TRACK-TBI LONGITUDINAL (TRACK-TBI LONG) Protocol
Version 3
May 21, 2019

The 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.

TRACK-TBI LONG is funded by the **National Football League Scientific Advisory Board Funding Opportunity and gift money awarded from the National Football League**.

Participating Sites and dates of first eligible LONG participant:

1) BCM-TIRR-UTHSCH, March 2016
2) MGH-SRH, March 2016
3) UCSF, February 2016
4) Univ. of Cincinnati, April 2016
5) Univ. of Maryland, June 2016
6) Univ. of Miami, April 2016
7) Univ. of Pittsburgh, March 2016
8) UT Austin, June 2016
9) UT Southwestern, July 2016
10) Univ. Washington, May 2016
11) VCU, May 2016
12) UPenn, December 2018
13) Emory Univ, May 2020
14) MCW, June 2019
15) Utah, January 2020
16) Indiana Univ, October 2019
17) Hennepin, August 2019
18) Denver-Craig, January 2020

Specific Aims of TRACK-TBI LONG. 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.[1-5] 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 proposal leverages the largest precision medicine short-term natural history study of TBI: Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI), which has been successfully executed by a multidisciplinary, collaborative network of academic, private, and public partners. Currently, participants are followed for 1 year from time of injury using a multidimensional outcome battery that includes the NINDS TBI Common Data Elements.[6] 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 will be 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 2-4, to be added to study activities at a future date) and, if indicated, receive appropriate clinical referral.

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.[7] 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.[4] 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.[8, 9] 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.

Recruitment
All participants in the TRACK-TBI U01 cohort will be given the opportunity to participate in the TRACK-TBI LONG arm of the TRACK-TBI study. The additional study activities prescribed by LONG will involve re-contact of TRACK-TBI participants/legally authorized representatives (LARs) 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 additional 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.

Screening
All participants enrolled in the TRACK-TBI U01 cohort (enrolled February 2014-August 2018), who are at least two years post injury, will be eligible to take part in the additional longitudinal study activities called TRACK-TBI LONG.

Informed Consent Procedures
Prospective participants or their LAR, will be given as much time as needed to consider consenting into these additional study activities.
Participants who self-consented prior to completion of the 12M TRACK-TBI visit
Study staff will present the TRACK-TBI LONG study activities to TRACK-TBI 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 the 12M 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 the 12M TRACK-TBI visit, study staff will obtain verbal consent from the participant. In the event that a participant does not have capacity to sign their informed consent document (i.e., participant still has a LAR), verbal consent (including waiver of documentation of consent) by phone will be obtained from the LAR as governed by local IRB standards.

Figure 1 shows the algorithm we will use to obtain consent from patients and LARs. This algorithm is intended to provide stepwise guidance on the process sites will undertake to determine the proper course for longitudinal follow-up with TRACK-TBI participants in accordance with IRB standards.

