: 1) to evaluate disability due *only* to the TBI (GOSE-TBI) or, 2) accounting for the TBI *plus* peripheral traumatic injuries sustained in the incident (GOSE-all). According to its developers, the GOSE measurement approach should be selected based on the purpose of the research. Unfortunately, the option of administering the measure 2 ways is not widely recognized (for example, the NINDS TBI Common Data Elements do not have a variable to indicate which approach was taken). It is not clear whether and how large an effect the scoring methodology decision may have for those patients classified with a TBI assessed at GCS 13-15, or for the calculation of statistical power or required sample size for a clinical treatment trial that does not target TBI and peripheral injuries equally. This analysis uses data from the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study to assess differences in distributions of GOSE scores depending whether data are collected to assess TBI-related disability alone (GOSE-TBI), or global disability associated with an injury that includes mTBI (GOSE-all).

Methods: TRACK-TBI is a multi-center prospective longitudinal study of TBI, with an enrollment goal of 3000 participants and examination of outcome at 2 weeks, 3 months, 6 months, and 12 months after injury. The study enrolls participants with presenting TBI across the injury (GCS 3-15) and demographic spectra, along with controls, at 18 Level 1 trauma centers geographically distributed across the US. Starting approximately 6 months into enrollment, TRACK-TBI began collecting both GOSE-TBI and GOSE-all scores. As of March 2018, TRACK-TBI has 663, 708, 788, and 772 participants (with a GCS of 13-15) and the GOSE scored both ways at 2-weeks, 3-months, 6-months, and 12-months post-injury, respectively. Participants were divided into subgroups defined by whether there were intracranial abnormalities on their acute CT (i.e., CT-positive vs. CT-negative), and further divided into those who had sustained moderate other system injuries (Non-TBI Injury Severity Score [ISSnon] = 0-8 or not admitted to hospital) and those with serious other system injuries (ISSnon ≥9). Within each of the resulting 4 subgroupings and at each of the 4 timepoints post-injury, the distributions of GOSE-TBI and GOSE-all scores were compared in terms of the proportions of participants at or below each possible GOSE score. Differences of <5, 5-10, 10-20, and >20 percentage points between the proportions of GOSE-all vs. GOSE-TBI scores at a given score were considered to reflect small, moderate, large, and extreme differences, respectively. Data will be presented as stacked bars within each subgroup and at each timepoint.

Results: Moderate differences were seen at 2 weeks for those with CT abnormalities and moderate other system injuries (e.g., 75% of GOSE-all scores and 66% of GOSE-TBI scores fell at or below 6, a difference of 9 percentage points). In contrast, at 2-week follow-up extreme differences were seen in all other groups (e.g., for those with normal CT and moderate other system injuries, 68% of GOSE-all scores and 44% of GOSE-TBI scores fell at or below 6, reflecting a difference of 24 percentage points). At 3-months post-injury extreme differences were seen for those with normal CT and serious other system injuries; large differences for those with normal CT and moderate other injuries, or abnormal CT and serious other injuries;

and moderate differences for those with abnormal CTs and moderate other injuries. At 6-month follow-up, large differences were seen in those with serious other injuries, and moderate differences were seen in those with moderate other injuries, regardless of CT status. By 12 months, moderate differences were seen in those with serious other injuries and those with no CT abnormalities, while those with CT abnormalities and moderate other injuries had small differences.

Conclusion: GOSE-TBI and GOSE-all scores differed substantially in their score distributions. Differences diminished over time, but persisted even at 12-month follow-up. The magnitude of differences depended both on CT findings and other system injury severity, with participants without intracranial CT abnormalities and those with serious other system injuries displaying greater discrepancies between GOSE-TBI and GOSE-all score distributions. These results indicate that the selection of the GOSE scoring method for those with a TBI of GCS 13-15 may have substantial impact on the observed magnitude and distribution of functional outcome post-injury. Selecting GCS 13-15 participants with CT abnormalities may reduce these differences. Further research is needed to explore the effect of these differences on the sample size needed for clinical trials.

Glasgow Outcome Scale Extended—Differences Counting Disability from Only Brain Injury versus Including Peripheral Injuries in those with GCS 3-12

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Objectives:
To determine the extent scores differ if disability from only the brain injury is counted compared to if disability from brain injury and other injuries occurring in the same event are included.

To determine the effect on sample size for a clinical trial of including disabilities from other injuries in the GOSE when the treat affects the disability only from the TBI.
Method: This is secondary analysis of data from a clinical trial. At 1, 3, and 6 months post-injury, about 450 cases with moderate or severe traumatic brain injury (TBI) were asked the structured interview for the Glasgow Outcome Scale Extended (GOSE) first considering only their brain injury. After each section they were then asked whether their answer would change if other system injuries were included. The distribution of scores are summarized by time after injury, brain injury severity (Moderate-Glasgow Coma Scale motor [GCSm] score 5-6 or Severe-GCSm1-4) and other system injury severity (Injury Severity Score excluding the brain (ISSnon)= 0-8, 9-15, or >=16) and presented as stacked bar graphs.

The relative effect on sample size was determined by simulation. Data from 6 months after injury were used since that is the most common time to evaluate endpoints for a treatment for moderate to severe TBI.

Results: At 1 month, differences were slight (<5 percentage points at any dichotomization cutpoint) for almost all cases with mild ISSnon; moderate differences of 5 to 10 percentage points became more common with increasing other system injury severity. At 3 months there were only slight differences for ISSnon 0-8, a few moderate differences with ISS non 9-15 and moderate or large differences >=10 percentage points for ISSnon >=16, especially with moderate TBI severity. The pattern was similar at 6 months, with only a small decrease in the differences.

When the analysis compared the mean GOSE score, the sample size needed if the disability included other system injuries increased by 10% when those with substantial other system injuries (ISS>=16) could enroll. The increase was under 5% when only those with severe TBI and ISS<=15 were included.

The effect on sample size was much larger when the analysis compared the percent with favorable outcome (GOSE>=5). The sample needed to be over 1/3 larger when including disability from other system injuries when those with substantial other system injuries (ISS>=16) could enroll. The increase was 16% to 21% when those with moderate to severe TBI were included but enrollment was restriceted to those with ISS<=15. With enrollment restricted to severe TBI and ISS<=15, sample size increases were under 5%.

Conclusions: GOSE scores varied considerably depending on whether other system injuries were included in the scoring. This has implications for clinical trials and other studies using GOSE as an endpoint. Whether to rate GOSE on the brain injury alone or include all injury-

related disability should be decided depending on the goals of the study, staff should be trained and data monitored accordingly, and sample size should be determined depending on the expected or important differences in the measure as it will be administered.

The Functional Status Examination as a Measure of Functional Status Following Mild Traumatic Brain Injury

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Abstract

Background: The Functional Status Examination (FSE) is a comprehensive measure of functional status post-traumatic brain injury (TBI) that has been primarily used in studies of moderate-to-severe TBI. The present study examines functional status among ED-admitted patients who had sustained mild traumatic brain injuries (mTBIs; defined as GCS = 13-15 at admission). Study aims included examining the course of functional status following mTBI, as well as exploring relationships of functional status to other relevant constructs among the mildly brain injured. Methods: Subjects were drawn from the larger subject pool of the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study, a large-scale multi-center research effort assessing outcomes related to closed TBIs of all severities. A sample of 141 individuals (Mage = 41.4 [SD = 17.71; range = 18-88]; 33.3% female; 65.2% White, 29.1% minority, 5.7% did not identify racial/ethnic background; 77.3% GCS = 15) were assessed at 2 weeks, 3 months, 6 months, and 12 months post-injury for changes in functional status resulting both (a) from all injuries and (b) from TBI only. Post-traumatic symptoms, neuropsychological performance, life satisfaction, global psychiatric well-being, depression, and symptoms of post-traumatic stress were also assessed. Results: Among seven domains of day-to-day life functioning, participants generally experienced the greatest disruption in their primary activity (work or school) and in leisure and recreation. Subjects' overall functional status tended to improve over time, with sharpest increases in functionality occurring in the first three months post-injury. Most subjects experienced substantial improvements in functional status when considering all injuries; however, a sizable minority of participants reported no meaningful change in functional status with respect to TBI-specific impairments by one year post-injury. Functional status was largely unrelated to neuropsychological functioning, but related strongly to post-traumatic symptoms, life satisfaction, and emotional well-being, particularly at three months post-injury and beyond. Conclusion: Findings indicate that functional impairments related to mTBI may be more likely to persist than widely believed, with those who experience lingering functional deficits also reporting greater emotional health difficulties.

