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

TRACK-TBI BIO
Transforming Research and Clinical Knowledge in Traumatic Brain Injury Biomarker Project

TRACK-TBI EPI
Transforming Research and Clinical Knowledge in Traumatic Brain Injury Epileptogenesis

Standard Operating Procedures for Telephone Assessments and In-person Assessments for Longitudinal Follow-ups with TRACK-TBI Participants

Version 4, September 1, 2020

Supported by:
TRACK-TBI LONGITUDINAL (TRACK-TBI LONG)
TRACK-TBI BIOMARKERS (TRACK-TBI BIO)
TRACK-TBI EPILEPTOGENESIS (TRACK-TBI EPI)

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Introduction and TRACK-TBI Consortium History

This Standard Operating Procedures (SOP) document describes the longitudinal follow-up activities to be conducted with participants formerly enrolled in a Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study. The TRACK-TBI Consortium is a partnership of top tier academic and Level 1 Trauma Centers across the United States. The current infrastructure was seeded in 2009 with the TRACK-TBI Pilot study (NIH RC2 NS069409). The TRACK-TBI Pilot validated the NINDS TBI Common Data Elements (TBI-CDEs) and collected detailed clinical data on 650 subjects across the injury spectrum, along with CT/MRI imaging, blood biospecimens, and detailed outcomes. With seed and ongoing financial and in-kind support from a patient advocacy foundation and private industry partners in the neuroimaging, pharmaceutical, device, and data management and analytic spaces, the TRACK-TBI Pilot built an infrastructure of integrated clinical databases, imaging repositories, biosample repositories, and coordinated multisite/multidisciplinary expertise. From 3 enrolling sites during its pilot phase, TRACK-TBI grew to 11 sites with the launch of the TRACK-TBI U01 phase in 2013 (NINDS U01 NS086090). Further expansion during the U01 phase (2017) resulted in 7 new institutions joining the consortium resulting in a total of 18 enrolling clinical sites with additional sites providing analytic support. The goals of TRACK-TBI were to describe the natural history of TBI and establish more precise methods for its diagnosis and prognosis, refine outcome assessments, and compare the effectiveness and costs of TBI care.

TRACK-TBI's extensive protocol empowers rich, multidimensional characterization of the clinical, neuroimaging, and blood-based biomarker features of TBI. Participants were followed longitudinally for one year from time of injury, using the NINDS TBI Common Data Elements (CDEs), which were conformed to CDISC standards, as encouraged by the U.S. Food and Drug Administration (FDA) for use in IND and other applications. TRACK-TBI has amassed the world's largest and most comprehensive serial collection of standardized TBI neuroimaging (CT and MRI), using structural, functional, and diffusion phantoms for quantitative imaging, and developed automated pipelines for imaging quality assurance. With the close of TRACK-TBI U01 funding in 2018, continued enrollment into the TRACK-TBI protocol was supported by an unrestricted gift from the National Football League (i.e., "Post-U01 cohort" – for more information about this cohort, see the below section "TRACK-TBI U01 vs. "Post-U01"). As of July 2020, TRACK-TBI U01+Post-U01 has enrolled >3050 TBI subjects and >350 orthopedic control subjects. The goal of the longitudinal follow-up activities described in this SOP is to connect with as many of these TRACK-TBI subjects as possible to assess their functional status two or more years after their original study injury.

The current protocol seeks to conduct longitudinal follow-ups with the various TRACK-TBI cohorts. There are multiple arms to this overall study with separate funding mechanisms supporting each study arm/cohort as well as multiple regulatory bodies reviewing the study activities for each study arm. The first sections of this SOP describe the original submissions for the various funding mechanisms, and clearly delineates how these funding mechanisms and regulatory bodies will interact in support of this overall protocol. The remaining sections in this SOP detail the assessment procedures that will be implemented to collect longitudinal data on these TRACK-TBI participants.

TRACK-TBI LONGITUDINAL: Background, Specific Aims, and Study Design from the Original Proposal

Background and Significance

Annually, at least 2.5 million people in the United States suffer a traumatic brain injury (TBI) and TBI is a contributing factor in a third of all injury-related deaths. An estimated 3.2-5.3 million people live with the long-term physical, cognitive, and psychological health disabilities of TBI, with annual direct and indirect costs estimated at over $76.5 billion.[1] Although recent efforts have increased our understanding of the acute pathophysiology of TBI, critical questions remain about its long-term outcomes across the lifespan. Fundamental gaps exist in our understanding of the natural history of TBI. For a subset of patients, TBI may evolve after the acute period and initial recovery.[2] For others, recovery will stabilize with persistent significant sequelae. Thus, TBI is best conceptualized as a chronic health condition triggered by injury, with potentially lifelong effects on multiple health outcomes.[3] Outcomes after 12 months [3] may progress along 3 trajectories: improvement, stabilization, or deterioration. After moderate to severe TBI, by 5 years post-injury, 35-55% of patients have stabilized or improved, 25-40% have deteriorated, and 20-25% of those alive at 1 year have died.[4, 5] There are no reliable prognostic biomarkers to identify those at risk of decline and, consequently, no effective therapies to prevent or slow this process. The knowledge gaps that we aim to resolve center on enhancing characterization of recovery trajectories and identifying those individuals most at risk for progressive neurodegeneration.

Specific Aims

Understanding the natural history of disease is prerequisite to developing effective treatments. Traumatic brain injury (TBI) is a complex pathophysiological process with variable outcomes; it may be self-limiting or have lifelong consequences.[2, 3, 6-8] Progress has been limited by the lack of objective biomarkers for diagnosis, a paucity of proven treatments, imprecise outcome measures, and controversy regarding pathology and risk factors of long-term sequelae. **This TRACK-TBI LONG study leverages the largest precision medicine short-term natural history study of TBI: Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI; funded by NINDS U01NS086090), which has been successfully executed by a multidisciplinary, collaborative network of academic, private, and public partners.** During the study, participants were followed for 1 year from time of injury using a multidimensional outcome battery that includes the NINDS TBI Common Data Elements.[9] We have amassed the world's largest serial collection of TBI neuroimaging (CT and MRI), proteomic, and genomic biospecimens, with clinical outcome assessments captured across physical, cognitive, psychological, and functional domains of function. By extending follow-up of the deeply phenotyped TRACK-TBI cohort into the chronic phase, TRACK-TBI LONG is the first and largest study of incident TBI to couple comprehensive multi-year clinical trajectories with advanced neuroimaging and proteomic biomarkers. This will further elucidate TBI's natural history, identify those individuals most at risk for unfavorable outcomes, and lead to the development of diagnostic, prognostic, and therapeutic/ management tools for this heterogeneous condition.

Specific Aim 1. Characterize the long-term effects of TBI in the TRACK-TBI cohort. We will extend follow-up of TRACK-TBI brain-injured (n = 2700) and control (n = 300) participants beyond the current 1-year post-injury timeframe with up to 3 additional annual telephone follow-ups in the TRACK-TBI cohort.

- **Sub-Aim 1.1** will capture and differentiate outcome trajectories up to 7 years post-injury. Telephone-administered outcome measures will assess persistent symptoms that affect physical, cognitive, psychological health, and functional status domains.

- **Sub-Aim 1.2** will screen for symptoms of neuropsychiatric disorders (e.g., depression, anxiety, etc.) and neurodegenerative disorders (e.g., dementia, Alzheimer's disease [AD], chronic traumatic encephalopathy [CTE], Parkinson's disease, amyotrophic lateral sclerosis [ALS]) and post-traumatic neurological disorders, including epilepsy. Consented participants who screen positive (expected n≈400) will undergo extended in-person cognitive and neuroimaging assessments with biospecimen collection (**Aims 2-3**) and, if indicated, receive appropriate clinical referral.

Specific Aim 2. Characterize the relationship of imaging biomarkers to the long-term trajectory following TBI. Through the telephone interviews conducted in Aim 1, we will identify subjects who screen positive for post-traumatic disorders and concern for accelerated neurodegeneration (**Sub-Aim 1.2**). A subset of these individuals, and a subset of those who have experienced continued improvement or stability of neurologic function, will be invited for in-person visits, which will include MRI imaging, with DTI, rs-fMRI, and high-resolution structural studies.

Specific Aim 3. Characterize the relationship of proteomic biomarkers to the long-term trajectory of neurocognitive/psychological function in TBI. From those who screen positive in **Sub-Aim 1.2** and consent for in-person visits for MRI imaging, we will obtain serum and plasma to compare long-term proteomic biomarkers with existing acute, 2-week, and 6-month markers collected under the original TRACK-TBI study protocol.

TRACK-TBI U01 vs. "Post-U01"

The TRACK-TBI U01 study (NINDS U01NS086090) enrolled 2698 adult and pediatric TBI participants and 299 adult orthopedic controls between February 2014 to July 2018. Upon completion of study activities in July 2018, enrollment under the TRACK-TBI protocol continued with separate funding for the purpose of completing enrollment for several "add-on" studies that leverage the TRACK-TBI infrastructure (e.g., "Spreading Depolarization II" W81XWH-16-2-0020, "High Definition Fiber Tracking" W911QY-14-C-0070, Abbott i-STAT pilot, etc.). **Participants enrolled under the TRACK-TBI protocol after July 2018, with funding separate from the original NINDS grant, are considered "Post-U01" participants.** These subjects will also be enrolled into the annual Telephone Assessments and subsequent In-person Assessments, should they be eligible and consent to participate.

Enrollment of Post-U01 participants under the TRACK-TBI protocol is still underway (as of July 2020). In order to increase the number of eligible participants for the In-person Assessment, Post-U01 participants will also be eligible for annual Telephone Assessments and subsequent In-person Assessments.

Study Design

TRACK-TBI LONG is designed to leverage the original TRACK-TBI study protocol. Both TBI and Control participants from the TRACK-TBI U01 study (n~3000), as well as additional participants enrolled under the Post-U01 phase of the study (n~400+ as of July 2020), will be eligible for up to 3 annual TRACK-TBI LONG Telephone Assessments. The definition of a "Post-U01" participant can be found in the previous section. The data collected during the TRACK-TBI LONG Telephone Assessments will provide a platform by which to identify those individuals who will be invited for an In-Person Assessment to collect further information

from participants, including imaging and biofluid biomarkers. See **Figure 1** for a depiction of the TRACK-TBI LONG study design.

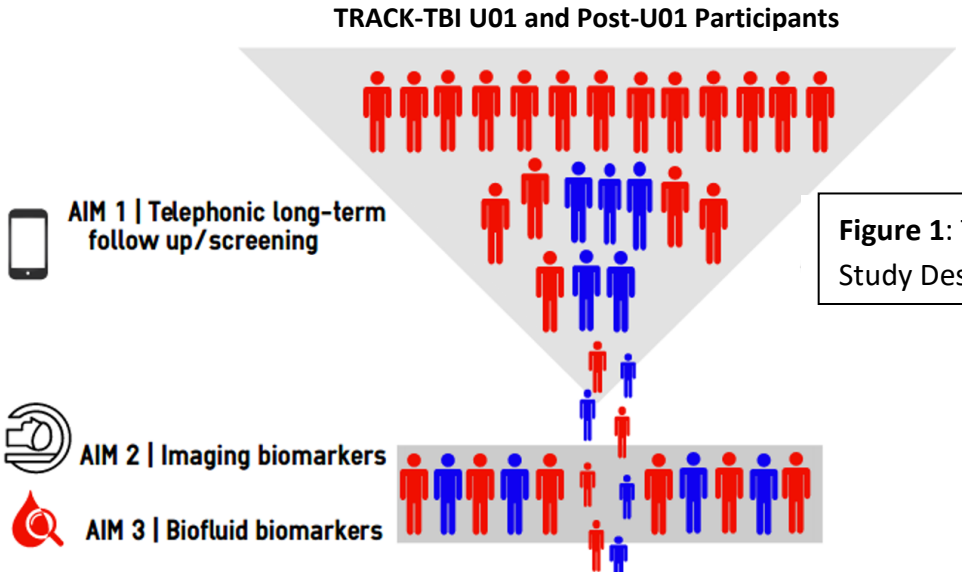

Figure 1: TRACK-TBI LONG Study Design

TRACK-TBI BIOMARKERS: Background and Specific Aims from the Original Proposal

Background: Traumatic brain injury (TBI) is one of the leading causes of mortality and morbidity affecting humanity, and a recognized risk factor for late-life neurodegenerative disorders. The absence of validated biomarkers in the neurotrauma field is a barrier to drug development in this area, and consequently, there are currently no disease-modifying therapies that limit the burden of TBI. Traumatic axonal injury (TAI) is a common pathologic consequence of TBI and underlies some of the most disabling consequences of injury, including cognitive and affective problems. Recent breakthroughs in pre-clinical models indicate that novel therapeutic interventions are effective in promoting resilience of injured axons and improving neurologic outcome after experimental TBI. Successful translation of such therapies will require prognostic biomarkers that can measure TAI in individual patients, as well as pharmacodynamic biomarkers to measure the efficacy of such treatments. Currently, the best biomarker for TAI is fractional anisotropy (FA) and mean diffusivity (MD) of white matter tracts, measured using diffusion tensor imaging (DTI) MRI. This technique, while robust, is poorly suited for dynamic longitudinal assessments, and measures the end-result of axonal degeneration, rather than earlier stages in the neurodegenerative process. The recent ability to assay axonal proteins in peripheral blood has made it potentially feasible to assess TAI rapidly, inexpensively, and longitudinally. The goal of this project is to clinically validate the axonal protein neurofilament light chain (NfL) as a prognostic biomarker of TAI.