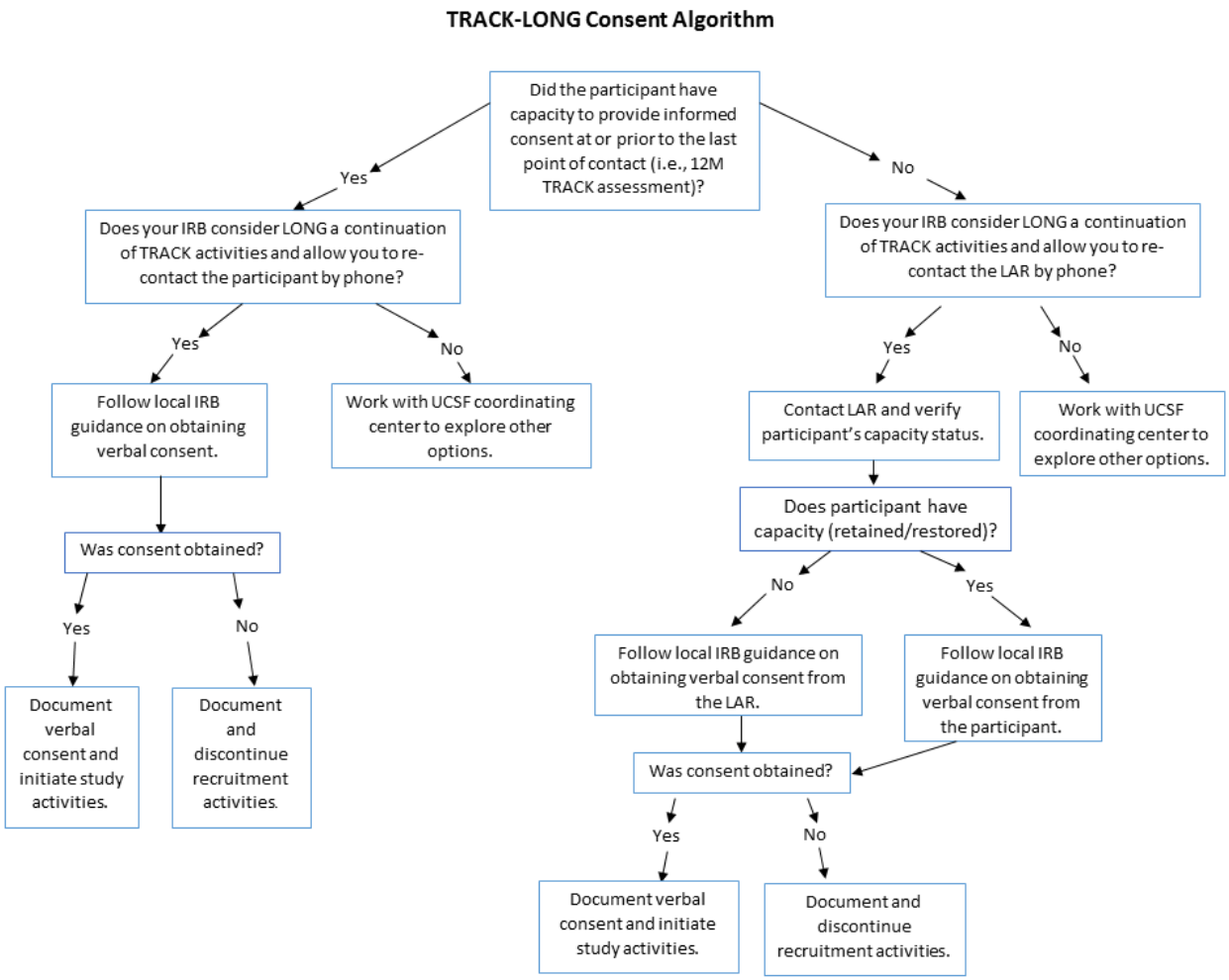

Figure 1. TRACK-TBI LONG Consent Algorithm

Enrollment

Enrollment is signified upon obtaining verbal or written consent.

Inclusion/Exclusion Criteria

All participants enrolled in the TRACK-TBI U01 cohort (enrolled February 2014-August 2018) , who are at least two years post injury, will be eligible to take part in the additional longitudinal study activities called TRACK-TBI LONG.

Informants

TRACK-TBI LONG study activities will include an evaluation of the health of the LONG 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 LONG 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. These questions are included as part of the same measures administered to participants (i.e., GOSE and FSE) or a new/modified measure administered to participants (i.e., DEX-R-I and Informant Interview). 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. If the participant (or their LAR) nominates a loved one or caregiver who has had monthly contact with the participant over the last three months but does not meet the criteria for knowing the participant at least 3 months prior to injury, this person still qualifies as an informant. These informants will be interviewed with a modified battery (see more details about this modified battery below in TRACK-TBI LONG Assessments) to capture the current health status of the participant. If the participant (or their LAR) nominates a caregiver to be an informant, but the proposed informant does not currently have contact with the subject, the person cannot serve as the informant.

TRACK-TBI LONG Assessments

LONG participants will be administered the LONG Assessment Battery. The Battery 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, and global functional status measures. Participants who do not have decision-making capacity will only be asked to complete the BTACT, following LAR consent.

In addition to the LONG Assessment Battery, participants will be asked to contact an informant and put them in touch with study staff. The informant will answer some questions in the Informant Battery, similar to those posed to the LONG participant, to help determine the participant's current level of function and health compared to their pre-injury level of function and health. The Informant Battery consists of the Informant Interview, Dysexecutive Questionnaire Revised Independent-Rating (DEX-R-I), and the two global functional status measures (i.e., GOSE, FSE). The discussion with the informant to collect this data will take approximately 30-45 minutes of the informant's time. The Informant will complete the same Informant Battery regardless of the participant's decision-making capacity.