Functional Status Examination in Patients with Moderate-to-Severe Traumatic Brain Injuries

Joan Machamer, MA, Research Scientist, Nancy R. Temkin, PhD, Professor, Geoffrey T. Manley, MD, Professor, Sureyya Dikmen, PhD, Professor

The assessment of functional status after traumatic brain injury (TBI) is important. The Glasgow Outcome Scale (GOS) and its revised version Glasgow Outcome Scale Extended (GOSE) have been used most frequently in TBI research but there are concerns about **the sensitivity of** these measures. The current study evaluated the psychometric properties of the Functional Status Examination (FSE) using a sample of 448 moderately to severely injured subjects with traumatic brain injury (TBI). The FSE is significantly related to other measures of functional status including the GOSE, Short Form Health Survey and EuroQol Checklist($p < .001$), is sensitive to TBI severity ($p < .001$), and is responsive to recovery from 3 to 6 months post-injury ($p < .001$). In addition, there was a significant agreement ($r = .817$, $p < .001$) between the patient and significant other's assessment of functional status on the FSE at 6-months post-injury. The FSE may be a valuable measure of functional status after TBI given its strong psychometric properties including validity, sensitivity to brain injury severity, and recovery over time.

Prevalence and predictors of suicidality following mild TBI

Lauren B. Fisher, Stephanie Agtarap, Sonia Jain, Xiaoying Sun, Geoffrey Manley, Joseph T. Giacino, Murray B. Stein, on behalf of the TRACK-TBI Investigators

Background

Individuals who have sustained traumatic brain injuries (TBI) demonstrate elevated risk for suicidal ideation, suicidal behavior, and completed suicide compared to the general population.[1] Rates of suicide attempts after TBI range from less than 1% to 60%[2-3] depending on methodology, timeframes, and samples used. Similarly, estimated rates of suicidal ideation following TBI have ranged from 7% to 28%.[3-4] Limited research has examined predictors of suicidal behavior following TBI, though preliminary findings demonstrated that severity of depression soon after injury, history of prior suicide attempt, history of bipolar disorder, and having less than a high school education are predictive of suicidal ideation one-year post TBI.[5] Post-injury psychiatric disturbance is strongly associated with post-injury suicidality.[2] Lastly, pre-morbid history of aggression/hostility in psychiatric patients may be a risk factor for post-injury suicidality in individuals with mild TBI.[6] Such studies have provided initial insight into potential risk factors of suicidal ideation and suicidal behavior, but additional research is needed to determine reliable risk factors for suicidality following injury. Given this, the aims of the current study were to (1) determine the prevalence of suicidal ideation and behavior in the first year after TBI; and (2) identify predictors of suicidal ideation at 6-months post-TBI.

Methods

Patients were enrolled in the prospective, multi-center study Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI). Participants completed several self-report measures at 2 weeks, 3 months, 6 months, and 12 months post-injury. Participants who endorsed suicidal ideation on the Patient Health Questionnaire (PHQ-9) suicide item (item 9 ≥ 1) or Brief Symptom Inventory (BSI) suicide item (item 18 ≥ 1) then completed the Columbia Suicide Severity Rating Scale (C-SSRS) to further assess current (past month) and lifetime suicidal ideation and behavior. Demographic (age, race/ethnicity, education), pre-injury (history of psychiatric disorder, history of TBI) and injury-related variables (loss of consciousness, post-traumatic amnesia, ICU admission, mild TBI) were also collected. A propensity score weight-adjusted logistic regression model was constructed to assess the baseline risk factors associated with suicide ideation at 6-month follow-up.

Results

The current study utilized data from the first 1352 TRACK-TBI patients, 91% of whom sustained a mild TBI (GCS = 13-15), were on average middle-aged (*M* = 39.98, *SD* = 17.02), male (66.9%), non-Hispanic (78.2%), Caucasian (77.5%), and educated beyond high school (M_{yrs} = 13.51, *SD* = 2.87). The majority of participants had no history of psychiatric history (79.8%) or prior TBI (71.4%). Prevalence of suicidal ideation (SI) in the past 30 days was estimated at three months (3.70%), six months (3.80%), and twelve months (3.60%) post-injury. Prevalence of suicide attempt(s) within the past year was estimated at 12 months (0.2%) post-injury. At 6-month follow-up, history of mental illness (OR = 6.29 [2.34-16.92], $p <$ .001) and prior TBI (OR = 2.77 [1.23-6.28], p = .014) predicted greater risk of suicidal ideation following the most recent TBI. Conversely, presence of PTA (OR = 0.35 [0.14-0.89], p = .027) predicted reduced risk of suicidal ideation six months following the most recent TBI.

Conclusion

Results from the present study provide rates of suicidal ideation and behavior throughout the first year after TBI in a large, national sample. The prevalence of SI and suicidal behavior in this sample were generally low compared to other studies of individuals with TBI using similar assessment timeframes,[3,5] which may be explained by several factors, including the predominance of mild injuries compared to other studies with a wider range of injury severity. Psychiatric history and/or prior TBI may put individuals at higher risk for suicidal ideation up to 6 months after TBI. PTA may be protective of suicidal ideation at 6 months after TBI; this finding should be replicated in additional samples. Given the paucity of longitudinal research examining predictors of suicidality after mild TBI, the current findings add significantly to the literature and suggest the potential importance of screening for suicide risk among individuals with pre-injury psychiatric history and/or prior TBI in order to prevent suicide.

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An Evidentiary Review of the Glasgow Outcome Scale – Extended: Is it Appropriate for Use in TBI Clinical Trials

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Background:

The 8-point Glasgow Outcome Scale – Extended (GOS-E; Jennett et al., 1981) has been the cornerstone in traumatic brain injury (TBI) outcome assessment since its development nearly 40 years ago. The extension of the 5-point GOS to 8-point GOS-E was in response to criticisms about the scale's lack of sensitivity to detecting important differences in global functional outcome. The GOS-E is among the most widely used measures in studies investigating TBI natural history, prognosis and treatment. It has been recommended by the National Institute of Child Health and Development–sponsored Traumatic Brain Injury Clinical Trials Network for use in Phase III clinical trials and, more recently, has been designated as the only 'core' TBI Common Data Element (TBI-CDE) for use in clinical outcome assessment by National Institute of Neurological Disorders and Stroke (NINDS). The GOS-E is also the only clinical outcome assessment measure (COA) accepted by the FDA for determination of therapeutic effectiveness in TBI-related drug and device development trials. Looming against this backdrop is the overwhelming failure of several recent high-profile, well-designed TBI clinical trials, including, "PROTECT" and "SyNAPSe," to significantly impact outcome. This has led to increased scrutiny concerning the psychometric integrity of the GOS-E within specific "Contexts of Use (COUs)." The FDA defines a COU as the pre-specified circumstances, including (sub)population and purpose, under which a COA is qualified for use as a drug development tool (DDT). While the GOS-E's basic measurement properties have generally been reported to be adequate, it has never been subjected to a rigorous evidence-based evaluation to determine its performance in the context of treatment effectiveness. Thus, the purpose of this study was to review the evidence supporting use of the GOS-E for determination of TBI treatment effectiveness. We used the recently-developed Evidence-Based Clinical Outcome Assessment Platform ("EB-COP") to conduct the assessment. The development of the EB-COP was funded by a seed grant administered through the Department-of-Defense-sponsored "TBI Endpoint Development (TED)" initiative (PI: Geoff Manley). The primary objective of the EB-COP project was to develop an efficient, transparent, systematic and COU-specific platform for grading TBI COAs to determine their suitability for use in FDA drug and device development trials.

Methods:
The GOS-E was evaluated using the EB-COP, a six-step procedure informed by the Institute of Medicine's "Standards for Systematic Reviews," (Eden et al., 2011) the American Academy of Neurology's (AAN) "Clinical Practice Guideline Process Manual" (AAN 2011) and the FDA's "COA Roadmap." The purpose of the EB-COP is to guide the user through an evidentiary review process that employs well-accepted "quality indicators (QIs)" (e.g., reliability, validity) associated with specific COUs. The EB-COP platform is comprised of the following 6 steps: 1) specify the COU and frame the evidence question, 2) evaluate the fundamental operating characteristics (e.g., relevance of item content, clarity of administration and scoring instructions, feasibility of application within the intended COU), 3) complete an exhaustive literature search to identify studies addressing pertinent QIs of the COA, 4) assess the relevance and strength of the qualifying QI studies to ensure that only methodologically-sound studies are reviewed, 5) extract, analyze and integrate the evidence for the QIs using pre-established data synthesis rules and 6) evaluate the strength of the evidence for each QI against predetermined thresholds for "adequacy." Based on the results of the review, the COA is graded using a four-level recommendation scheme that rests on the number of QI criteria met: Grade I: *Recommended without reservation,* Grade II*: Recommended with reservations,* Grade III*: Not currently recommended,* Grade IV: *Recommended against ("fatal flaw")*. A COA is "recommended against" if 1 or more QIs are confirmed to be inadequate. Inclusion criteria for qualifying COAs studies include (1) a final minimum sample size of 20 individuals from the pre-specified TBI population and (2) the investigation of one or more of the COU-specific QIs. Studies that *use* the COA to measure the intended outcome, but that do not *assess* its psychometric soundness, are excluded. Two independent reviewers complete the review and extract relevant data using standardized data extraction forms implemented in the Qualtrics Survey Software. Data synthesis is performed after summary spreadsheets are automatically populated with extracted QI data.