Specific Aims

Specific Aim 1*. Reference intervals (RIs) for NfL will be determined according to Clinical Laboratory Standards Institute (CLSI) guidelines, using commercially available assays (Quanterix, LLC, Lexington, MA).

Specific Aim 2*. NfL levels will be measured in existing serum samples from participants enrolled in a multi-center observational study (TRACK-TBI) who also have MRIs at 2 weeks and 6 months post injury. The relationship between NfL elevations and neuroimaging measures of TAI (DTI measure of FA at the 2-week scan) and axonal degeneration (white matter volume at 6 months after injury) will be assessed.

Specific Aim 3. The follow-up period will then be extended for a subset of TRACK-TBI participants from 1 year to 5 years after injury, to assess the relationship between persistent NfL elevations and neurodegeneration. The existing clinical, imaging, and biomarker data in these participants will be leveraged to identify risk factors, comorbidities, and prognostic biomarkers of long-term TBI-associated degeneration.

Specific Aims 1 and 2 describe retrospective analyses of already collected TRACK-TBI samples. This protocol describes only study procedures conducted under **Specific Aim 3.*

TRACK-TBI EPILEPTOGENESIS: Background, Hypotheses, and Specific Aims from the Original Proposal

Background

Post-traumatic epilepsy (PTE) is a common complication of traumatic brain injury (TBI), occurring in up to 20% of civilian patients and as many as 50% of military service members who suffer severe brain trauma, and 3-5% of those who suffer moderate TBI.[10] Epilepsy resulting from brain trauma is often difficult to control with medical therapy, and is the cause of epilepsy in approximately 5% of patients referred to specialized epilepsy centers. PTE can be the result of TBI of any severity, although the risk is higher from severe TBI. PTE can arise through a variety of mechanisms, which may co-exist within a single patient.[11] Focal brain injury, which results from penetrating trauma or focal contusions can result in epileptogenesis. Closed head injury can also produce diffuse injury, with shearing of axons and blood vessels, diffuse edema and ischemia, and secondary cellular damage through the release of inflammatory mediators. The clinical features of epilepsy, such as the frequency and severity of seizures, prevalence of associated co-morbidities, and responsiveness to therapy, may differ among these diverse mechanisms. Additionally, the neurophysiologic, and imaging features of epileptogenicity also likely differ, and it is likely that a sophisticated understanding of the subtypes of epilepsy resulting from brain trauma will be required to successfully develop anti-epileptogenic therapies.

This proposed longitudinal observational study is part of the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) initiative, a multi-institutional study funded by NINDS and DoD (RC2 NS069409, 2010-2011; U01 NS086090, 2013 – 2019; W81XWH-14-0176, 2014 - 2019) designed to characterize the acute and longer-term clinical, neuroimaging, and blood biomarker features of TBI. To date, TRACK-TBI has enrolled over 2800 subjects with TBI at 18 Level 1 Trauma Centers in the US, across the age and injury spectrum. While TRACK-TBI collects detailed phenotypic information about the acute injury and hospital course, information about PTE is limited to a screening questionnaire administered at 6 and 12 months after injury. We propose to extend the follow-up period for TRACK-TBI participants from 1 year to 5 years. In addition, the follow-up period for a TRACK-TBI affiliated DoD-funded study, Spreading Depression-2 (SD-2), which complements TRACK-TBI by focusing on the most severe forms of TBI, will be extended from 6 months to 2 years.

Hypotheses

We propose one **primary hypothesis** and several **secondary hypotheses** for TRACK-TBI EPI:
Primary Hypothesis (1): PTE is independently associated with negative TBI outcomes, such as memory problems, depression, and sleep disorders, compared with subjects with comparable TBI without PTE.
Secondary Hypothesis (2): Control of post-traumatic seizures (with or without anti-epileptic medications) is associated with improvement in outcomes after TBI, such as memory problems, depression, and sleep disorders, compared with PTE subjects with TBI of similar severity whose seizures are refractory to medical therapy.
Secondary Hypothesis (3): Disruption of thalamo-cortical and hippocampal connections, assessed by diffusion tensor imaging (DTI) MRI, is associated with increased risk of PTE after TBI.

Exploratory Hypothesis (4): Blood biomarkers of neural injury and neuroinflammation, including GFAP, UCHL1, tau, neurofilament light chain (NF-L) and pro-inflammatory cytokines (e.g. interleukin (IL)-1β, IL-6, tumor necrosis factor alpha (TNF-α), measured in the acute period following injury, are associated with increased risk of PTE.

Specific Aims

We will obtain evidence in support of these hypotheses through the following **Specific Aims:**

- **Specific Aim 1: Extend the follow-up period of TRACK-TBI participants from 1 to 5 years.** TRACK-TBI has enrolled 2800 subjects with TBI from 2/2014 – 10/2018, with the last follow-up assessment scheduled at 1 year after injury. Since only half of PTE presents within 1 year of injury, we propose extending the follow-up period to 5 years, which will allow ascertainment of PTE in >90% of those who will eventually develop post-traumatic seizures. The extensive clinical, imaging, and biomarker data that has already been collected in these subjects will be leveraged to identify risk factors, co-morbidities, and prognostic biomarkers of PTE.
- **Specific Aim 2: Extend the follow-up period of the TRACK-TBI affiliated study, SD-2, from 6 months to 2 years.** SD-2 complements TRACK-TBI by exclusively enrolling patients with severe TBI. SD-2 started enrolling subjects in 2017 and 39 (out of a target 189) have been enrolled as of 7/2018. The last planned follow-up for SD-2 is at 6 months post-injury, which will identify less than half of patients who will ultimately develop PTE. TRACK-TBI Epi will extend follow-up of these severe TBI patients through 2 years after injury, identifying over 75% of those who eventually will develop PTE.
- **Specific Aim 3: To conduct specialist epileptologist evaluation for all TBI patients who screen positive for PTE.** Participants who answer yes to screening questions for PTE will be invited for in-person evaluations by an expert epileptologist at each site. Epilepsy Clinic visits will include an outpatient EEG and a research-grade MRI. A subset of participants with TBI from each parent study that do not screen positive for possible PTE, matched by age, gender, and injury characteristics, will also be invited for an in-person evaluation.
- **Specific Aim 4: To measure candidate blood biomarkers to determine if they are prognostic for epileptogenesis.** We will use existing blood samples collected from participants in TRACK-TBI and SD-2 during the acute hospitalization, as well as samples collected in the subacute and chronic periods, and those collected during the Epilepsy Clinic visit. We will measure specific molecular biomarkers of neural injury and neuroinflammation/autoimmunity using highly sensitive multiplexed immunoassays.

Protocol Funding Sources

- TRACK-TBI LONG is funded by the **National Football League Scientific Advisory Board Funding Opportunity** ("NFL award") and gift money awarded from the **National Football League** ("NFL gift").
    - TRACK-TBI LONG funding will support data collection during all Telephone Assessments conducted with **U01** subjects.

- TRACK-TBI BIO is funded by the **National Institute of Neurological Disorders and Stroke** (NINDS U01NS114140).
    - TRACK-TBI BIO funding will support data collection during all Telephone Assessments conducted with **Post-U01** subjects as well as all In-person Assessments (no PTE) with **U01 and Post-U01** participants.

- TRACK-TBI EPI is funded by the **U.S. Army Medical Research and Development Command** (USAMRDC EP180013).
    - TRACK-TBI EPI funding will support data collection during In-person Assessments with U01 and Post-U01 participants who screen positive for post-traumatic epilepsy (PTE).

The funding relationship between TRACK-TBI LONG, BIO, and EPI is depicted in **Figure 2**.

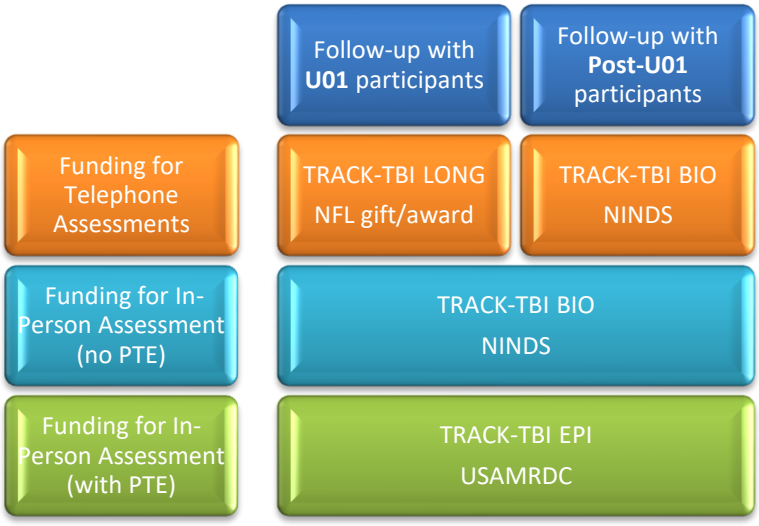

Figure 2. TRACK-TBI LONG, BIO, and EPI Funding Relationship

TRACK-TBI LONG, BIO, and EPI Longitudinal Follow-up Study Goals and Protocol Relationship

Study Goals

- The overarching goal of the "**TRACK-TBI Longitudinal**" (TRACK-TBI LONG) study is to improve understanding of the long-range natural history of TBI by extending follow-up of the TRACK-TBI cohort beyond the first 12 months after injury.

- The overarching goal of the "**Clinical Validation of Serum Neurofilament Light as a Biomarker of Traumatic Axonal Injury**" (TRACK-TBI BIO) study is to extend the follow-up periods for TRACK-TBI participants. Further, the extensive clinical, imaging, and biomarker data that has already been collected in these subjects during earlier TRACK-TBI studies will allow for the identification of risk factors, co-morbidities, and prognostic biomarkers of TBI. Consequently, the extension of study follow-up will help to determine negative neurological and psychological outcomes of individuals who experienced a TBI compared to healthy controls.

- The overarching goal of the "**TRACK-TBI Epileptogenesis Project**" (TRACK-TBI EPI) is to extend the follow-up period of the TRACK-TBI cohort (n = 2800) up to 5 years after injury, which will allow identification of >90% of those who may have developed PTE. Using the TRACK-TBI NINDS PTE Screening Questionnaire, we will identify participants who screen positive for PTE and consent them to undergo a detailed clinical evaluation with an epileptologist. This data will provide the first comprehensive longitudinal phenotyping of subjects with PTE from the moment of TBI through their epilepsy diagnosis and treatment.

Study Protocol Relationship

As described above, the overarching goals for these studies are synergistic, and the guidance provided in this Standard Operating Procedures (SOP) document will pertain to study procedures for all three studies. In addition to having multiple funding sources, this protocol will be supported by two Coordinating Centers and will have study activities monitored by different IRBs. See below for more information about the Coordinating Centers and IRB Oversight Plan.

Coordinating Centers, Institutional Review Board Oversight Plan, and Participating Sites

Study Coordinating Center Information

The Coordinating Center for our studies is responsible for:

1. Subcontracting with each site participating in the study;
2. Creating and disseminating all study materials (e.g., Study Protocol, recruitment materials, consent templates, etc.);
3. Managing study-wide data collection and data curation;
4. Training sites on relevant study documents and procedures;
5. Reimbursing sites for all milestone achievements.

- The Coordinating Center for TRACK-TBI LONG is the **University of California, San Francisco** (PI Geoffrey Manley).
  - All sites participating in the Telephone Assessment with TRACK-TBI U01 subjects will subcontract with UCSF.
- The Coordinating Center for TRACK-TBI BIO is the **University of Pennsylvania** (PI Ramon Diaz-Arrastia).
  - All sites participating in the Telephone Assessment with TRACK-TBI Post-U01 subjects will subcontract with UPenn.
  - All sites participating in the In-person Assessment (no PTE) will subcontract with UPenn.
- The Coordinating Center for TRACK-TBI EPI is the **University of Pennsylvania** (PI Ramon Diaz-Arrastia).
  - All sites participating in the In-person Assessment of participants with PTE will subcontract with UPenn

See **Figure 3** for a diagram of study activities by Coordinating Center.