For informants that 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).

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

Schedule for Follow-Up Assessment Windows and Extensions

Telephone Follow-up Assessment Window	
All Cohorts	Outcomes: At least 2 years post-injury and ± 90 days from Month and Day of injury

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 all of the outcome measures are obtained, and the participant indicates willingness to complete the assessment, the examiner should email Dr. Sabrina Taylor (Sabrina.Taylor@ucsf.edu) 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.

Similarly, if the informant interview cannot take place within 14 days of the participant interview, an extension request should be made to collect the information outside of the window.

Participation Stipends

Participants in TRACK-TBI LONG study activities will receive financial compensation in recognition of the time required by the study. Individual sites have the ability to determine their own reimbursement rate per time point within the constraints of their budget and as approved by local IRB. The suggested compensation is $100 for each telephone battery collected from a LONG participant. Informants will not receive compensation. Participants who do not have capacity to consent and only complete the BTACT will not receive compensation.

TRACK-LONG Assessment Battery and Order of Administration (*Italics* = new measure for TRACK-LONG**).**

Domain	Subdomain	Instrument	Administration Time (~105 min)	Order of Administration
History	Participant Interview (or Informant Interview)	*Interview to update occupational status; living situation; medical history (e.g., known neurologic, cognitive, psychiatric conditions)*	20 min[#]	8
Daily/Global Function	Global Outcomes	Glasgow Outcome Scale Extended (GOSE)	15 min[#]	2
		Functional Status Exam (FSE)	10 min[#]	1
Psychological Health/ Neurobehavioral Symptoms	Depression, Anxiety, Somatic	Brief Symptom Inventory-18 (BSI-18)	3 min	9
	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
	Suicide	Columbia Suicide Severity Rating Scale Screening Version	--^	---
	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
	Alcohol	Alcohol Use Disorders Identification Test Screener (AUDIT-C)	--*	---
	Other Drugs	Drug Abuse Screening Test (DAST-10)	--*	---
	Behavioral control	*Dysexecutive Questionnaire Revised (DEX-R) (self and informant report)*	20 min[#]	7
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
Neurologic Screen	Epilepsy	*Posttraumatic Epilepsy (PTE) Screening Form*	--*	---
	Neurodegeneration	*Gardner Motor/Parkinsonism/ Neurodegenerative Disease Screen*	--*	---

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

*Questions asked within Participant/Informant Interview

[#]Measures asked within the Informant Battery

TRACK-TBI LONG Assessment Battery: Description of Measures

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 TRACK-TBI LONG participant interview is based on the TRACK-TBI 3M follow-up participant interview and adds a neurologic screen for both Epilepsy and Parkinsonism.

Informant Interview

The informant interview consists of questions concerning the functional level, health, and behavior of the TRACK-TBI LONG participant.

Measures of Daily/Global Function

Functional Status Exam (FSE)

The FSE[10] 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. 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, 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. This measure will also be collected from the LAR/ Informant as part of the Informant Battery. 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.

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 TRACK-TBI LONG. This measure will also be collected from the LAR/Informant as part of the Informant Battery.

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, 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 TRACK-Long battery.

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.

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.

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.

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.

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.

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.

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

The Screening Version of the Columbia will be administered 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.[11] 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. TRACK-TBI LONG will administer a shortened form of the DEX-R using a 26-item version. 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-I will also be collected from the LAR/Informant as part of the Informant Battery.

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).

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. Unlike all other measures in the LONG Participant Battery, this measure will be administered 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.

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 subjects can do so after completion of the LONG 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 TRACK LONG 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 LONG 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 LONG 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 the TRACK-TBI battery will only be required to prepare video simulations for new measures that have been added to the LONG battery.

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.**

Videos and CRFs can also be sent to the following address:
Dr. Sabrina Taylor
University of California, San Francisco and Zuckerberg San Francisco General Hospital
1001 Potrero Ave
San Francisco, CA 94118

415-206-4457
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