Results:
The GOS-E evidence question formulated for this review was, "*In adult patients with moderate to severe TBI from blunt trauma of subacute duration, for the purpose of detecting treatment effects, is global function adequately measured by the English version of the GOS-E structured interview?*". Following a review of the instrument and early articles describing its development, we deemed the GOS-E's fundamental QIs regarding relevance of item content, feasibility and face validity to be adequate for the intended COU. We then searched OVID MEDLINE, EMBASE, PsycINFO, EBSCO CINAHL and SCOPUS and identified 2849 abstracts, 90 of which were brought forward for full-text review. Only articles with a classification of evidence equivalent to or higher than Class II (ie, moderate risk of bias; AAN, 2011) were considered in the final grading. After applying all the mandatory review criteria for high-quality study methodology, only one study (Pettigrew et al, 2003) met the criteria for assessment of QI adequacy. In this study, only one QI was investigated with inconclusive findings due to broad confidence intervals. Thus, although none of the 16 mandatory QIs required for assessment of treatment effectiveness were deemed inadequate, more than two QIs were indeterminate, resulting in a Grade III rating (i.e., "not currently recommended").

Conclusion:
Despite broad acceptance and widespread use in trials of therapeutic effectiveness in adults with mod-severe TBI, there is insufficient psychometric evidence to support the use of the GOS-E as a primary outcome measure in studies evaluating the effectiveness of therapeutic interventions for TBI. Additional high-quality studies evaluating key psychometric properties including test-retest and interrater reliability, criterion or construct validity, floor and ceiling effects, external responsiveness and the minimum clinically important difference (MCID) are warranted to justify its selection as a "core" common data element for TBI and its use in TBI trials.

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The Validity of the Rivermead Post-Concussion Questionnaire in Detection and Monitoring of Post-Concussive Symptoms

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Background:
Mild TBI (mTBI) has become a growing public health concern, particularly in athletic and military settings, where up to 3.8 million sports-related TBIs occur annually (Langlois et al., 2006) and more than 20% of deployed service personnel screen positive for mTBI, respectively (Iverson et al., 2009). The American Congress of Rehabilitation Medicine (ACRM, 1993) defines mTBI as a traumatically-induced acute alteration in brain function that presents with any loss of consciousness ≤30 minutes, any PTA ≤24 hours, any alteration in mental status at time of accident (eg, confusion) and/or focal neurologic deficits and a Glasgow Coma Scale score ≥13 after 30 minutes. When positive findings are noted on neuroimaging, the term, "complicated mTBI" is applied (Williams et al., 1990). Mild TBI may be accompanied by a variable constellation of cognitive, emotional and physiological symptoms, including headache, dizziness, imbalance, fatigue, and sleep disturbance. In most individuals, these 'post-concussive' symptoms resolve within days or weeks. There is a growing body of evidence to suggest that in up to 40% of individuals (Voormolen et al., 2018), symptoms persist beyond 6 months, leading to the diagnosis of "post-concussive syndrome" (PCS). Recent initiatives have called for more robust clinical outcome assessment measures (COAs) to better understand the incidence and severity of post-concussive symptoms, and their progression to PCS. The Rivermead Post-Concussion Questionnaire (RPQ; King et al., 1995) is a widely-used patient-reported COA that compares the presence and severity of symptoms experienced over the last 24 hours to pre-injury levels. While the RPQ has undergone psychometric validation, uncertainty remains regarding its performance within specific contexts of use (COU). The FDA defines COU as the pre-specified circumstances, including (sub)population and purpose, under which a COA is qualified for use as a drug development tool. The aim of this study is to use the recently-developed Evidence-Based Clinical Outcome Assessment Platform ("EB-COP") to assess the validity of the RPQ within three specific COUs- symptom detection, patient stratification and natural history of change. The EB-COP guides the user through an evidentiary review process that employs well-accepted "quality indicators (QIs)" (e.g., reliability, validity) associated with specific COUs. The EB-COP's basic framework was informed by the Institute of Medicine's "Standards for Systematic Reviews" (Eden et al., 2011), the American Academy of Neurology's (AAN) "Clinical Practice Guideline Process Manual" (AAN 2011) and the FDA's "COA Roadmap." Funding was provided by a seed grant administered through the Department-of-Defense-sponsored "TBI Endpoint Development (TED)" initiative (PI: Geoff Manley).

Methods:
We are employing the EB-COP's six-step evidentiary review process to assess the RPQ. In Step 1, the user specifies the COU and frames the evidence question. In Step 2 the fundamental operating characteristics (e.g., relevance of item content, clarity of administration and scoring

instructions) are evaluated. In Step 3, an exhaustive literature search is conducted to identify studies addressing pertinent QIs. In Step 4, the relevance and strength of the qualifying QI studies is assessed to ensure that only methodologically-sound studies are reviewed. In Step 5, the user extracts, analyzes and integrates the evidence for the QIs using pre-established data synthesis rules. Finally, in Step 6, the strength of the evidence for each QI is evaluated against predetermined thresholds for "adequacy" and the COA is graded using a four-tiered recommendation scheme based on the number of QI criteria met: Grade I: *Recommended without reservation,* Grade II*: Recommended with reservations,* Grade III*: Not currently recommended,* Grade IV: *Recommended against ("fatal flaw")*. A COA is "recommended against" if 1 or more QIs are confirmed to be inadequate. Studies were required to meet the following criteria for inclusion- (1) minimum sample size of 20 subjects from the pre-specified TBI population and (2) one or more of the COU-specific QIs had to be investigated. Studies that *used* the COA to measure the intended outcome, but did not *assess* its psychometric soundness, were excluded. Two independent reviewers will complete the review and extract and synthesize relevant data using standardized electronic data extraction forms supplied by Qualtrics Survey Software.

Results:

We have completed the first two steps of the EB-COP review process. The RPQ evidence question has been formulated as follows (Step 1): *"In adult patients with mTBI of subacute duration, for the purpose of (1) detecting post-concussive symptom sequelae, (2) stratifying individuals with mTBI based on the constellation or severity of the symptoms and (3) monitoring the resolution or progression of the symptoms, are post-concussive symptoms adequately measured by the English-language version of the RPQ?"* In Step 2, we accessed publically-accessible documents that describe the development, administration, scoring and interpretation of the RPQ and found sufficient evidence to support face validity, the relevance of the item content and feasibility of administration and scoring relative to the intended COUs. We have initiated Step 3 and have identified 437 abstracts using OVID MEDLINE, EMBASE, PsycINFO, EBSCO CINAHL and SCOPUS. The abstracts are currently undergoing review by two independent reviewers for relevance. Abstracts that are brought forward for full-text review will be evaluated for methodological quality (Step 4), and we will retain only the studies with a classification of evidence equivalent to or higher than Class II (ie, moderate risk of bias; AAN, 2011) for data synthesis (Step 5). In Step 6, we will assign a grade that provides a recommendation for use of the RPQ in each of the three specified COUs.

Conclusion:

This evidentiary review of the RPQ using the EB-COP will determine whether the RPQ can detect, monitor and discriminate subtypes of mTBI in the subacute period following TBI. Systematic review of the RPQ using evidentiary standards will clarify its psychometric validity and guide recommendations for its use in TBI research.