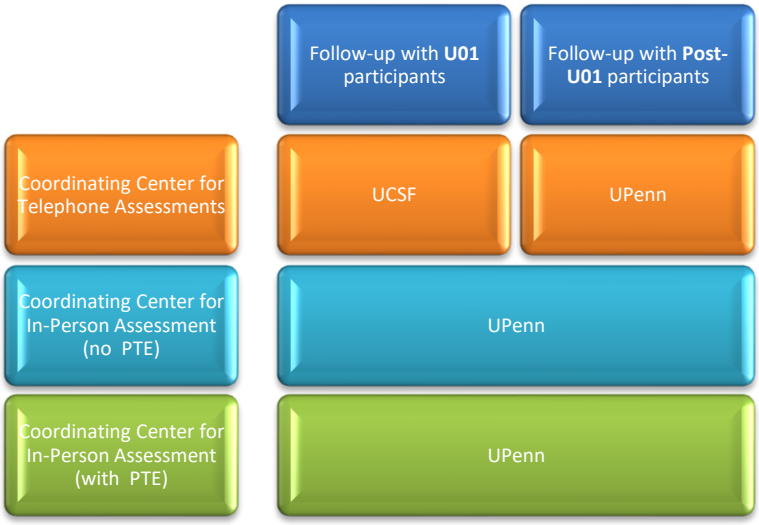

Figure 3. Study Activities by Coordinating Center

Institutional Review Board Oversight Plan and Study Initiation Timeline

IRB review of the Telephone Assessment

- Initiation of the Telephone Assessment study activities with TRACK-TBI U01 participants began Spring 2019.
    - IRB oversight for the Telephone Assessment with TRACK-TBI U01 participants is managed **locally at each site**.
- Expansion of the Telephone Assessment criteria to include Post-U01 subjects began Summer 2020.
    - IRB oversight for the Telephone Assessment with Post-U01 participants is managed **locally at each site**.

IRB review of the In-person Assessment (no PTE)

- Initiation of the In-person Assessment (no PTE) study activities began Summer 2020. IRB oversight for the In-person Assessment is managed at the **University of Pennsylvania as the IRB of Record**.

IRB review of the In-person Assessment (with PTE)

- Initiation of the study activities for the In-person Assessment of participants with PTE began Summer 2020. IRB oversight for the In-person Assessment (with PTE) is managed at the **University of Pennsylvania as the IRB of Record**.

See **Figure 4** for a diagram of the IRB oversight plan by study activity.

Figure 4. IRB Oversight Plan by Study Activity

Participating sites and date first participant is eligible for the Telephone Assessment

Site #	Site Name	PI Name	Date Eligible
Site 1	Baylor College of Medicine The Institute for Rehabilitation and Research U of Texas Health Science Center at Houston	Claudia Robertson Mark Sherer Ryan Kitagawa	March 2016
Site 2	Massachusetts General Hospital Spaulding Rehabilitation Hospital	Ann-Christine Duhaime Joseph Giacino	March 2016
Site 3	University of California, San Francisco	Geoffrey Manley	February 2016
Site 4	University of Cincinnati	Laura Ngwenya	April 2016
Site 6	University of Miami	Gillian Hotz	April 2016
Site 7	University of Pittsburgh	David Okonkwo	March 2016
Site 8	University of Texas, Austin	David Schnyer	June 2016
Site 9	University of Texas, Southwestern	Christopher Madden	July 2016
Site 10	University of Washington	Nancy Temkin	May 2016
Site 11	Virginia Commonwealth University	Alex Valadka	May 2016
Site 12	University of Pennsylvania	Ramon Diaz-Arrastia	December 2018
Site 14	Medical College of Wisconsin	Michael McCrea	June 2019
Site 15	University of Utah	Ramesh Grandhi	January 2020
Site 18	Denver Health Craig Hospital	Mitchell Cohen Cindy Harrison-Felix	January 2020

Table 1. Participating Sites

Study Arm Designations and Relationship Summary

In order to delineate the financial and regulatory relationships between the longitudinal study activities/cohorts, we have defined the study arms as follows:

- **Study Arm A:** Telephone Assessments with U01 participants coordinated by UCSF, reviewed by local site IRBs, and funded by the TRACK-TBI LONG mechanism (NFL gift and NFL award). This arm was initiated in Spring 2019 and is currently ongoing.
- **Study Arm B:** Telephone Assessments with Post-U01 participants coordinated by UPenn, reviewed by local site IRBs, and funded by the TRACK-TBI BIO mechanism (NINDS).
- **Study Arm C:** In-person Assessments (no post traumatic epilepsy) with U01 and Post-U01 participants who are eligible for this arm based on their participation in either Arm A or Arm B. Arm C is reviewed by UPenn as the IRB of record under the same IRB protocol as that for Arm B. Arm C is funded by the TRACK-TBI BIO mechanism (NINDS).
- **Study Arm D:** In-person Assessments (with PTE) with U01 and Post-U01 participants who are eligible for this arm based on their participation in either Arm A or Arm B, and who screen positive for post-traumatic epilepsy PTE. Arm D is reviewed by UPenn as the IRB of record under a separate IRB protocol from all other Study Arms. Arm D is funded by the TRACK-TBI EPI mechanism (USAMRDC).

The procedures in this SOP will refer back to these study arm designations. See **Figure 5** for a depiction of these relationships.

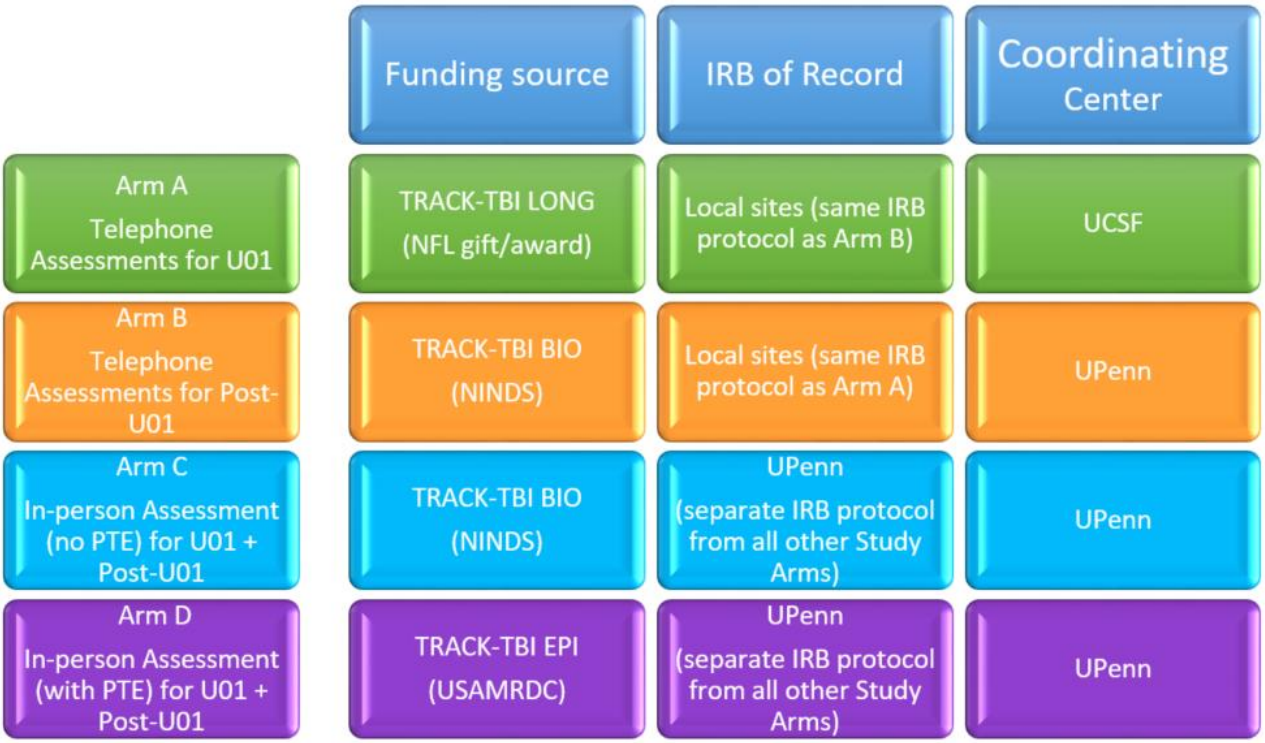

Figure 5. Study Arm Funding Source, IRB of Record, and Coordinating Center Diagram (Relationship Summary Diagram)

Longitudinal Follow-Up Standard Operating Procedures

Longitudinal follow-up eligibility

Telephone Assessment Eligibility (Arm A/B)

All participants enrolled in TRACK-TBI (U01-Arm A, or Post-U01-Arm B), who are at least two years post injury and who completed at least 1 GOSE during the TRACK-TBI follow-up assessments, will be eligible to take part in the Telephone Assessments.

Telephone Assessments as Screen for In-person Assessment

Data collected during the Telephone Assessment will provide the platform on which additional screening into the In-person Assessment (Arm C/D) will be completed. Screening criteria are described in the "Inclusion/Exclusion Criteria" section below.

Inclusion/Exclusion Criteria

For the Telephone Assessments (Arm A/B)

All participants enrolled in TRACK-TBI (U01-Arm A, or Post-U01-Arm B), who are at least two years post injury and who completed at least 1 GOSE during the TRACK-TBI follow-up assessments, will be eligible to take part in the Telephone Assessments (n=~2700 study-wide).

For the In-person Assessment (Arm C/D)

The Telephone Assessment (Arm A/B) will subsequently determine a participant's eligibility for the In-person Assessment (Arm C/D). A participant will be eligible for an In-person Assessment if they complete at least one Telephone Assessment and fall into one of the following four groups:

- **Group 1**- completed a TRACK-TBI 6M MRI and are stable or improved with regard to the Criteria for Establishing Decline (described below) (n=~50 study-wide);
- **Group 2**- Criteria for Establishing Decline (described below) met when comparing the Telephone Assessments to the last completed TRACK-TBI assessment (n=~100 study-wide);
- **Group 3**- all TRACK-TBI orthopedic controls (n=~50 study-wide);
- **Group 4 (Arm D)***- endorsed any one of four post-traumatic epilepsy (PTE) items from the Patient Interview at the 6 or 12 month TRACK-TBI follow-up or a Telephone Assessment and did not have a diagnosis of epilepsy prior to the index TBI (n=~50 study-wide).

**If participants meet the criteria for Group 4, they will be eligible to participate in the In-person Assessment with additional procedures for assessing Post-traumatic Epilepsy (Arm D). Participants will enroll into either Arm C or Arm D; they cannot enroll into both study arms.*

In-person Assessment Criteria for Establishing Decline

Decline is identified by comparing the first Telephone Assessment to the most recently completed TRACK-TBI U01/Post-U01 assessment (unless otherwise specified below).

Comprehensive Assessment Battery (CAB) Cohort under original TRACK-TBI protocol ***Criteria for Decline (3 of 4 required)***	**Abbreviated Assessment Battery (AAB) Cohort under original TRACK-TBI protocol** ***Criteria for Decline (1 of 2 required)***
1. Patient subjective report of decline or Informant endorsement of patient decline on Participant/ Informant Interview	1. Informant subjective report of decline on Informant Interview
2. Decline in performance on one or more BTACT subtests between 6M U01 and Telephone Assessments: Word List Immediate (decreased ≥3.90) Word list delayed (decreased ≥4.26) Backward digit span (decreased ≥2.52) Category fluency (decreased ≥8.53) Number series (decreased ≥2.14) Backward counting (decreased ≥10.31)	2. Decline of one or more points on GOSE
3. Decline of one or more points on GOSE	
4. Positive RCI on the BSI (calculated as an increase of ≥11 points) using orthopedic control data from U01 at 12M compared to Telephone Assessments).	

Recruitment Methods

Re-contact of eligible participants/legally authorized representatives (LARs) will be through email, letter, newsletter, and/or by phone. The preferred method of reaching participants will be by phone in order to decrease the time and travel burden on participants. Once contact is re-established through the abovementioned methods, research staff will introduce the study activities (i.e., longitudinal follow-up visits) to the participant and initiate the informed consent process or, if the participant does not have capacity to consent, their LAR will be approached and the informed consent process initiated.

Informed Consent Procedures

Consent Procedures for the Telephone Assessments (Arm A/B)

Prospective participants, or their LAR, will be given as much time as needed to consider consenting into these study activities.

Participants who self-consented prior to completion of the 12M TRACK-TBI visit or at their last Telephone Assessment

Study staff will present the study activities to potential participants either verbally by phone, or in-person, with an IRB-approved script. Procedures for obtaining a waiver of documentation of consent and verbal consent by phone will be governed by local IRB standards.

Participants who completed their last TRACK-TBI visit under legally authorized representative consent

Study staff will ascertain the decision-making capacity of the participant during the introduction of the study activities using the IRB-approved script. If the participant has regained decision-making capacity

since their last TRACK-TBI visit, study staff will obtain verbal consent from the participant. In the event that a participant does not have capacity to provide verbal consent (i.e., participant still has a LAR), verbal consent (including waiver of documentation of consent) will be obtained from the LAR by phone as governed by local IRB standards.

Informed Consent Procedures for In-Person Assessments (Arm C/D)

Once In-person Assessment eligibility is determined according to the abovementioned criteria (see "Inclusion/Exclusion Criteria" section above), study staff will call participants to inform them of their eligibility and ask that the participant (and LAR, if applicable) come for an in-person visit. Study staff will explain the In-person Assessment procedures, review the Informed Consent form, and obtain consent. Prospective participants or their LAR, will be given as much time as needed to consider consenting into these additional study activities. Based on previous interactions with the participant, we may also communicate with them through letters, emails, phone calls and/or newsletters, depending on what has been the most convenient for them in the past.

Electronic Informed Consent (eConsent)

To accommodate any current and future local restrictions on enrollment into research studies during COVID-19, and other similar circumstances, sites should comply with the IRB of Record's practices/guidance regarding informed consent procedures. If informed consent can be obtained remotely (i.e., by eConsent) through a secure and approved platform (e.g., RedCap, DocuSign, etc.), sites should get IRB approval to do so. All eConsent procedures should be documented according to approved procedures, and included in the participant's study record in the TRACK-TBI electronic database (i.e., QuesGen).

If study staff find themselves uncertain of the participant's capacity at any point during the study procedures (i.e., due to a perceived decline or another reason), administer the Speech Intelligibility measure followed by the Galveston Orientation and Amnesia Test. If the participant does not pass the GOAT (score $\leq$75), study staff should approach the LAR for consent as described above.

Enrollment

Enrollment is signified upon obtaining verbal or written consent for any study arm.

Informants

Study activities will include an evaluation of the health of the participant by an Informant. Participants (or their LAR) will be asked to name a loved one or caregiver (can be family/non-family) **who knew the participant at least three months prior to injury and who has had at least monthly contact (on average) with the patient over the last three months prior to the current follow-up**. Participants (or their LAR) will be asked to put the named person in contact with study staff. This person will be considered the "Informant" on the study and will be asked to answer certain questions pertaining to the functional level and health of the participant.

- If the participant/LAR nominates an Informant who has had monthly contact with the participant over the last three months, but who **does not meet the criteria for knowing the participant at least 3 months prior to injury**, per the definition of the "Informant", this person still qualifies as an informant but data collection from these Informants will be modified. See "Data Collection from Informants" section below.

- If the participant/LAR nominates an Informant, but the identified Informant **does not currently have contact with the subject**, per the definition of the "Informant", the person cannot serve as the Informant.
- If the identified Informant was also the LAR/caregiver during the TRACK-TBI U01 phase of the study or a previous TRACK-TBI LONG telephone assessment, study staff can use the already collected contact information to contact the Informant. (Site-specific as allowed by local IRB guidelines).

Additional Guidance for Identifying the Informant

- The LAR can also serve as the Informant as long as the LAR meets the required "Informant" definition above.
- The Informant does not need to be the same person for any potential subsequent annual phone calls.

Consenting Informants

Requirements to consent Informants to complete these surveys/questions about the participant will be determined by the IRB of Record.

Data Collection from Informants

For a complete list of the measures administered to the Informant, see the Outcome Assessment Battery and Order of Administration tables below. For either the Telephone or In-person Assessment, if the participant is unable to answer questions on the Participant Interview, the Informant can help answer those questions.

Informants who had monthly contact with the participant over the last three months, but who do not meet the criteria for knowing the participant at least 3 months prior to injury will be interviewed with a *modified battery* to capture the current health status of the participant. See more details about this modified battery below in the "Outcome Assessments for Study Informants" section.

Outcome Assessments for Telephone and In-Person Assessments

Comprehensive Assessment Battery for Study Participants

Participants will be administered the Comprehensive Assessment Battery (CAB). The CAB is comprised of measures of cognition (i.e. attention, memory, information processing speed, executive functions), mood (i.e., depression, anxiety), social participation, subjective well-being, post-traumatic stress, interviews, global functional status measures, and a COVID-19 questionnaire. The specific assessments to be administered during a Telephone Assessment (Arm A/B) vs. the In-person Assessment (Arm C/D) to a participant are listed in the Comprehensive Assessment Battery and Order of Administration table below (**Table 3**). See **Figure 6** for the Comprehensive Assessment Battery (CAB) Telephone Assessment Order of Administration Flow Chart for Study Participants. See **Figure 8** for the Comprehensive Assessment Battery (CAB) In-Person Assessment Order of Administration Flow Chart for Study Participants.

Outcome Assessments for Study Informants

Participants will be asked to provide contact information for an Informant or to put an Informant in touch with study staff. The Informant will answer some questions in the Informant Battery, similar to those posed to the participant, to help determine the participant's current level of function and health compared to their pre-injury level of function and health. The specific assessments to be administered during a Telephone Assessment (Arm A/B) vs. the In-person Assessment (Arm C/D) to an Informant are listed in the Comprehensive Assessment Battery and Order of Administration table below (**Table 3**). The discussion with the informant to collect this data will take approximately 30-45 minutes of the Informant's time. See **Figure 7** for the Comprehensive Assessment Battery (CAB) Telephone Assessment Order of Administration Flow Chart for Study Informants. See **Figure 9** for the Comprehensive Assessment Battery (CAB) In-Person Assessment Order of Administration Flow Chart for Study Informants.

For Informants who do not meet the criteria of knowing the participant 3 months prior to injury, but do meet the criteria of having monthly contact with the participant over the last 3 months (i.e., knows the participant well now but did not know them prior to the study injury), examiners should administer only the DEX-R-I and applicable questions from the Informant Interview (i.e., Q4c and 4d, as well as Q5 a-d).

Abbreviated Assessment Battery (AAB)

Participants who do not have decision-making capacity will be asked to complete a modified assessment battery, called the Abbreviated Assessment Battery (AAB), following LAR consent (see **Table 4** for the list of AAB measures).

- The AAB Telephone Assessment (Arm A/B) consists of the Speech Intelligibility, GOAT, and BTACT measures (see **Figure 10**). If administration of the three measures are complete and valid, study staff should attempt to complete the CAB Telephone Assessment. Study staff should discontinue testing if a status of "test attempted and not completed" is obtained for any three measures in the battery. Informants for participants in the AAB Telephone Assessment cohort will complete the GOSE, FSE, DEX-R-I, and the Informant Interview (see **Figure 11**).
- Participants without decision-making capacity at an In-person Assessment (Arm C/D) will be administered the Speech Intelligibility, GOAT, and CAP and/or CRS-R (see **Figure 12**). In-person Assessment of participants without decision-making capacity will follow the same rules and

procedures as that for the Abbreviated Assessment Battery conducted during the TRACK-TBI U01 and described in the TRACK-TBI U01 Outcomes SOP (Page 36 of Version 10). Informants for participants in the AAB In-person Assessment cohort will complete the GOSE, DEX-R-I, and the Informant Interview (see **Figure 13**). More information about the measures administered in the Abbreviated Assessment Battery can be found in the "Abbreviated Assessment Battery and Order of Administration" table (**Table 4**) and in the "Outcome Assessment Battery: Description of Measures" section below.

Battery administrators should continue to refer to the TRACK-TBI U01 Outcomes Assessment SOP for proper administration and scoring of all original TRACK-TBI measures. See the below sections "Outcome Assessment Battery and Order of Administration" and "Outcome Assessment Battery: Description of Measures" for further information about the measures in the Telephone Assessment and In-person Assessment batteries.

Minimizing in-person outcome assessment procedures and conducting remote study activities

To accommodate any current and future local restrictions on research study activities during COVID-19, and other similar circumstances, sites should comply with local practices/guidance and reach out to the appropriate Coordinating Center if they require further guidance on completion of TRACK-TBI-related study activities.

- **Self-report/Interview measures**: If the PI and study team deem that it is safer to minimize study staff and subject face-to-face contact for TRACK-TBI study visits that would otherwise be in-person, all self-report and interview outcome measures can and should be completed remotely (e.g., telephone, secure Zoom, or other supported and secure platform) with application of the appropriate test completion code of "1.3 valid administration collected by phone" (even when using Zoom or other, similar platform) with a note added into QuesGen that the visit was conducted by phone due to COVID (or other similar circumstance).
- **Cognitive Measures**: If it is possible to conduct a shortened in-person visit to administer the cognitive measures that must be collected in-person, sites should do so following all TRACK-TBI procedures and implementing all local safety practices. If it is deemed unsafe to have a shortened in-person visit to collect these cognitive measures, a test completion code of "3.6 Test not attempted due to logistical reasons" should be entered on the electronic and paper CRFs (if paper CRFs are able to be used) with a note added into QuesGen that the visit was conducted by phone due to COVID (or other similar circumstance).
- **In-person procedures that cannot be completed remotely**: Procedures, such as MRI and blood collection, that can only be conducted in-person and should only be attempted once TRACK-TBI leadership has given approval, and any local restrictions on in-person research study activities has been lifted.
- **Paper case report form completion during remote study activities**: The standard for TRACK-TBI studies is to directly enter data onto paper case report forms and then enter the data into the QuesGen electronic database. If remote collection of data is necessary and access to a printer is limited, **direct data entry into QuesGen is acceptable**. That said it would be best to have loose-leaf paper available when administering the BTACT. The created BTACT CRF should include the Patient Number, date/time, and start/end time of the assessment, and it should be kept securely and placed within the subject's binder once physical access to those binders has been re-established.

Schedule for Follow-Up Assessment Windows and Extensions

Follow-up Assessment Windows	
Telephone Assessments (Arm A/B)	Outcomes: At least 2 years post-injury and ± 90 days from Month and Day of injury AND at least 90 days from an In-person Assessment
In person Assessment (Arm C/D)	Outcomes: At least 90 days from the last Telephone Assessment MRI: ± 7 days of the outcomes Blood: ± 3 days of the MRI

- ❖ If the assessment battery cannot be completed on the scheduled day, testing should be completed within **72 hours** of the date it was initiated.
- ❖ If the participant agrees, the interview with the informant should take place **within 14 days of the participant follow-up assessment**.

Follow up window extension requests

In situations in which the follow up assessment window closes before each of the outcome measures are obtained, and the participant indicates willingness to complete the assessment, the examiner should email the appropriate Coordinating Center to request permission to complete the assessment outside of the window. The email should include a brief description of the circumstances that led to the delay, and should spell out the original due dates for the outcome battery, the outcome measures that were not completed, and the anticipated completion date of these measures. The request will be triaged by the Executive Committee and a decision will be communicated within two working days of the request. The overarching objective is to acquire as many of the outcome metrics as possible within the specified assessment window.

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*Requests for Informant batteries conducted outside of window **do not need to be submitted for EC approval**, but protocol deviations should continue to be submitted.*

Study Participation Stipends

Participants will receive financial compensation in recognition of the time required by the study. The suggested compensation is in **Table 2** below. While these are the suggested compensation rates for the study, **individual sites have the ability to determine their own reimbursement plans** for participants and Informants as well as a rate per time point within the constraints of their budget and as approved by the IRB of Record.

Study Activity	Suggested Compensation Amount
Participant Telephone Assessment (Arm A/B)	$100
Participant In-Person Assessment (Arm C/D)	$200
Informant Assessment (All study arms)	No compensation

Table 2. Suggested Study Compensation Amounts

Table 3. Comprehensive Assessment Battery and Order of Administration

Domain	Subdomain	Instrument	Administration Time	Order of Administration Telephone (Arm A/B) (~108 min)	Order of Administration In person (Arm C/D) (~99 min)
History	Participant Interview (or Informant Interview)	Interview to update occupational status; living situation; medical history (e.g., known neurologic, cognitive, psychiatric conditions) includes a brief survey of COVID-19 impact	20 min[#]	8	1
Daily/Global Function	Global Outcomes	Glasgow Outcome Scale Extended (GOSE)	15 min[#]	2	2
		Functional Status Exam (FSE)	10 min[#]	1	
	ADLs/IADLs	Functional Activity Questionnaire from Alzheimer's Disease Centers' Uniform Dataset	Questions asked within Participant/Informant Interview[#]		(1)
Psychological Health/ Neurobehavioral Symptoms	Depression, Anxiety, Somatic	Brief Symptom Inventory-18 (BSI-18)	5 min	9	6
	TBI-Related Symptoms	Rivermead Post-Concussion Symptom Questionnaire (RPQ)	3 min	10	
	Depression	Patient Health Questionnaire 9 (PHQ-9) Depression Inventory	3 min	11	
	Post-traumatic stress	PTSD Checklist for DSM-5 (PCL-5)	3 min	6	
	Stress/Trauma Exposure	Stress/Trauma Questionnaire (adapted)	3 min		12
	Suicide	Columbia Suicide Severity Rating Scale Screening Version[+]	5 min	As needed	As needed
	Life Quality (General)	Short Form Health Survey (SF-12)	3 min	4	
	Life Quality (Brain)	Quality of Life after Brain Injury Overall Scale (QoLIBRI-OS)	3 min	5	
	Sleep	Insomnia Severity Index	3 min	13	
	Alcohol	Alcohol Use Disorders Identification Test Screener (AUDIT-C)	Questions asked within Participant/Informant Interview[#]	(8)	
	Other Drugs	Drug Abuse Screening Test (DAST-10)	Questions asked within Participant/Informant Interview	(8)	
	Behavioral control	Dysexecutive Questionnaire Revised (DEX-R) (self and informant report)	20 min[#]	7	
Response bias and effort	Symptom Validity	Structured Inventory of Malingered Symptomatology (SIMS)	10 min		7
	Cognitive Test Validity	Test of Memory Malingering (TOMM, Trial 1 of the 50 item version)	5 min		8
Social Support	Social Isolation	PROMIS Social Isolation Short Form	2 min	12	