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Feasibility assessment of a Flexible Outcome Assessment Battery for use in longitudinal TBI Research

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Background

There is increasing recognition that traumatic brain injury (TBI) is a global health problem that evolves across the lifespan[1] and is associated with significant personal, socioeconomic and societal consequences. [2] Despite the enormity of the financial investment to mitigate its effects (ie, CDC estimated total economic cost in 2010 is approximately $76.5 billion), [3] all previously-completed acute clinical trials have either failed to improve long-term outcome or produced small effect sizes. [4] The relative futility of these studies has engendered debate about the potential contribution of non-injury factors to these results. In this context, the sensitivity of TBI clinical outcome assessment measures (COAs) has received heightened attention. The NINDS-funded "Transforming Research and Clinical Knowledge in TBI (TRACK-TBI)" study was designed to better characterize and stratify patients with mild to severe TBI, allow meaningful comparisons of treatments and outcomes, and improve the next generation of clinical trials. A specific aim of TRACK-TBI was to develop and evaluate a Flexible Outcome Assessment Battery ("FAB") comprised of a broad range of TBI common data elements (CDEs) that would enable assessment of multiple outcome domains in patients at all levels of TBI severity across all phases of recovery. The FAB incorporates 22 measures to accommodate patients at varying levels of testability. The four-item Abbreviated Assessment Battery (AAB) is designed for use with subjects who have ongoing confusion or disturbance in consciousness, and includes the Coma Recovery

Scale- Revised (CRS-R) and the Cognitive Impairment subscale from the Confusion Assessment Protocol (CAP-COG). For subjects who are cognitively intact enough to undergo standardized neuropsychological testing, the 18-item Comprehensive Assessment Battery (CAB) employs performance-based cognitive measures (i.e. attention, memory, information processing speed, executive functions), self-report measures of mood (i.e. depression, anxiety), social participation, subjective well-being and post-traumatic stress. Both batteries also include global functional status ratings (i.e., Glasgow Outcome Scale Extended, Expanded Disability Rating Scale Post-Acute Interview). Measures were prioritized based on their designation as TBI CDEs and their suitability for repeated assessment. Selection of the appropriate test battery is determined based on a decision-making algorithm that guides the examiner through a screening protocol and on to either the AAB or CAB. To catalogue reasons for missing data and potential validity threats, Test Completion Codes were developed. The purpose of this investigation is to present the results of the FAB feasibility assessment.

Methods

The FAB was administered in-person at two weeks, six months, and twelve months post-injury, and by telephone at three months post-injury, to all adult subjects enrolled in the TRACK-TBI study. Data were retrieved from the electronic QuesGen database on all subjects who completed the 12-month follow-up by October 31, 2016. We operationally-defined “feasibility” as the number of AAB or CAB measures completed per subject, divided by the number of measures expected to be completed per subject. We assessed the cross-sectional feasibility of the FAB by calculating the percentage of subjects with valid performance on all measures (CAB or AAB) at each time point, and identified reasons for missing data by analyzing frequency counts for each Test Completion Code. We investigated longitudinal follow-up rates by calculating the percentage of subjects (CAB or AAB) who completed all 4 follow-ups in part or in full. In the final step of the analysis, we calculated the percentage of subjects who transitioned from the AAB to the CAB at successive follow-ups. We excluded subjects who died, withdrew consent or were coded as a no-show at specific follow-up points.

Results

During the observation period, 2113 subjects were enrolled in the study. The sample size decreased to 990 after excluding subjects who died (n= 47), withdrew consent (n= 99) or had not yet completed the 12-month follow-up (n= 977). One additional subject was removed from the analysis due to assignment to a cohort that did not undergo psychometric assessment. Among the remaining 989 subjects, we excluded those who

failed to attend a scheduled follow-up. Thus, the total number of subjects available for cross-sectional feasibility analysis was 898 at 2 weeks, 831 at 3 months, 795 at 6 months and 746 at 12 months. Results indicated that over 95% of subjects completed the self-report and global functional status measures in a valid manner. The test completion rates ranged from 94.6% (at 12 months) to 96.1% (at 6 months) for the CAB, and 79.8% (at 12 months) to 95.8% (at 3 months) for the AAB. Completion rates for the performance-based measures of the CAB ranged from 73.3-75.2% for the NIH Toolbox to 83.3-91.2% for the Rey Auditory Verbal Learning Test, and were lower for the AAB performance-based measures (CRS-R or CAP COG), ranging from 72.8% at 2 weeks to 46.7% at 12 months. The most common reason for failure to complete the cognitive measures was a “logistical” problem (e.g., scheduling conflict, examiner not available). Looking across subjects, all measures of the CAB were coded as valid in 72.0% to 84.7% of subjects, as compared to 42.9% to 91.0% of AAB subjects. Regarding longitudinal follow-up rates, 64% of subjects assigned the CAB completed all four follow-up assessments in full or in part as compared to 71% of subjects assigned the AAB. Among subjects originally assigned to the AAB at the 2-week milestone, 46.3% transitioned to the CAB by the 3-month follow-up, 11% transitioned between 3 and 6 months and 6.1% transitioned between 6 and 12 months.

Conclusions

We conclude that it is feasible for TBI investigators to utilize a Flexible Outcome Assessment Battery that is guided by a pre-formulated test selection algorithm to conduct clinical outcome assessment and monitor recovery across the first year post-injury. We found generally high battery completion rates on the FAB (AAB and CAB), although rates were lower for performance-based measures requiring in-person administration. Follow-up rates can be expected to be lower in more severely-injured subjects and tend to trail off more sharply after 6 months post-injury. Logistical problems, rather than test burden, was the most frequent cause of missing or invalid data. Investigators should take steps to mitigate these obstacles, including the use of telephone-based assessment procedures. In addition to describing the advantages of the FAB for use in TBI clinical outcome assessment, the results of this study may also help inform sample size calculations for future investigations.

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Location of Brain Contusions and Outcome of GCS 9-15 TBI Patients in TRACK-TBI Pilot Study

Harvey Levin[1,2], Claudia Robertson[1], Pratik Mukherjee[3], Esther Yuh[3], Joseph Giacino[4], Nancy Temkin[5], Fangfang Yan[6], David Okonkwo[7], Alex Valadka[8], Geoff Manley[3,] and the TRACK-TBI Pilot Investigators

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We studied 6 month outcomes in TBI patients with GCS scores 9-15 and a left frontotemporal contusion (FTC, n=40) as compared with right FTC (n=42) or no contusion (NC, n=168) on acute computed tomography. Groups had comparable age, sex, education, and emergency department admission GCS scores (left: mean GCS=11.75, SD=4.71; right: mean GCS= 12.05, SD=3.95; NC: mean GCS= 12.76, SD=3.11). Six month GOSE [dichotomized as good recovery (GR) vs not (NGR)] and California Verbal Learning Test-2 (CVLT-2) (total recall, long delayed recall) were analyzed. Of 28 left FTC who had 6 month GOSEs, 7 (25.0%) had a GR as compared with 6/30 with right FTC (53.33%) and 55/115 (47.83%) NC. A higher proportion of right FTC had a GR than the left FTC, χ^2=4.86, p=0.028. The NC group also had a higher proportion of GR than left FTC, χ^2=6.67, p=0.010. The proportions with a GR did not differ between the right FTC and NC, χ^2=0.91, p=0.16. Total words recalled on the CVLT-2 at 6 months were reduced in the left FTC as compared with NC (left: mean: 42.83, SD=15.95, n=17; NC mean:50.09, SD=7.26, n=82; t=-2.06, p=0.043), but not as compared with the right FTC (right mean:46.58, SD=14.81, n=19, t=-0.73,p=0.47). The right FTC and NC total recall scores did not differ; (t=1.05, p=0.30). Delayed recall on the CVLT-2 was worse in the left FTC than the NC (left mean: 9.12, SD=4.41; NC mean:11.13, SD=3.38, t—2.12, p=0.04), but not as compared with the right FTC (right mean:10.53, SD=3.41, t=-1.08, p=0.29). The difference in delayed recall did not differ between the right FTC and NC, t=0.70, p=0.48. These preliminary data indicate greater disability at 6 months in GCS 9-15 patients with a left FTC as compared with right FTC and NC groups. Verbal memory was worse in left FTC (but not right FTC) patients than those without contusions, but the left and right FTC groups did not differ. Implications are left FTC on CT is a subacute biomarker for worse outcome after TBI GCS 9-15, and triage to follow-up. Replication in the TRACK-TBI project with measurement of contusion volume is planned.