Cognitive Performance	Episodic Memory, Working Memory, Executive Function, Reasoning, Processing Speed	Brief Test of Adult Cognition by Telephone (BTACT)	20 min	3	
	Episodic Memory	Rey Auditory Verbal Learning Test (RAVLT)	15 min		3 (delay after BSI-18 or SIMS)
	Executive Function	Trail Making Test	5 min		4
	Processing Speed	Wechsler Adult Intelligence Scale – 4th Edition Processing Speed Index (WAIS-IV) PSI	8 min		5
	Language	Boston Naming Test (BNT)	5 min		9
Neurologic Screen	Epilepsy	Posttraumatic Epilepsy (PTE) Screening Form	Questions asked within Participant/Informant Interview[#]	(8)	
	Prodromal Parkinsonism	REM-Sleep Behavioral Disorder Screening Test	Questions asked within Participant/Informant Interview[#]		(1)
Motor	Fine motor (Bradykinesia)	Finger tapping	5 min		10
	Gross motor/mobility	Short physical performance battery (SPPB)	5 min		11

[+]Triggered by PHQ-9/BSI-18

()Questions asked within Interview

[#]Measures asked within the Informant Battery

Comprehensive Assessment Battery Outcome Order of Administration Flow Charts

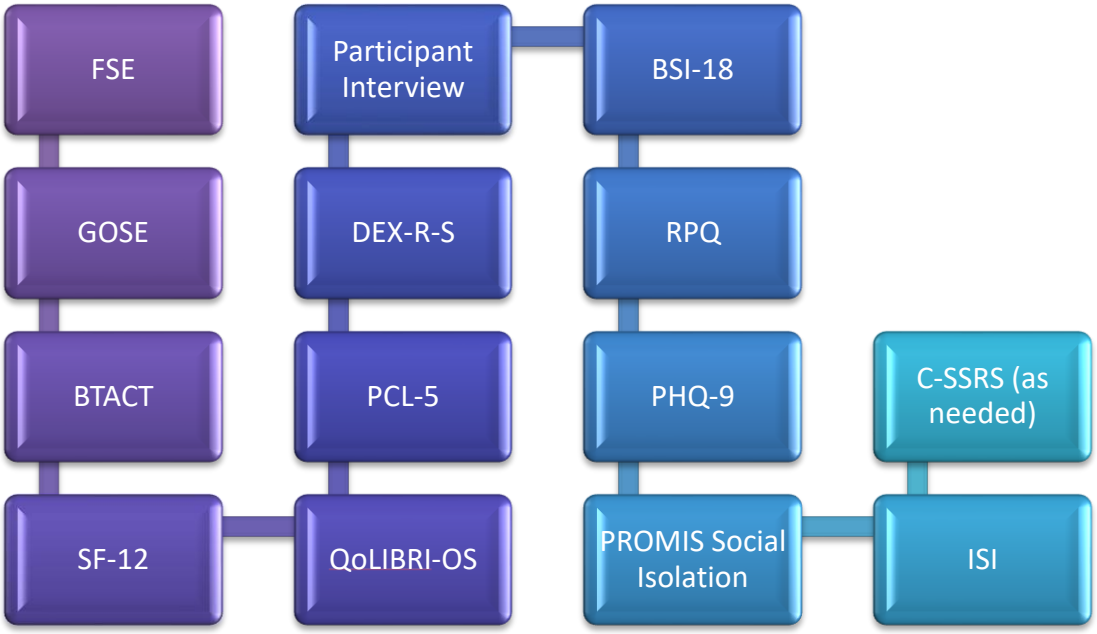

Figure 6. CAB Telephone Assessment (Arm A/B) Order of Administration Flow Chart for Study Participants

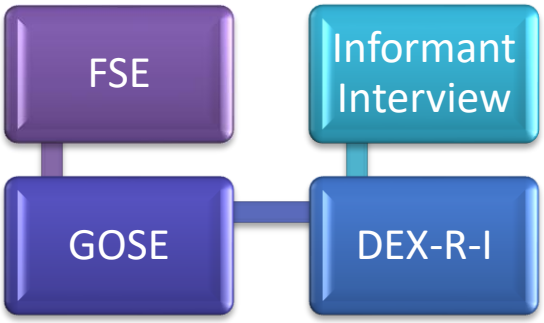

Figure 7. CAB Telephone Assessment (Arm A/B) Order of Administration Flow Chart for Study Informants

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If the Informant did not know the participant prior to the study injury, only the DEX-R-I and applicable questions on the Informant Interview should be collected. The FSE and GOSE will NOT be collected from these Informants.

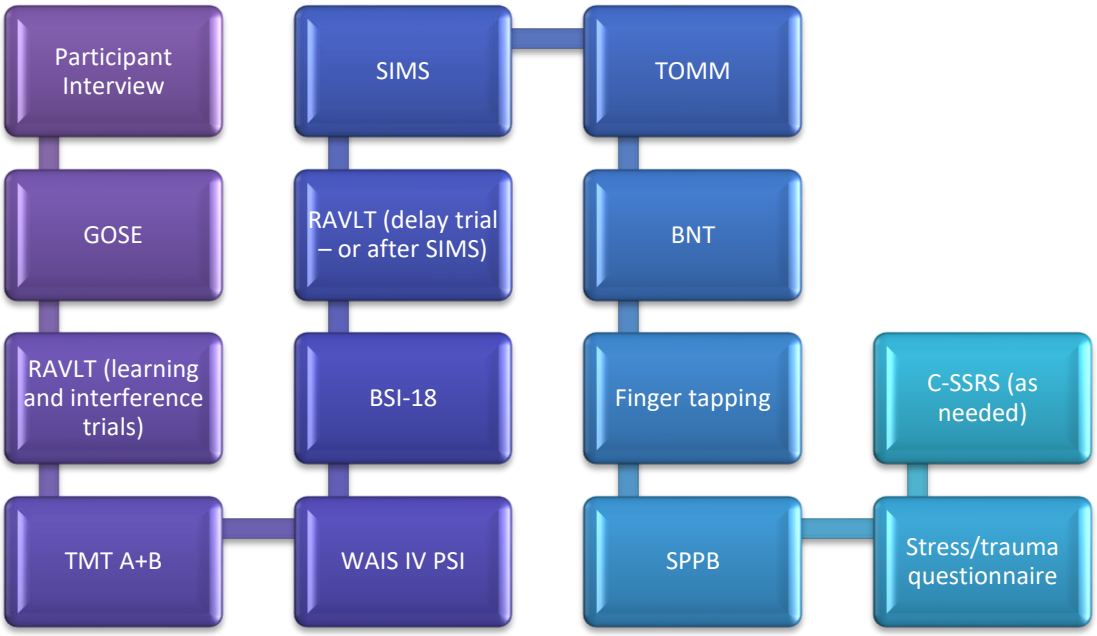

Figure 8. CAB In-Person Assessment (Arm C/D) Order of Administration Flow Chart for Study Participants

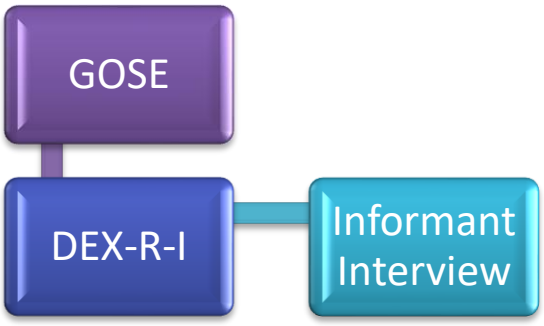

Figure 9. CAB In-Person Assessment (Arm C/D) Order of Administration Flow Chart for Study Informants

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If the Informant did not know the participant prior to the study injury, only the DEX-R-I and applicable questions on the Informant Interview should be collected. The GOSE will NOT be collected from these Informants.

Table 4. Abbreviated Assessment Battery and Order of Administration

Domain	Subdomain	Instrument	Administration Time	Order of Administration Telephone (Arm A/B) (~85 min)	Order of Administration In person (Arm C/D) (~92 min)
Screening	Screening	Assessment of Speech Intelligibility	2 min	1	1, and as needed
		Galveston Orientation and Amnesia Test	5 min	2	2, and as needed
History	Participant Interview (or Informant Interview)	Interview to update occupational status; living situation; medical history (e.g., known neurologic, cognitive, psychiatric conditions) includes a brief survey of COVID-19 impact	20 min[#]	7	5
Daily/Global Function	Global Outcomes	Glasgow Outcome Scale Extended (GOSE)	15 min[#]	5	3
		Functional Status Exam (FSE)	10 min[#]	4	
	ADLs/IADLs	Functional Activity Questionnaire from Alzheimer's Disease Centers' Uniform Dataset	Questions asked within Participant/Informant Interview[#]		(5)
Psychological Health/ Neurobehavioral Symptoms	Behavioral control	Dysexecutive Questionnaire Revised (DEX-R) (informant report)	20 min[#]	6	4
Consciousness and Basic Cognition	Confusion	Confusion Assessment Protocol (CAP)	15 min		6 Determined by Flexible Outcome Battery Flow Chart (page 18 of TRACK-TBI Outcomes SOP V 10)
	Consciousness	Coma Recovery Scale Revised (CRS-R)	15-30 min		
Cognitive Performance	Episodic Memory, Working Memory, Executive Function, Reasoning, Processing Speed	Brief Test of Adult Cognition by Telephone (BTACT)	20 min	3	

[+]Triggered by PHQ-9/BSI-18

()Questions asked within Interview

[#]Measures asked within the Informant Battery

Abbreviated Assessment Battery Outcome Order of Administration Flow Charts

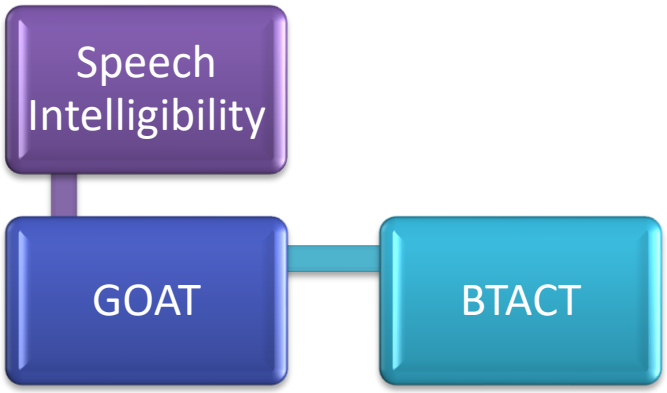

Figure 10. AAB Telephone Assessment (Arm A/B) Order of Administration Flow Chart for Study Participants

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If administration of the three AAB Telephone Assessment measures (Figure 10) to Study Participants are complete and valid, study staff should attempt to complete the full Telephone Assessment.

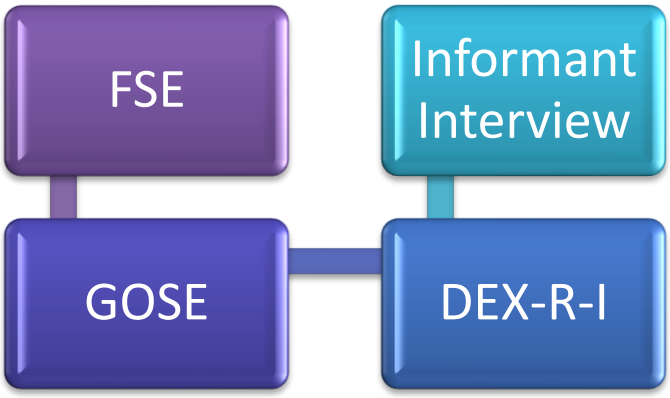

Figure 11. AAB Telephone Assessment (Arm A/B) Order of Administration Flow Chart for Study Informants

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If the Informant did not know the participant prior to the study injury, only the DEX-R-I and applicable questions on the Informant Interview should be collected. The FSE and GOSE will NOT be collected from these Informants.

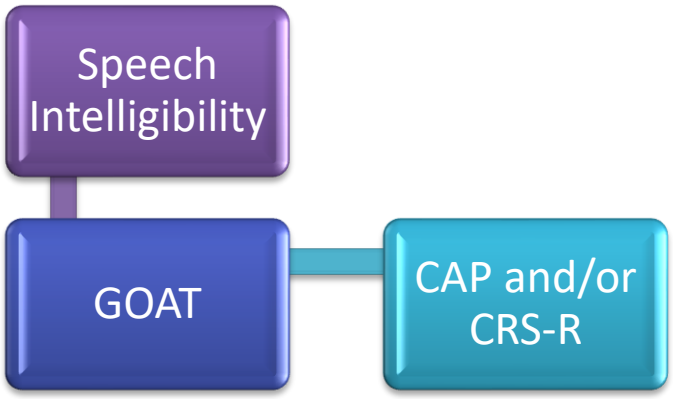

Figure 12. AAB In-person Assessment (Arm C/D) Order of Administration Flow Chart for Study Participants

Administration of the CAP and/or CRS-R will be determined by participant performance on the Speech Intelligibility measure. See the In-person Assessment Administration Algorithm Flow Chart (Figure 14) below for more information.