Appendix 7

DOE-TBI Collaboration Meeting
(ANL, LBNL, LLNL, UCSF, and TRACK-TBI)
Genentech Hall Room S201
UCSF Mission Bay Campus
600 16th Street, San Francisco, CA 94158
WebEx
9 AM to 3 PM PST

Thursday, September 6, 2018

8:30 a.m.	Arrival – continental breakfast	Genentech Hall – meet at guard desk in main lobby
9:00 a.m.	Welcome and introductions	Room S201
9:15 a.m.	High-level review of collaboration – progress to date, goals & tasks	
9:45 a.m.	TRACK-TBI U01/TRACK Pilot data overview and crosswalk; review of research projects/questions and deliverables charge to breakout sessions	
10:30 a.m.	Breakout sessions –Imaging pipeline (MRI Connectome and CT Registration Atlas); Machine Learning applied to Outcomes; Infrastructure/Data Transfer (Globus and ESNet)	TBD; Mission Hall (3-minute walk from Genentech Hall)
12:15 p.m.	Working lunch	Genentech Hall – Room S201
1:00-2:30 p.m.	**TBD:** Continuation of breakout sessions **or** Reconvene for discussion of forward planning	TBD
2:30 p.m.	Summary & forward planning	Genentech Hall – Room S201
3:00 p.m.	Depart	

Host:
Geoff Manley, Contact PI
Amy Markowitz, Program Manager
TBI Endpoints Development (TED) Initiative
Transforming Research and Clinical Knowledge in TBI (TRACK-TBI)

Amy's mobile phone: 415-307-0391

Administrative Contact:
Brian Fabian
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WebEx Information:
When it's time, join the WebEx meeting from here:
https://webmeeting.ucsf.edu/orion/joinmeeting.do?MeetingKey=993765545
Audio connection: 415-514-1000 | Meeting Number/ Access Code: 993 765 545

Attendees:

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8-30-2018: REVISED TRACK-TBI QUESTIONS FOR DISCUSSION WITH DOE GROUP

BACKGROUND: After the Toronto TRACK-TBI/National Neurotrauma Society meeting the TRACK-TBI Outcomes Core developed a set of potential questions that we could explore in collaboration with the DOE Labs. The hope, for now, is that the DOE collaborators can peruse these topics and think about whether the exploratory analyses we've done could inform these.

Question 1: Can neuropsychometric data be used as a biomarker?

Joe Giacino: Can neuropsychometric data can be used as a biomarker? That is, is there some combination of test scores that can reliably localize lesions? TRACK has 2 tests (RAVLT, Trails) and 3 composites (WAIS PSI, BTACT, NIH Toolbox) in its battery. Each of these has multiple indices/scores that could be thrown into the hopper. The cool thing about this exercise is that there may be some combination of scores that we would not expect (based on the face validity of the measures they're drawn from) to detect a lesion that indeed does.

Mike McCrea: At APA I saw a terrific lecture comparing clinical outcome assessments (COAs) to biomarkers (amyloid, other) in detecting/predicting onset of Alzheimer's disease. The end game likely turns out to be that a combination of biomarkers and COA's is most powerful. That also a) tempers the idea of a singular "biomarker" as end-all, be-all, and b) still adding an "objective" marker of injury and recovery to bolster the (sometimes subjective) COAs.

Murray Stein: On the mental health side, we are also concluding that our prediction models work best when they combine known non-biomarker predictors with bio-predictors (e.g., genomic).

Question 2: Can we leverage biomarkers to derive a 'total peripheral injury' score?

Lin Nelson: Could we integrate clinical and biomarker data to produce an index of peripheral/overall injury severity? We will have issues with every paper with estimating the role of non-brain injuries in findings, and presumably measures like AIS scores, length of stay in hospital, inflammatory biomarkers, etc. may be jointly leveraged to produce and validate a new index of peripheral injury in controls that could inform analyses of the TBI patients.

Question 3: Can we predict persistent post-traumatic symptoms?

Sureyya Dikman: I am interested in getting the assistance of the DoE group for studying the prediction/causes of persistent post-traumatic symptoms.

Question 4: Does location of injury matter?

From Harvey Levin: Rationale: Contusions are frequent focal lesions in acute TBI (non-missile, closed head trauma) which are often detected on CT within 24 hours, primarily involve the frontotemporal region, and occur in association with various levels of impaired consciousness. Depending on location, lateralization, and volume (hemorrhagic and non-hemorrhagic components), contusions are implicated in deficits including cognition, language, memory, speech, and behavioral regulation. Gaps in knowledge include the synergistic effects of contusions with other TBI-related pathologies, such as diffuse axonal injury, hematomas, and complications such as hypotension and hypoxia. The time course for resolution of contusions and associated changes in neurobehavioral functioning has not been studied extensively using advanced imaging techniques. Moderating effects of age, sex, handedness, cognitive reserve (education/occupation), genotype, total brain volume, and history of prior TBI are poorly understood. Finally, analysis of pathophysiological variables, individual non-injury characteristics, and time since injury as multidimensional predictors of return to pre-injury functioning (fitness for duty) is complex and generally beyond the scope of most studies.

1. How can we more precisely specify the location and volume of acute contusions by using a CT atlas and computations which adjust for total intracranial volume? How do the features of contusions change over time?
2. What is the correspondence between CT and MRI results in characterizing contusions? How do differences in characterization affect prediction of outcome?
3. What are the synergistic effects of brain contusions with concomitant pathologies including diffuse axonal injury (diffusion imaging) and hematomas?
4. How do individual characteristics (age, sex, handedness, cognitive reserve (education/occupation), genotype, and history of prior TBI) moderate the effects of brain contusions?
5. How well do contusions together with other pathophysiological variables, fluid biomarkers, and individual characteristics predict recovery (return to pre-injury functioning or a close approximation) at 6 months (and other endpoints) after TBI? What is the trajectory?
6. Can we develop individualized treatment/rehabilitation protocols based on the above variables?

Late-breaking additional questions

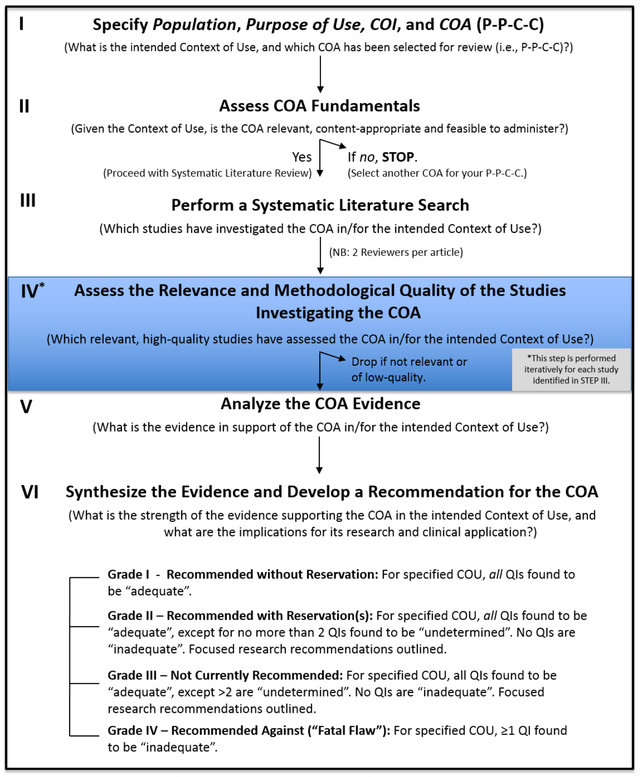
1. Which TBI pathologies imaged by acute CT most diminish neurobehavioral recovery from GCS 9-15?
2. What are the corresponding effects of these brain pathologies on return to work (or readiness to work) in persons who were employed preinjury?
3. Which non-brain injury variables and preinjury variables affect neurobehavioral recovery and return to work after controlling for brain pathologies imaged by CT?
4. How is prediction of neurobehavioral recovery and return to work after GCS 9-15 enhanced by including fluid biomarkers measured acutely?

syndrome (PCS), stratification of PCS sub-types and monitoring of natural history changes.

Background

- PCS symptoms commonly impact physical (eg, headache, double vision), emotional (eg, depression, irritability) and cognitive (eg, concentration and memory) functions following mild traumatic brain injury (mTBI (ie, GCS>12, confusion, loss of consciousness <30 mins, post-traumatic amnesia <24 hours).
- RPQ is a widely-used TBI clinical outcome assessment measure (COA) that assesses the presence and severity of PCS symptoms in the past 24 hours relative to pre-injury levels.
- RPQ is an NINDS common data element (CDE) for use in research concerning mTBI and sports-related concussion, however, its psychometric integrity and factor structure have not been evaluated for specific "Contexts of Use (COUs)".

Methods



COI, "Concept of Interest" or trait being measured; COU, the intended population and purpose of the COA; PoU, "Purpose of Use"; QI, quality indicator or psychometric property

The RPQ was evaluated using the Evidence-Based Clinical Outcome Assessment Platform ("EB-COP") (left), which relies on:

- Pre-determined quality indicators for specific PoUs;
- High-quality (Level I and II) evidence;
- Transparent and standardized criteria for establishing recommendations.

I. Evidence Question (P-P-C-C)

In adult patients with mTBI of subacute (<6mo) duration, for the purpose of (1) detecting PCS, (2) stratifying sub-types, or (3) monitoring the resolution or progression of PCS, are PCS adequately measured by the English version of the patient-reported RPQ?

COI and PoU; content and face validity; feasibility; data quality - missingness) adequate?

- Evidence or support for each fundamental QI provided in the original description by King et al., 1995, namely: It is an easy to use 16-item questionnaire of most commonly cited symptoms following mTBI with 5 symptoms ratings (0 – no experience at all; 1- no more of a problem; 2 – a mild problem; 3 – a moderate problem; 4 – a severe problem) and a total score that sums each response, excluding 1's. The total score ranges from 0 to 64.

III. Which studies have investigated QIs of the RPQ?

- 437 abstracts drawn from OVID Medline, Embase, PsycINFO, and SCOPUS (searched through to March 2018) were identified for review. One additional study was identified via ResearchGate.

IV. How many high-quality studies have assessed the RPQ in/for the selected COUs?

Abstract Review* — **438 abstracts**

A: Assess Relevance to P-P-C-C and Sample Size — *Excluded*: **359** Not relevant in terms of population (not TBI), COA (not RPQ), QI (using & not assessing RPQ) or sample size (N<25)

Full-text Review* — **79 full texts**

B: Confirm Relevance to P-P-C-C and Sample Size — *Excluded*:
- **31** Conference abstracts, books or other reviews
- **33** non-English versions, inappropriate population (severity, chronicity) and/or no investigation of a QI of the RPQ
- **10** biased sampling, high rates of missingness (>20%), unreported or insufficient percentage (<80%) with mTBI and/or altered administration or scoring of RPQ
- **1** exploratory analysis of RPQ in a multivariate prognostic model

C: Assess Overall Methodological Quality and Generalizability to P-P-C-C

D: Assess the Methodological Quality at the Level of the QI (ie, modified COSMIN criteria (Terwee et al. 2007)).

4 studies

** Completed by 2 independent reviewers (AC, SA).*

V. What is the evidence in support of the RPQ within each COU?

Study	Population (age, severity, chronicity)	Sample Size (% male)	QI and Results ([1,2,3] refer to relevant PoUs from Step I)	EB-COP Cut-off for Adequacy	EB-COP Rating
de Guise et al. 2016.	adult (mean 39.3yo), mTBI, 2-12 days and 22-137 days post injury	47 (48.9%)	prognostic validity w/ cut-off[2]: RPQ≥35 identifies individuals with moderate-severe limitations (on Mayo-Portland Adaptability Inventory-4 (MPAI-4)) w/ 90% sensitivity, 60% specificity (ROC AUC: 0.777 [95% CI: 0.593-0.961])	sensitivity>0.80, specificity>0.60; ROC≥AUC0.80	Mixed/Undetermined
King et al. 1995.	adult (mean 31yo), mTBI, 7-10 days post injury	41 (54%)	test-restest reliability (cross-sectional)[1,2,3]: Spearman's=0.90	≥0.70	Adequate
King et al. 1996.	adult (mean 33yo), mTBI, RPQ at 7-10 days and 3 months post-injury	50 (46%)	score variability and floor/ceiling effects[1,3]: >80% of sample with score <31 for both time-points; ceiling effects=36% at 3 months	Floor/Ceiling Effects <15%	Adequate (7-10days); Inadequate (3 months)
King et al. 1999.	adult (mean 32yo), mTBI, RPQ at 7-10 days and 6 months post-injury	66 (65%)	score variability and floor/ceiling effects[1,3]: >80% of sample with score <31 for both time-points; ceiling effects=19% at 6 months	Floor/Ceiling Effects <15%	Adequate (7-10days); Inadequate (6 months)

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Contacts:

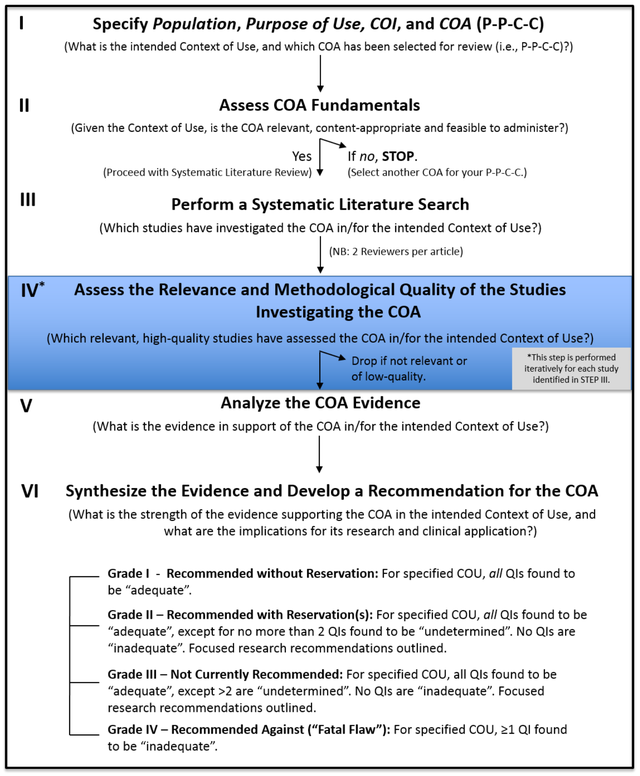
To determine the strength of the evidence supporting the use of the Glasgow Outcome Scale – Extended (GOS-E) for the detection of treatment effects in TBI clinical trials.

Background

- The GOS-E is one of the most widely used clinical outcome assessment measures for persons with mild to severe TBI.
- It is recommended as a 'core' NINDS common data element (CDE) for use in research for TBI; historically, it is the only COA that has been accepted by the FDA for the determination of therapeutic effectiveness in TBI-related trials.
- Concerns have been raised that the failure of all previously completed clinical trials may be due to over-reliance on the GOS-E without clear evidence of its 'readiness' to perform in these trial-based "Contexts of Use (COU)"[1].

[1]Defined by the FDA as the pre-specified circumstances, including (sub)population and "Purpose of Use" (eg, diagnosis vs treatment effects), under which a COA is qualified for use as a drug development tool.

Methods



COI, "Concept of Interest" or trait being measured; COU, "Context of Use" or the intended population and purpose of the COA; PoU, "Purpose of Use"; QI, quality indicator or psychometric property

The GOS-E was evaluated using the Evidence-Based Clinical Outcome Assessment Platform ("EB-COP") (left), which relies on:

- Pre-determined quality indicators for specific PoUs;
- High-quality (Level I and II) evidence;
- Transparent and standardized criteria for establishing recommendations.

I. Evidence Question (P-P-C-C or COU):

In adult patients with moderate to severe TBI of subacute (~1-6mo) duration, for the purpose of detecting treatment effects, is global function adequately measured by the English version of the GOS-E structured interview?

II. Are the fundamental QIs (ie, documented development; specification of population, COI and PoU; content and face validity; feasibility; data quality - missingness) adequate?

- Evidence in support of the GOS-E's fundamental QIs is provided in the original descriptions of the GOS (Jennett et al., 1991) and GOS-E structured interview (Wilson et al., 1998). As a clinician or observer-reported COA, it is used to assign individuals to one of 8 categories based on their global function and ability to live independently or socially integrate following TBI.

III. Which studies have investigated QIs of the GOS-E?

- 2846 abstracts drawn from OVID Medline, Embase, PsycINFO, and SCOPUS (searched through to October 2016) were identified for review. An additional 3 were identified and added manually.

IV. How many high-quality studies have assessed the GOS-E in/for the selected COUs?

Abstract Review* — **2849 abstracts**

A: Assess Relevance to P-P-C-C and Sample Size → *Excluded*: **2757** Not relevant in terms of population (not TBI), COA (not GOS-E), QI (using or not assessing GOS-E) or sample size (N<25)

Full-text Review* — **90 full texts**

B: Confirm Relevance to P-P-C-C and Sample Size → **79** Conference proceedings/books/reviews, non-English versions, inappropriate population (severity, chronicity) and/or no investigation of a QI of the GOS-E

C: Assess Overall Methodological Quality and Generalizability to P-P-C-C → **10** biased sampling, high rates of missingness (>20%), unreported or insufficient percentage (<80%) with mod-severe TBI in subacute phase and/or altered administration or scoring of GOS-E

***D**: Assess the Methodological Quality at the Level of the QI (ie, modified COSMIN criteria (Terwee et al. 2007)).*

1 study

** Completed by 2 independent reviewers (AC, MB).*

V. What is the evidence in support of the GOS-E within the pre-specified COU?

- One study survived the EB-COP Review, providing high-quality evidence for a QI that is relevant to the specified COU (see Step I) and with less than moderate risk of bias (AAN, 2011):

Study	Population (age, severity, chronicity)	Sample Size (% male)	QI and Results	EB-COP Cut-off for Adequacy	EB-COP Rating
Pettigrew et al., 2003. Reliability of ratings on the Glasgow Outcome Scales from in-person and telephone structured interviews. *Journal of Head Trauma Rehabilitation*, 18(3): 252-8.	adult (mean 38.9yo); mixed severity (mild-severe TBI); mean 192 days post-injury	56 (82%)	**Cross-sectional inter-rater reliability between in-person and phone-based structured interview:** subset of 22 participants with severe TBI extracted from mixed sample and analyzed separately, resulting in an overall agreement rate of 68% and reliability estimates of kappa=0.59 (95% CI: 0.51-1.00) and weighted kappa=0.89 (0.51-1.00).	≥0.70	**Undetermined** on basis of broad 95% confidence intervals (CI), spanning 0.70 cut-off in both directions.