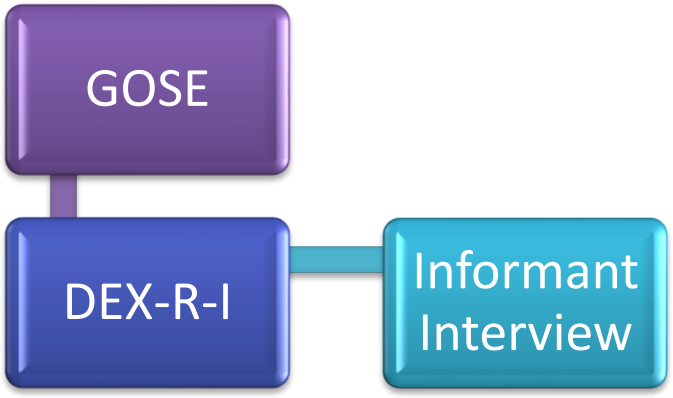

Figure 13. AAB In-person Assessment (Arm C/D) Order of Administration Flow Chart for Study Informants

If the Informant did not know the participant prior to the study injury, only the DEX-R-I and applicable questions on the Informant Interview should be collected. The GOSE will NOT be collected from these Informants.

In-Person Assessment (Arm C/D) Outcome Battery Administration Algorithm Flow Chart

Figure 14 illustrates the decision-making algorithm for administration of the In-Person Assessment Battery (Arm C/D).

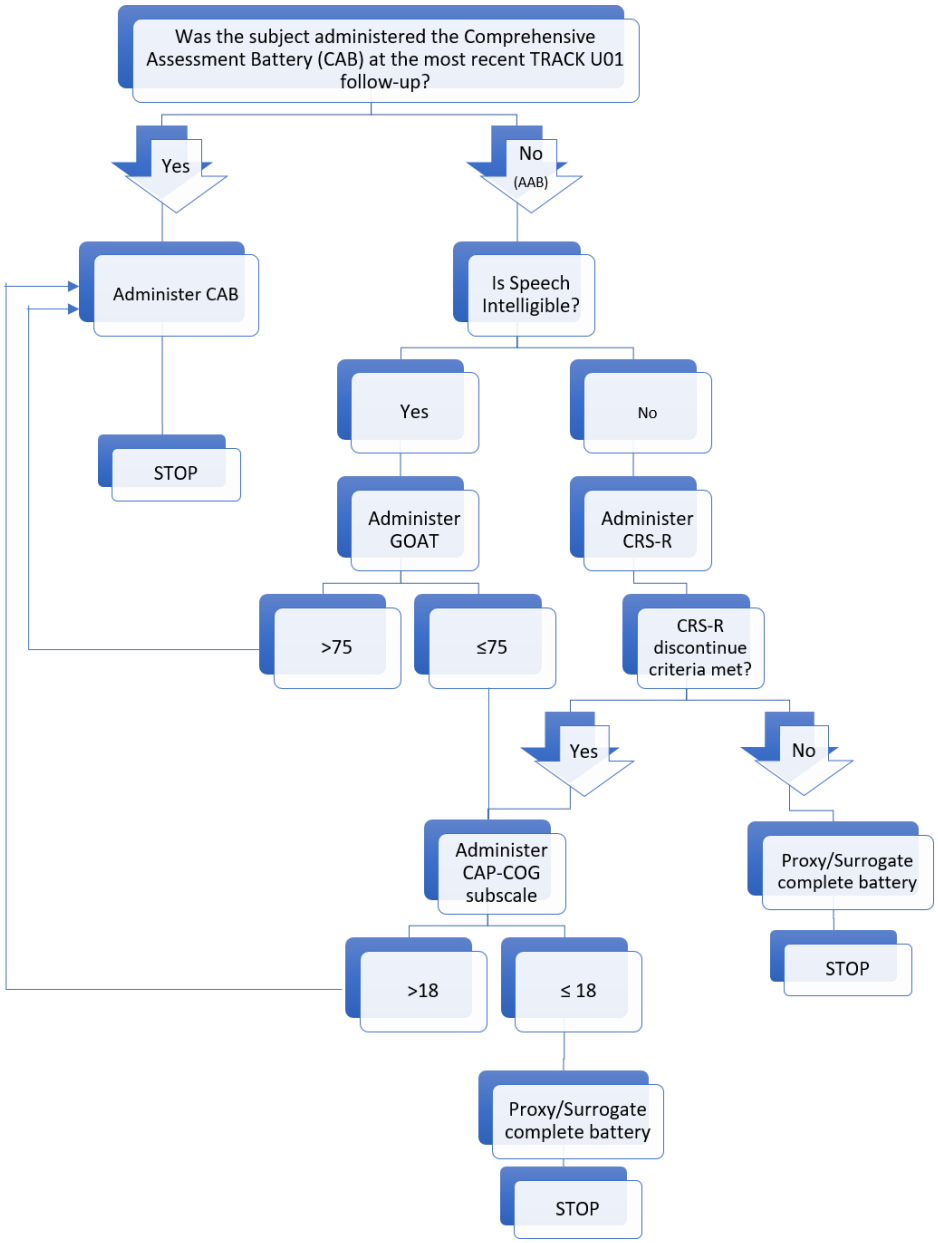

Figure 14. In-Person Assessment (Arm C/D) Outcome Battery Administration Algorithm Flow Chart

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Note that if the participant appears to have declined from a previously higher level of function and does not appear to be able to complete the CAB, study staff should administer the Speech Intelligibility measure and proceed as directed by the algorithm.

Outcome Assessment Battery: Description of Measures

Screening for Capacity and the Abbreviated Assessment Battery

Speech Intelligibility

This measure is administered and scored in the same way as described in the TRACK-TBI Outcomes Assessment SOP. The Speech Intelligibility measure is administered during the In-person Assessment to determine if the Abbreviated Assessment Battery should be collected and whether to administer the CAP and/or CRS-R (see below for more information about these measures). This measure can also be administered at any point during the Telephone or In-person Assessment, if the study coordinator has any concerns about the participant's capacity to consent and complete an assessment.

Galveston Orientation and Amnesia Test

This measure is administered and scored in the same way as described in the TRACK-TBI Outcomes Assessment SOP. The GOAT measure is administered during the In-person Assessment to determine if the Abbreviated Assessment Battery should be collected and whether to administer the CAP and/or CRS-R (see below for more information about these measures). This measure can also be administered at any point during the Telephone or In-person Assessment, if the study coordinator has any concerns about the participant's capacity to consent and complete an assessment.

Interviews

Participant Interview

This interview is administered and responses recorded in the same way as described in the TRACK-TBI Outcomes Assessment SOP for the Participant/Surrogate Interview. The Participant Interview is based on the TRACK-TBI 3M follow-up participant interview and adds a neurologic screen for both Epilepsy and Parkinsonism as well as questions pertaining to sleeping patterns and the impact of the COVID-19 pandemic. The Covid-19 survey questions will assess the impact COVID-19 had or is having on the participant and/or someone close to the participant. The Participant Interview will be administered during both the Telephone and In-person Assessments.

Informant Interview

The informant interview consists of questions concerning the functional level, health, and behavior of the study participant. The Informant Interview will be administered during both the Telephone and In-person Assessments as part of the Informant Battery.

Measures of Daily/Global Function

Functional Status Exam (FSE)

The FSE[12] measures change in functional status specifically due to traumatic injury. The measure can be administered in relation to changes due to TBI only or both the changes associated with TBI and peripheral injuries. For this study, the FSE will be administered to gather information around both the changes associated with TBI and peripheral injuries. This measure covers 7 areas of functioning: personal care, ambulation, mobility, major activities (i.e. work, school), home management, leisure and recreation and social integration. These areas are evaluated using the concept of dependency to operationally define outcome at four levels. The first level signifies no change, the second level signifies difficulty in performing the activity although the person is still independent, the third level signifies dependence on others some of the time or a decrease in the activity/elimination of an activity compared to status before the injury, and the fourth level signifies nonperformance or inability to perform the activity or total dependence on others. A total score is generated by summing scores from the 7 categories, yielding a range from 0 (return to pre-

injury baseline in all areas) to 21 (total dependence on others or can no longer perform any activities across functional areas). Persons who die are assigned a total score of 22. Additional information regarding the administration of the FSE can be found in the pdf called "Functional Status Examination Manual" on Dropbox (Dropbox\1-TRACK TBI Doc Share\TRACK LONG\LONG outcomes training and administration guidance. The FSE will be administered only during the Telephone Assessments to both the participant and the informant.

Glasgow Outcome Scale- Extended (GOSE)

This measure is administered and scored in the same way as described in the TRACK-TBI Outcomes Assessment SOP except only the "All" score will be calculated for each participant. A "TBI" score will not be collected for the purposes of this study. The GOSE will be administered during both the Telephone and In-person Assessments to both the participant and the informant.

Scoring the GOSE in Relation to the FSE

There is considerable overlap in the item content of the FSE and GOSE. Because the FSE is administered before the GOSE during the Telephone Assessments, the examiner will have extracted information from the subject during administration of the FSE that can be used to score the GOSE. Although it is necessary to independently administer and score *all* the GOSE items, information obtained during the FSE interview that relates to a specific GOSE item can be directly applied to the GOSE rating. This approach will minimize subject "burden" and help reduce the completion time of the Outcome Assessment Battery.

Functional Activity Questionnaire from National Alzheimer's Coordinating Centers' Uniform Dataset

The Functional Activities Questionnaire[13] (FAQ) was developed as an informant-based assessment of instrumental activities of daily living in older adults with varying degrees of cognitive impairment. The intent is to capture changes in functional activities, relative to previously attained abilities, that are caused by cognitive dysfunction. This measure presents a forced choice among levels of performance of 10 activities. For each activity, four levels ranging from normal to dependent are presented. "Normal" indicates that the subject is independent and has no difficulty with the activity. "Has difficulty" indicates that while the subject still completes the activity independently (e.g., without the assistance of another person), the activity is more difficult for the subject than it used to be. "Requires assistance" indicates that the subject requires some help from another person to complete the activity, but is still able to participate in completing the activity on some level (e.g., still writes the checks, but no longer balances the checkbook). "Dependent" indicates that the subject is now fully dependent on the help of another individual to complete the activity and no longer participates even partially in the activity. In the event that the subject *never* did the specified activity, then the interviewer should probe further to determine whether the informant thinks the subject *could* do the task, if absolutely necessary, and then score based on the speculated level of function. Only if further probing does not help tease out the level of function, then the interviewer should select, "Not applicable." The category "unknown" should only be selected if the informant believes that the subject previously did the activity but cannot comment on the subject's potential changes in the activity. These questions will be asked within the Informant Interview and only during the In-person Assessment.

Measures of Psychological Health/Neurobehavioral Symptoms

Brief Symptom Inventory 18 (BSI-18)

This measure is administered and scored in the same way as described in the TRACK-TBI Outcomes Assessment SOP. The BSI-18 will be administered during both the Telephone and In-person Assessments to the participant. **This measure is proprietary, and the site should ensure they have an appropriate supply of forms (reach out to the appropriate UCSF contact, if additional forms are required).**

Rivermead Post-Concussive Symptom Questionnaire (RPQ)

This measure is administered and scored in the same way as described in the TRACK-TBI Outcomes Assessment SOP. The RPQ will be administered during the Telephone Assessments to the participant.

Participant Health Questionnaire- 9 (PHQ-9)

This measure is administered and scored in the same way as described in the TRACK-TBI Outcomes Assessment SOP. The PHQ-9 will be administered during the Telephone Assessments to the participant.

Posttraumatic Stress Disorder Checklist (PCL-5)

This measure is administered and scored in the same way as described in the TRACK-TBI Outcomes Assessment SOP. The PCL-5 will be administered during the Telephone Assessments to the participant.

Stress/Trauma Questionnaire

This measure is adapted from the Army STARRS Life Stressors Questionnaire and is designed to capture stressful life events that occurred in the past 12 months. The Stress/Trauma Questionnaire will be administered to the participant during the In-person Assessment. Should the participant indicate emotional distress about any of the presented stressful life event options, study staff should implement the "**Action Plan for Managing Emotional Distress During/After Administration of the Stress/Trauma Questionnaire**" described below.

Action Plan for Managing Emotional Distress During/After Administration of the Stress/Trauma Questionnaire.

Many of the items in the Stress/Trauma Questionnaire ask about events that most people would perceive to be emotionally distressing. It is important to be attentive to this and to be prepared to provide support and, if needed, assistance in finding help. If you believe the participant is emotionally distraught and may be in need of help for any reason, say, **Thank you for sharing this with me. I am so sorry that you have experienced/are experiencing these difficult events. There are resources that can help. I would be happy to provide you with contact information for an organization that can help locate assistance in your area. Would you like me to give you this information when we are finished? [*Share National Support and any Local Support options – see below for National Support resources for domestic violence, sexual assault,* substance abuse and mental health resources, and add any local resources].**

While there do not appear to be any mandatory domestic violence reporting requirements for non-healthcare professionals, sites are advised to review and implement any local statutes.