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- Terwee e
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Contact: achristoforou@partners.org

Appendix 10

Tier 1 COAs

Glasgow Outcome Scale – Extended (GOS-E)
Trail Making Test
PTSD Checklist
Satisfaction with Life Survey
California Verbal Learning Test II
Brief Symptom Inventory
WAIS Processing Speed

Tier 2 COAs

Brief Test of Adult Cognition by Telephone
Controlled Oral Word Association
Grooved Pegboard
Symbol-Digit Modalities Test
Wechsler Abbreviated Scale of Intelligence II - Reasoning & Vocabulary
Wechsler Adult Intelligence Scale
Alcohol Use Disorders Identification Test
Center for Epidemiologic Studies Depression Scale
Drug Abuse Screening Test
Galveston Orientation and Amnesia Test
Head Injury Symptom Checklist
Patient Health Questionnaire
Rivermead Post-Concussion Symptoms Questionnaire
Socioeconomic Composite Index

Tier 3 COAs

Craig Handicap Assessment and Reporting Technique Short Form
Disability Rating Scale (DRS)
Expanded Disability Rating Scale Post-Acute Interview
Concussion Evaluation
Confusion Assessment Protocol
Brief Visuospatial Memory Test
The Edinburgh Handedness Inventory
WAIS Digital Span
Connor David Resilience Measure
Handedness

Appendix 11

US Department of Energy S1 Visit to UCSF

July 19, 2018
10:00am to 12:00pm
UCSF/ZSFG Brain and Spinal Injury Center (ZSFG Campus)
Chancellors Conference Room, Mission Hall (Mission Bay Campus)

DOE Attendees:

The Honorable Rick Perry, Secretary of Energy, U.S. Department of Energy
Morgan Luttrell, Senior Advisor, U.S. Department of Energy
Bambi L. DeLaRosa, Senior Program Manager for U.S. Department of Energy
Dimitri Kusnezov, Chief Scientist & Senior Advisor to the Secretary, National Nuclear Security Administration, U.S. Department of Energy
Dan Wilmot, Deputy Chief of Staff, Office of the Secretary, U.S. Department of Energy

UCSF and UCOP Attendees:

Janet Napolitano, President, University of California
Sam Hawgood, Chancellor, UCSF
Keith Yamamoto, Vice Chancellor for Science Policy and Strategy, Director, UCSF Precision Medicine, Professor of Cellular Molecular Pharmacology, UCSF
Geoff Manley, Chief of Neurosurgery, Zuckerberg SF General Hospital and Trauma Center, UCSF
Sergio Baranzini, Professor of Neurology, UCSF
Kimberly S. Budil, Vice President for National Laboratories, University of California
Atul Butte, Director, Bakar Computational Health Sciences Institute, UCSF and Chief Data Scientist, University of California Health System (UC Health)
India Hook-Barnard, Director of Research Strategy and Associate Director, UCSF Precision Medicine, UCSF
Sharat Israni, Executive Director, Bakar Computational Health Sciences Institute, UCSF
Amy Markowitz, Program Manager, TRACK-TBI/TED Research Network, UCSF
Pratik Mukherjee, Professor of Radiology, UCSF
Eva Palacios, Specialist, Department of Radiology, UCSF
Sandy Weill, Business Executive and Philanthropist

LLNL, LBNL, and Argonne Attendees:

Kristofer Bouchard, Research Scientist, Computational and Systems Neuroscientist, Lawrence Berkeley National Laboratory
Jim Brase, Deputy Associate Director for Computation, Lawrence Livermore National Laboratory
Bill Goldstein, Director, Lawrence Livermore National Laboratory
Alan Kaplan, Computer Vision Group Leader, Lawrence Livermore National Laboratory
Paul Kearns, Director, Argonne National Laboratory
Ravi Madduri, Scientist, Data Science and Learning, Argonne National Laboratory
Mary Maxon, Associate Laboratory Director for Biosciences, Lawrence Berkeley National Laboratory
Shankar Sundaram, Director of Bioengineering Center, Lawrence Livermore National Laboratory
Michael Witherell, Director, Lawrence Berkeley National Laboratory

US Department of Energy S1 Visit to UCSF

July 19, 2018
10:00am to 12:00pm
UCSF/ZSFG Brain and Spinal Injury Center (ZSFG Campus)
Chancellors Conference Room, Mission Hall (Mission Bay Campus)

10:00 am	Arrival at ZSFGH – Dr. Manley and Dr. Sue Carlise will be outside
10:00 - 10:20 am	**Tour Neurotrauma Intensive Care Unit (Geoff Manley)**
10:20 – 10:35 am	Questions and Discussion of TBI Patient Needs
10:35 – 11:00 am	Travel to Mission Hall (escorted from lobby to Chancellor's Conference Room)
11:00 – 11:20 am	**UCSF Precision Medicine/National Labs Collaboration (Atul Butte)**
11:20 – 11:30 am	**SPOKE: Scalable Precision Open Knowledge Engine (Sergio Baranzini)**
11:30 am	UC President Janet Napolitano and UCSF Chancellor Sam Hawgood will join meeting
11:30 – 11:45 am	**ACTIV: Progress to Date (LLNL, LBNL, Argonne) Data Transfer, Imaging Analytics (MRI and CT), Outcome Assessment (Mukherjee, Bouchard, Kaplan, Madduri)**
11:45 – 12:00 pm	**From Precision Medicine to Personalized Care: Weill Institute of Neuroscience TBI Clinic (Geoff Manley)**

Locations and Addresses

Zuckerberg San Francisco General Hospital (ZSFGH) 1001 Potrero Ave, San Francisco, CA 94110
UCSF Mission Bay, Mission Hall 1760 4th Street, San Francisco, CA 94158

BANYAN BIOMARKERS

April 3, 2018

Geoffrey T. Manley, M.D., Ph.D.
Professor and Vice Chairman of Neurological Surgery
University of California, San Francisco
Chief of Neurosurgery, Zuckerberg San Francisco General Hospital and Trauma Center
Co-Director, Brain and Spinal Injury Center (BASIC)
1001 Potrero Avenue, Building 1, Room 101
San Francisco, CA 94110

Dear Dr. Manley,

On February 14, 2018, the U.S. Food and Drug Administration (FDA) granted the De Novo request for the commercialization of the Banyan BTI™ (Brain Trauma Indicator), an *in vitro* diagnostic blood test to aid in the evaluation of patients with suspected TBI and concussion. The assay results obtained from serum collected within 12 hours of suspected head injury are used, along with other available clinical information, to aid in the evaluation of patients 18 years of age and older with suspected traumatic brain injury (Glasgow Coma Scale score 13-15). A negative assay result is associated with the absence of acute intracranial lesions visualized on a head CT (computed tomography) scan.

FDA reviewed the Banyan BTI™ under the Breakthrough Devices Program, which is intended to facilitate the development and expedite the review of innovative breakthrough technologies. The Breakthrough Devices Program permits commercialization of medical devices that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. Banyan BTI™ identifies two brain-specific protein biomarkers (Ubiquitin Carboxy-terminal Hydrolase-L1 or UCH-L1 and Glial Fibrilliary Acidic Protein or GFAP) that rapidly appear in the blood after a brain injury, providing objective information to assess patients with suspected mild TBI. The goal of the study was to identify patients with head trauma who could safely forego the need for a CT scan thereby avoiding unnecessary radiation to the brain and reduce costs of care.

Banyan has been part of the TRACK-TBI and TED Initiatives' public-private partnership from their inceptions. **We want to formally acknowledge the pioneering work these teams have done to lay important groundwork for Banyan's recent FDA approval.** The researchers from these teams have shared with Banyan their valuable clinical insights and study results, and Banyan has undeniably benefited from TRACK-TBI and TED's contribution of information dossiers and communication with FDA about the need for validation of TBI biomarkers, and in fact, the specific biomarkers Banyan proffered for the Breakthrough program, GFAP and UCHL-1.