Sites may also wish to add local community resources to the template table below.

National Support		
Resource	**Contact Information**	**More Info**
National Domestic Violence Hotline	1-800-799-SAFE (7233) www.thehotline.org (online chat function) Text LOVEIS to 22522 (texting support)	National Hotline and online resources that are confidential and free.

	http://www.thehotline.org/help/ http://espanol.thehotline.org/	Provide immediate help and pathways to safety and provide additional options for legal support and finding shelters.
National Sexual Assault Hotline Rape, Abuse and Incest national Network (RAINN)	1-800-656-HOPE (4673) https://www.rainn.org/get-help/national-sexual-assault-hotline	Trained staff member from a sexual assault service provider in your area. Confidential Referrals to local resources and information about laws in your area
Substance Abuse and Mental Health Services Administration (SAMHSA) Treatment Referral Helpline	1-877-726-SAMHSA7 (1-877-726-4727)	Speak to a live person Monday through Friday from 8:00am to 8:00 pm EST.
Local/Community Support		
Resource	**Contact Information**	**More Info**

12-Item Short Form Survey- Version 2 (SF-12v2)

This measure is administered and scored in the same way as described in the TRACK-TBI Outcomes Assessment SOP. The SF-12 v2 will be administered during the Telephone Assessments to the participant.

Quality of Life After Brain Injury- Overall Scale (QOLIBRI-OS)

This measure is administered and scored in the same way as described in the TRACK-TBI Outcomes Assessment SOP. The QOLIBRI-OS will be administered during the Telephone Assessments to the participant.

Insomnia Severity Index (ISI)

This measure is administered and scored in the same way as described in the TRACK-TBI Outcomes Assessment SOP. The ISI will be administered during the Telephone Assessments to the participant.

Columbia Suicide Severity Rating Scale (C-SSRS) Screening Version

The Screening Version of the Columbia will be administered at any assessment if participants answer ≥1 on either Q#9 of the PHQ-9 or Q#17 of the BSI-18 (this is the same triggering criteria in TRACK-TBI U01). This measure will be used regardless of any prior administration of the C-SSRS during TRACK-TBI U01. The Screening Version is a shortened form of the original Baseline and Since Last Visit forms that assesses suicidal ideation and behavior in the last month, and offers helpful triage categories based on severity. If the participant endorses YES on any question considered "Moderate Risk" (i.e., orange level) or "High Risk" (i.e., red level), examiners should proceed to administer the **TRACK-TBI Suicide Protocol and Safety Plan** found on Dropbox in the "Outcomes Core SOP" folder.

Dysexecutive Questionnaire Revised (DEX-R) – self and informant versions

The DEX-R is an extension and revision of the Dysexecutive Questionnaire, which was originally developed to assess everyday problems associated with frontal systems dysfunction.[14] The DEX-R is comprised of some original items, items that have been re-worded to improve clarity and 14 new items intended to broaden the range of frontal lobe functions assessed. The current 37-item version of the DEX-R is designed to assess executive cognition, metacognition, behavioral-emotional self-regulation and regulation of activation functions. A shortened, 26-item version of the DEX-R will be used in this study. The DEX-R has two forms, Self (DEX-R-S) and Informant (DEX-R-I; family member or caregiver), both of which contain the same items, but phrased appropriately. Items are rated in terms of frequency on a 5-point scale: 0 (never), 1 (occasionally), 2 (sometimes), 3 (fairly often), 4 (very often). Scores are summed with total scores ranging from 0 to 80, with higher scores indicating greater difficulty with executive functioning. The scale can also be used as a measure of self-awareness by calculating a discrepancy score between the self and informant responses. The discrepancy score ranges from -80 to +80 with scores in the positive direction indicating that the informant endorses problems with greater frequency than the patient, suggesting diminished patient self-awareness. The DEX-R-S will be administered to participants during the Telephone Assessments. The DEX-R-I will be collected from the LAR/Informant as part of the Informant Battery during the Telephone Assessments, and when the participant is administered the AAB during the In-person Assessment.

Measures of Social Support

PROMIS Social Isolation Short Form

The PROMIS Social Isolation item bank assesses perceptions of being avoided, excluded, detached, disconnected from, or unknown by, others. The item bank does not use a time frame (e.g., over the past seven days) when assessing social isolation. The item bank consists of 14 questions. This study will be using a short form version of this item bank consisting of 4 questions, which measure the participant's perception of the availability or adequacy of resources provided by others. Items are rated using a 5-point Likert scale ranging from 1 (never) to 5 (always). The PROMIS Social Isolation short form will be administered during the Telephone Assessments to the participant.

Measures of Cognitive Performance

Brief Test of Adult Cognition by Telephone (BTACT)

This measure is administered and scored in the same way as described in the TRACK-TBI Outcomes Assessment SOP. The BTACT will be administered to the participant during the Telephone Assessments regardless of whether the participant retains decision-making capacity or not at the time of consent, should the LAR provide consent for this measure to be collected. If the participant continues to struggle to understand the instructions after providing repetition and/or clarification, it is not necessary to attempt to administer every item on each subtest. Use your best judgement and apply the appropriate Test Completion Code for each BTACT subtest.

Rey Auditory Verbal Learning Test (RAVLT)

This measure is administered and scored in the same way as described in the TRACK-TBI Outcomes Assessment SOP. Word List 2 will be used for the In-person Assessment. The Delayed Recall Test can be administered after the BSI-18 or the SIMS during the In-person Assessment depending on the appropriate timing needed. The RAVLT will be administered to the participant during the In-person Assessment.

Trail Making Test (TMT A + B)

This measure is administered and scored in the same way as described in the TRACK-TBI Outcomes Assessment SOP. The TMT will be administered to the participant during the In-person Assessment.

Wechsler Adult Intelligence Scale – 4th Edition Processing Speed Index (WAIS-IV) PSI

This measure is administered and scored in the same way as described in the TRACK-TBI Outcomes Assessment SOP. The WAIS-PSI will be administered to the participant during the In-person Assessment. **This measure is proprietary, and the site should ensure they have an appropriate supply of forms (reach out to the appropriate UCSF contact, if additional forms are required).**

Boston Naming Test (BNT)

The BNT[15], consisting of 60 black and white line-drawn objects, is a measure of confrontation naming that measures word retrieval. It is based on the premise that patients with dysnomia often have greater difficulties with the naming of low frequency objects. Thus, items on the BNT are ordered according to the frequency with which they occur in the English vocabulary. Sites will be sent a Stimulus Book for the BNT.

The participant is instructed to name each picture presented and, when unsure, to give their best guess. A 20-second response interval is allowed for each item. If the participant misperceives the picture (e.g., says, "umbrella" for mushroom), the examiner should provide a stimulus prompt (e.g., "This is a type of plant") and allow an additional 20 seconds to respond. If the participant names the wrong part of the picture (e.g., say, "doorknob" instead of doorknocker), the examiner should say, "No, it's this," while pointing to the correct part of the picture. If the participants fails to provide the correct response, a phonemic prompt (i.e., the initial phoneme underlined on the CRF) may be given. The first item to be administered is item #30. If the participant fails to correctly name the first 8 items administered, after the first error, the examiner should go back to item #29 and continue administering items in reverse order until the participant provides 8 consecutive correct responses. After the 8th correct response, the examiner should return to the item after the one that was missed, and continue administering items in forward order. The test is discontinued after item #60 is administered, or after 8 consecutive errors. The following scores should be recorded: 1) number of correct spontaneous responses, 2) number of correct responses following a stimulus cue and 3) number of correct responses following a phonemic cue. The BNT will be administered to the participant during the In-person Assessment. **This measure is proprietary, and the site should ensure they have an appropriate supply of forms (reach out to the appropriate UCSF contact, if additional forms are required).**

Measures of response bias and effort

Structured Inventory of Malingered Symptomatology (SIMS)

The Structured Inventory of Malingered Symptomatology™ (SIMS™)[16] is a multi-axial, self-administered measure developed to serve as a screening tool for the detection of feigned or exaggerated psychiatric disturbance and cognitive dysfunction among adults ages 18 years and older across a variety of clinical and forensic settings. The SIMS consists of 75 items that yield a summary score reflective of a general feigning presentation (Total score). The SIMS also includes five independent, non-overlapping scales that reflect theoretical and statistical considerations of the more commonly feigned or exaggerated disorders, including: (a) Psychosis, (b) Neurologic Impairment, (c) Amnestic Disorders, (d) Low Intelligence, and (e) Affective Disorders. The SIMS is scored by summing the responses on five independent subscales, each containing 15 items. The SIMS Total score is an overarching summary score that incorporates all of the SIMS scales. The SIMS total score provides an overall estimate of the likelihood that an individual is feigning/exaggerating symptoms of psychiatric or cognitive dysfunction. The SIMS will be administered to the participant during the In-person Assessment. **This measure is proprietary, and the site should ensure they have an appropriate supply of forms (reach out to the appropriate UCSF contact, if additional forms are required).**

Test of Memory Malingering (TOMM)

The Test of Memory Malingering (TOMM)[17] was developed to provide an objective, criterion-based test that is able to discriminate between individuals with bona fide memory impairment and those with feigned symptoms of impaired memory. The TOMM consists of two learning trials and a retention trial. The learning trials consist of a learning phase and a test phase. The study portion of each learning trial contains 50 line-drawn pictures (targets), each presented for 3 seconds with a 1-second interval between pictures. The same 50 pictures are used on each learning trial. However, they are presented in a different order on the second trial. During the test phase, each target is paired with a new line drawing (distractor). The position of the target is counterbalanced for the top and bottom positions. The person is required to select the correct picture (i.e., target) from each panel. **For each answer, the examiner provides feedback about the correctness of the response.** Total score is computed for each learning trial separately (out of 50 possible) based on the sum of correct responses for the trial. A delayed retention trial, consisting only of the test phase, is administered approximately 15 to 20 minutes after completion of the two learning trials. Sites will be sent the Stimulus Booket for the TOMM. **For purposes of this study, only the booklet for Trial 1 of the 50-item version will be administered; total score is computed based on the number of correct responses out of a possible 50.** The TOMM will be administered to the participant during the In-person Assessment. **This measure is proprietary, and the site should ensure they have an appropriate supply of forms (reach out to the appropriate UCSF contact, if additional forms are required).**

Motor Assessments

Finger Oscillation (Tapping) Test (FTT)

The Finger Tapping Test (FTT) measure is one of the most widely used measures of motor functioning. While there are several FTTs available, the most popular and well-known administration of this test is as part of the Halstead–Reitan Neuropsychological Test Battery (HRNB)[18]. The purpose of this test is to measure the tapping speed of the index finger of each hand. A finger tapping counter device ("key") is provided and should be used for this test. Sites will be provide the device. Examinees are instructed to place their hand on the board, allowing only the index finger to move. The base of the hand (not the palm), the thumb and the tips of the other fingers should rest on the board (the hand will be slightly cupped). They then raise and lower the index finger of their dominant hand as fast as they can for five consecutive trials, each lasting 10 seconds, enough to cause the counter on the device to record each tap (or oscillation). This procedure is then repeated for the non-dominant hand, with the requirement that the individual completes five trials within 5-point range. **For purposes of this study, two 10-second trials will be given for each hand during the In-person Assessment.** Total number of finger taps for each trial on each hand should be recorded

Instructions for administrators. Tell the Participant:

NOW WE ARE GOING TO DO A TEST TO SEE HOW FAST YOU CAN TAP. WE WILL USE THIS LITTLE KEY HERE (show the key to the subject) **AND I WANT YOU TO TAP JUST AS FAST AS YOU CAN, USING THE FOREFINGER** (point to the subject's index finger) **OF YOUR RIGHT HAND** (or left, if the subject is left-handed). **WHEN YOU DO IT, BE SURE TO USE A FINGER MOVEMENT: DO NOT MOVE YOUR WHOLE HAND OR YOUR ARM. WHEN YOU TAP THIS KEY, YOU WILL HAVE TO REMEMBER TO LET THE KEY COME ALL THE WAY UP AND CLICK EACH TIME, OR ELSE THE NUMBER ON THE DIAL WILL NOT CHANGE.**

> (Demonstrate to the subject how the key operates and how it should be allowed to "click." Also, demonstrate actual tapping, for a five or six second period, going as fast as possible).

NOW YOU MOVE THE BOARD TO A COMFORTABLE POSITION FOR YOUR HAND AND TRY IT FOR PRACTICE. After a brief practice period, say: **REMEMBER TO TAP AS RAPIDLY AS YOU POSSIBLY CAN.** Be sure that the subject knows what to do and is properly challenged to tap as fast as possible.

Then say: **ALRIGHT. READY! GO!**

Begin timing with a stopwatch when the participant's finger touches the key. At the end of 10 seconds, say: **STOP!**

Note the number of taps on the dial when saying "STOP" as some participants may continue tapping. The subject may rest his or her hand after any trial.

After completing the test consisting of two 10-second trials with the preferred hand, finger tapping speed for the index finger of the non-preferred hand is determined with two 10-second trials. Do not alternate between right and left-hand trials.

SCORING: The total number of finger taps for each trial on each hand should be recorded. Therefore, a total of 4 raw scores will be recorded (2 for each hand).

Issues in administration

1. The base of the hand (not the palm), and other fingers should rest gently on the tapping board. The hand will have a slightly cupped look allowing the participant to reach the key easily.
2. At times, the participant's middle finger or thumb will also move as they are tapping. Cue the participant to keep their other fingers still. If it is still a problem, the examiner may hold down the middle finger. Usually placing your finger lightly on their fingernail is enough to prevent extra movement.
3. Some participants will want to make a fist. This can be allowed but for many participants using this method will cause excess movement in the hand. The examiner may want to encourage them to spread their hand out as described above.
4. If the participant is tapping but not bringing the key up far enough to record the tap, the examiner can remind them to do so. "Remember to bring the key all the way back up."

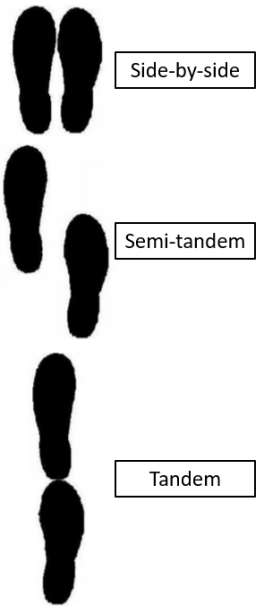
*When demonstrating speed for a significantly impaired participant, it is not necessary to go as fast as you can. Instead, demonstrate a moderated speed.

Short physical performance battery (SPPB)

The SPPB is a performance-based, three-part assessment that measures functional status and predicts future functional decline. The SPPB assesses gait speed, balance, and lower extremity strength (gross motor ability). The SPPB takes approximately 5-10 minutes to administer and will be assessed during the In-person Assessment. An online training video with a detailed explanation and administration instructions can be found here: https://www.youtube.com/watch?v=N_rJOGhQqZ4. This measure will require a Timer and measuring tape to administer.

You will be testing the patient in three areas: Balance, Gait speed, and Lower Extremity strength. Each section is scored out of 4 points, so the highest total score for the SPPB is 12 points. Use the scoring sheet to calculate the total points.

Balance Test (3 different positions - The patient must be able to stand on their own without an assistive device, though you can help the patient get up if needed. If the patient cannot hold a posture for 10 seconds, skip the remaining balance postures and move to the next section of the test.)



"I would like you to try to maintain your balance in different positions. I will describe and show each position to you, then I would like you to try to do it. If you cannot do a particular position or feel it would be unsafe, tell me and we will move onto the next activity. I do not want you to try any exercise you feel might not be safe. Do you have any questions before we begin?"

"Now I will show you the first position". (Demonstrate stance. Don't let the patient start yet)

"You will stand with your feet together, side-by-side, for ten seconds. You may use your arms, bend your knees, or move your body to maintain your balance, but try not to move your feet. Try to hold this position until I tell you to stop."

(Have patient assume position. Assess safety: be ready to stabilize patient if needed. Get ready with timer)

"Ready?" … "Begin" (Start Timer and tell patient to stop after 10 seconds.)

Demonstrate and give instructions for the semi-tandem and tandem foot positions. Stop after 10 seconds for each position. Assess the safety of patient for each stance. If the patient cannot hold a position for 10 seconds, score the section and move to Gait Speed Test.

Gait Speed Test (Make sure you have a 4-meter course measured out in advance and a timer that goes to the hundredths mark. If the patient uses a cane or other walking aid and feels they need it to walk a short distance, they can use it)

"Now I'm going to observe how you normally walk. Here is our walking course. I want you to walk to the other end of the course at your usual speed, as if you were walking down the street to go to the grocery store. Walk all of the way PAST the end of the tape before you stop. Do you feel this would be safe?"

(If the patient appears unstable, tell them that you will walk next to them.) (Demonstrate the walk for the patient. Have the patient stand with both feet touching the starting line. Prepare the timer.)

"Ready?" … "Begin" (Start timer when the patient's foot crosses the line. Walk next to the patient for safety. Stop timer when BOTH of the patient's feet cross the line.)

If they score less than 4 points, repeat the walking test a second time and record the fastest time.

Chair Stand Test (Before testing the patient, you will make sure it is safe by having the patient complete one untimed chair stand. Ensure the chair is stable before continuing)

"The last test measures the strength in your legs. Do you think it would be safe to try to stand up from the chair without using your arms?" (If no, stop and record score as zero for this section.)

"Fold your arms across your chest and sit so that your feet are flat on the floor. Now stand up keeping your arms folded across your chest." (If patient cannot rise without using their arms, this is the end of their test. Record the results on the scoring sheet. If they are able to rise with their arms folded, continue with the chair stand test.)

"Do you think it would be safe for you to try to stand up from a chair five times without using your arms?" "Please stand up straight as QUICKLY as you can five times, without stopping in between. After standing up each time, sit down and then stand up again. Keep your arms folded across your chest. I'll be timing you with a stopwatch. Let me demonstrate. (Demonstrate)

Do you have any questions? Remember to do this as QUICKLY as you can five times. Ready? ... Stand." (Begin timing when the patient starts to rise. Count out loud as the patient stands each time, up to 5 times. Stop if the patient becomes tired or short of breath during repeated chair stands. Stop the stopwatch when the patient has straightened up completely for the fifth time. Also stop if the patient uses their arms, has not completed 5 rises by 1 minute, and at your discretion if you are concerned for patient safety.)

Consciousness and Basic Cognition

Confusion Assessment Protocol (CAP)

This measure is administered and scored in the same way as described in the TRACK-TBI Outcomes Assessment SOP. This measure will only be administered to a participant at the In-person Assessment during the Abbreviated Assessment Battery.

Coma Recovery Scale Revised (CRS-R)

This measure is administered and scored in the same way as described in the TRACK-TBI Outcomes Assessment SOP. This measure will only be administered to a participant at the In-person Assessment during the Abbreviated Assessment Battery.

Protocol for Sharing Outcome Data with Participants

Release of outcomes testing results is a site-by-site issue to be addressed in accordance with local IRB and Risk Management policies. Upon request, sites that agree to provide results to participants can do so after completion of the Telephone or In-person Assessment battery using the following guidance:

- Information will be released only after a written request has been made by the subject or the guardian.
- The study PI should ensure that the results are communicated only by a licensed psychologist (neuropsychologist) who is familiar with the Outcome Assessment Battery, and has been authorized by the site PI to serve in this capacity. This consultation can be completed in-person or over the telephone.
- If a licensed psychologist is not available, the information should be released in the form of raw data with the name of the measure and the score without any interpretation. A disclaimer

statement must be included in the released records (i.e. “These data are not meant to replace diagnostic testing/evaluation that would be ordered by a personal physician. We cannot interpret the data and provide recommendations as the data we collect is meant for research purposes only.”)

- Test record sheets should not be released under any circumstances (risk of copyright violation and test invalidation), and any outcome data provided will be stripped of the Study ID.

Examiner Training and Certification Procedures

All examiners are required to complete CITI and HIPAA training in accord with local IRB requirements. In addition, they will be required to demonstrate competency in administration and scoring of all the measures included in the Outcome Assessment Battery. Training seminars will be conducted via webinar and will be supplemented with printed materials. Training materials and CRFs for all assessment measures can be found on Dropbox. Competency in administration and scoring of the measures in the Outcome Assessment Battery will be established through review of videotaped simulated assessment sessions prepared by the examiner. Videotapes will be reviewed and certified by members of the Outcomes core. Examiners who have been previously certified on a TRACK-TBI battery will only be required to prepare video simulations for new measures that have been added to the Outcome Assessment Battery used in this study. After recording simulated test administration, simulations and scanned copies of the paper CRFs should be uploaded to Dropbox electronically by requesting an invitation link from Dr. Sabrina Taylor (Sabrina.Taylor@ucsf.edu). **Do not post any videos containing test material to publically accessible websites such as YouTube.**

Magnetic Resonance Imaging (MRI) Procedures for In-person Assessments (Arm C/D)

The MRI procedures will align with the TRACK-TBI U01 procedures (see TRACK-TBI MRI Manual on Dropbox at Dropbox\1-TRACK TBI Doc Share\Imaging Core). Participants will undergo the same MRI procedures they were administered during the U01 study with the exception of the final MRI sequence modified to obtain data around seizures with a coronal T2 Inversion Recovery (IR) sequence.

Biospecimen Collection, Processing, Storage, and Shipping Procedures for In-person Assessments (Arm C/D)

The procedures around collection, processing, storage, and shipping of biospecimens collected during the In-person Assessment will align with the TRACK-TBI U01 procedures (see TRACK-TBI Biospecimens SOP on Dropbox at Dropbox\1-TRACK TBI Doc Share\biospecimens core).

TRACK-TBI EPI Clinical Assessment for Post-Traumatic Epilepsy (Arm D)

In addition to the MRI, blood, and outcome collection In-Person Assessment procedures detailed above, participants who screen positive for possible PTE will be invited for an in-depth, clinical evaluation with an epileptologist at each site. This evaluation may be conducted remotely or in person, as determined by the PI/epileptologist. That evaluation will use the Diagnostic Interview for Seizure Classification Outside of Video EEG Recording (DISCOVER), which contains items directed to the patient as well as the surrogate. The DISCOVER is a structured interview developed by the Human Epilepsy Project (HEP), which has been found to be highly accurate when compared to gold-standard video-EEG recording in an Epilepsy Monitoring Unit for classifying seizures. Lastly, if the clinical assessment is conducted in person, an electroencephalogram (EEG) evaluation will also be performed.

References

1. Finkelstein, E., P.S. Corso, and T.R. Miller, *The incidence and economic burden of injuries in the United States*. 2006, Oxford; New York: Oxford University Press.
2. Wilson, L., et al., *The chronic and evolving neurological consequences of traumatic brain injury.* Lancet Neurol, 2017. **16**(10): p. 813-825.
3. McMahon, P., et al., *Symptomatology and functional outcome in mild traumatic brain injury: results from the prospective TRACK-TBI study.* J Neurotrauma, 2014. **31**(1): p. 26-33.
4. Corrigan, J.D., et al., *US Population Estimates of Health and Social Outcomes 5 Years After Rehabilitation for Traumatic Brain Injury.* J Head Trauma Rehabil, 2014. **29**(6): p. E1-9.
5. Whitnall, L., et al., *Disability in young people and adults after head injury: 5-7 year follow up of a prospective cohort study.* J Neurol Neurosurg Psychiatry, 2006. **77**(5): p. 640-5.
6. Mac Donald, C.L., et al., *5-Year imaging sequelae of concussive blast injury and relation to early clinical outcome.* Neuroimage Clin, 2017. **14**: p. 371-378.
7. Mac Donald, C.L., et al., *Early Clinical Predictors of 5-Year Outcome After Concussive Blast Traumatic Brain Injury.* JAMA Neurol, 2017. **74**(7): p. 821-829.
8. Corrigan, J.D., et al., *Prior history of traumatic brain injury among persons in the Traumatic Brain Injury Model Systems National Database.* Arch Phys Med Rehabil, 2013. **94**(10): p. 1940-50.
9. Grinnon, S.T., et al., *National Institute of Neurological Disorders and Stroke Common Data Element Project - approach and methods.* Clin Trials, 2012. **9**(3): p. 322-9.
10. Annegers, J., *The epidemiology of epilepsy.* The treatment of epilepsy: principles and practice, 1996.
11. Diaz-Arrastia, R., et al., *Posttraumatic epilepsy: the endophenotypes of a human model of epileptogenesis.* Epilepsia, 2009. **50**: p. 14-20.
12. Dikmen, S., et al., *Functional status examination: a new instrument for assessing outcome in traumatic brain injury.* J Neurotrauma, 2001. **18**(2): p. 127-40.
13. Pfeffer, R.I., et al., *Measurement of functional activities in older adults in the community.* J Gerontol, 1982. **37**(3): p. 323-9.
14. Burgess, P.W., et al., *The ecological validity of tests of executive function.* J Int Neuropsychol Soc, 1998. **4**(6): p. 547-58.
15. Goodglass, H., E. Kaplan, and B. Barresi, *The assessment of aphasia and related disorders*. 2001: Lippincott Williams & Wilkins.
16. Smith, G.P. and G.K. Burger, *Detection of malingering: validation of the Structured Inventory of Malingered Symptomatology (SIMS).* J Am Acad Psychiatry Law, 1997. **25**(2): p. 183-9.
17. Tombaugh, T.N., *Test of memory malingering: TOMM*. 1996: Multy-Health Systems.
18. Reitan, R.M. and D. Wolfson, *The Halstead-Reitan neuropsychological test battery: Theory and clinical interpretation*. Vol. 4. 1985: Reitan Neuropsychology.