The Banyan BTI™ will permit more timely evaluation of mild TBI and advance the field's ability to manage these heterogeneous injuries. We look forward to continued opportunities to work with the world-class clinical researchers of the TED and TRACK-TBI studies. The entire field will benefit from the ongoing legacy provided by the multi-scalar and meticulously collected data they are amassing. Our military and civilian patients, across the spectrum of demographics and injury severity, stand to benefit from this crucial work.

Sincerely,

Ronald L. Hayes, PhD
Founder and Chief Science Officer

Steven P. Richieri
President & Chief Operating Officer

16744 West Bernardo Drive, San Diego, CA 92127 · Phone: (760) 710-0456 · Fax: (760) 268-0515

Appendix 13

Abbott Laboratories
100 Abbott Park Road
Abbott Park, IL 60064

Tel: 224 280 2989
beth.mcquiston@abbott.

Beth McQuiston MD, RD
Medical Director
Abbott Diagnostics Division

April 5, 2018

Dear Dr. Manley:

Abbott's request for inclusion of its TBI diagnostic test, the i-STAT, in the FDA's Breakthrough Devices Program was recently granted. The i-STAT TBI test is currently in the development process. The proposed initial "Indications for Use" state the i-STAT TBI test is a panel of in vitro diagnostic whole blood or plasma quantitative measurement of Glial Fibrillary Acidic Protein (GFAP) and Ubiquitin Carboxyl-Terminal Hydrolase L1 (ucH-L1) and a semi-quantitative interpretation of test results derived from these measurements, using the i-STAT Alinity instrument. The interpretation of test result is used to aid in the evaluation of patients, 18 years of age or older, presenting with suspected mild traumatic brain injury (Glasgow Coma Scale score 13-15) within 12 hours of injury, to assist in determining the need for a CT (computed tomography) scan of the head. A "not elevated" TBI test interpretation is associated with the absence of acute traumatic intracranial lesions visualized on a head CT scan. The test is to be used with venous blood collected with EDTA anticoagulant in point-of-care or clinical laboratory settings by a healthcare professional in conjunction with other clinical information.

A proof-of-concept, observational only study continues with prototype i-STAT TBI cartridges using the i-STAT Alinity Instruments at four of the TRACK TBI clinical sites using whole blood specimens from intended use patients. Initial results from TRACK researchers demonstrate that the test is capable of detecting both biomarkers in whole blood and in a rapid, clinically actionable timeframe of less than 15 minutes. Given the rapid diagnostic capabilities of the i-STAT TBI test, there is reasonable expectation that the device will help to provide for more complete evaluation of mTBI. It is designed to help clinicians with improved patient management by providing measurable information upon which to make a more informed decision.

The results of the research of Abbott's prototype TBI biomarkers led the TRACK/TED team to write a letter of support provided to the FDA which was instrumental in the FDA granting the i-STAT TBI test as a breakthrough pathway.

The TRACK and TED initiatives provided: (1) clinical insights, (2) a track record of contribution of information, and (3) communication with FDA about TBI biomarkers, including the specific biomarkers cited here, GFAP and UCHL-1, and were critical to Abbott's success in assay test development.

The U.S. Department of Defense estimates that 361,092 brain injuries have been sustained by members of the U.S. military, worldwide, since 2000. The TED Initiative was awarded funds by the DoD to advance the design of clinical trials that will lead to the first successful diagnostics and treatments of acute TBI. Abbott is proud to serve as a vital partner working with the TED Initiative, and has received separate financial development support from the US Military to advance a rapid TBI diagnostic test for the men and women serving our country and putting their lives at risk to protect our nation's freedom.

The Breakthrough Devices Program exists for certain medical devices that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. Abbott Point of Care's inclusion in this program should provide clinicians with a point of care rapid diagnostic TBI test that is designed to provide more timely information in the evaluation of mild TBI that will help triage critical interventions and facilitate injury management. Working with Abbott to expedite the development, evaluation, and review of their TBI diagnostic test is consistent with FDA's mission to protect and promote public health.

We are grateful for the opportunity to work with the fine scientists and cutting edge clinical researchers of the TED and TRACK-TBI studies. The breadth of the data you are collecting and analyzing, and the excellent care with which these data are collected and curated, have already advanced the field of TBI. You are accelerating our ability, collectively, to bring accurate, clinically actionable diagnoses and therapies to our patients, both military and civilian.

Sincerely,

Beth McQuiston
Medical Director

Appendix 14

C-Path and CHDI launch consortium to accelerate development of Huntington's disease therapies

Tucson, AZ, and New York, NY – March 28, 2018 – The Critical Path Institute (C-Path), together with CHDI Foundation, Inc. (CHDI), today announced the official launch of C-Path's Huntington's Disease Regulatory Science Consortium (HD-RSC). In addition to these cofounders, the consortium also includes more than 20 different member organizations, including industry partners, academic institutions, and nonprofit societies. HD-RSC members will work to advance innovation in regulatory science methods, supporting clearer development and regulatory pathways that lead to the approval of Huntington's disease (HD) therapeutics.

"C-Path has an established record of success in leading precompetitive consortia whose members collaborate to advance innovation in the regulatory science of drug development. We value this new partnership with CHDI, an organization that also embraces collaboration as a mechanism to more quickly and efficiently reach a common goal," said Martha Brumfield, PhD, President and CEO of C-Path. "We look forward to combining our strengths in this new consortium: C-Path's successful track record in overseeing global consortia and CHDI's HD therapeutic domain knowledge."

HD-RSC will provide the platform for the collaboration needed to facilitate clinical data sharing and standardization, to support the development of modeling tools, and to bring forward these tools as well as biomarkers and clinical outcome assessments for regulatory endorsement. These drug development tools will be made publicly available to help accelerate the time to drug approval and de-risk the drug-development pathway, thereby further incentivizing drug developers to enter the HD sphere. HD-RSC will work collaboratively with US Food and Drug Administration (FDA) and European Medicines Agency (EMA) staff to align on areas of high unmet need in developing therapies for this devastating disease.

"With this dedicated regulatory science consortium, stakeholders can share data and knowledge while avoiding duplication of efforts," said Robi Blumenstein, President of CHDI. "It provides a forum for everyone interested in HD therapeutics, including regulators, to participate in the development of an appropriate regulatory pathway that will deliver therapeutics to patients and families as soon as possible. This aligns perfectly with CHDI's mission to rapidly and collaboratively develop therapeutics that substantially improve the lives of individuals affected by Huntington's disease."

Charles Sabine, an HD patient-advocate, emphasizes the need to move forward with purpose in HD drug development: “We have hope,” he said, and “hope can only be built on the trust that everyone is working as fast as they can in the same direction.”

About Huntington’s Disease
Huntington’s disease (HD) is a rare genetic neurodegenerative disorder that results in behavioral, cognitive, and motor impairments. These symptoms progressively reduce an individual’s quality of life, and ultimately lead to death. HD is caused by a mutation in the huntingtin gene, which results in a toxic protein that damages neurons in the brain. Approximately one person in 10,000 carries the mutated huntingtin gene, and each child of a parent with a mutation has a 50% chance of inheriting the mutation. Current HD therapies only manage the severity of symptoms; there are no approved treatments to slow the progression of HD.

About the organizations:

CHDI Foundation, Inc. (CHDI), is a privately funded nonprofit biomedical research organization that is exclusively dedicated to rapidly developing therapies that slow the progression of Huntington’s disease. As a collaborative enabler, CHDI seeks to bring the right partners together to identify and address critical scientific issues and move drug candidates to clinical evaluation as quickly as possible. CHDI scientists work closely with a network of more than 700 researchers in academic and industrial laboratories and clinical sites around the world in the pursuit of these novel therapies, providing strategic scientific direction to ensure that our common goals remain in focus. More information about CHDI can be found at www.chdifoundation.org.

Critical Path Institute (C-Path) is an independent, nonprofit organization established in 2005 with public and private philanthropic support from the Arizona community, Science Foundation Arizona, and the US Food and Drug Administration (FDA). C-Path’s mission is to catalyze the development of new approaches that advance medical innovation and regulatory science, accelerating the path to a healthier world. An international leader in forming collaborations, C-Path has established numerous global, public-private partnerships that currently include over 1,450 scientists from government and regulatory agencies, academia, patient advocacy organizations, and dozens of major pharmaceutical companies. C-Path is headquartered in Tucson, Arizona. For more information, visit www.c-path.org.

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