TRACK-TBI Precision Medicine

Phase 2-Option I Clinical Protocol

April 07, 2021

Version 1.1

The goal of TRACK-TBI Precision Medicine **Phase 2 Option 1** is to validate early and ultra-early blood-based and novel imaging biomarkers of diffuse axonal injury (DAI), microvascular injury (MVI), and neuroinflammation that may serve as predictive and pharmacodynamic biomarkers in a new cohort of moderate-severe TRACK-TBI subjects.

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1. ORIGINAL TRACK-TBI PRECISION MEDICINE GRANT SUBMISSION BACKGROUND AND STUDY OVERVIEW

Effective treatment of traumatic brain injury (TBI) remains one of the greatest unmet needs in public health. According to a 2006 publication, each year in the United States, at least 1.7 million people suffer TBI; it is a contributing factor in a third of all injury-related US deaths. An estimated 3.2 to 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 $60 billion.[1] More recent publications have reported an increase in these numbers.[2] Recent efforts have increased our understanding of the pathophysiology of TBI; however, these advances have failed to translate into a single successful clinical trial or treatment.[2] These failures are largely attributable to the fact that TBI classification approaches are blunt and have not changed in more than 3 decades. TBI patients are divided into the crude categories of "mild", "moderate", and "severe", using the Glasgow Coma Scale (GCS)[3], and functional outcome is measured using the equally crude Glasgow Outcome Scale-Extended (GOSE).[4] These symptoms-based categories do not permit mechanistic targeting for clinical trials. Clinical research has also been underpowered, hampered by lack of data standardization, and with limited multidisciplinary collaboration. Workshops coordinated by the National Institute of Neurological Disorders and Stroke (NINDS), Department of Defense (DOD), and the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR) since 2007 identified the urgent need for improved TBI classification using more accurate diagnostic and outcome tools (beyond the GCS and GOSE), along with a standardized approach to data collection. A multidisciplinary effort was launched to develop TBI Common Data Elements (TBI-CDEs). Domains included clinical data, imaging, biospecimens, and outcomes.[5-8]

In 2009, the multicenter Transforming Research and Clinical Knowledge in Traumatic Brain Injury Consortium was implemented to characterize the clinical, magnetic resonance imaging (MRI), and blood-based biomarker features of TBI to inform design of next-generation precision medicine clinical trials in TBI. Over the past 10+ years, TRACK-TBI has been supported by NINDS, DoD, Department of Energy (DoE), the National Football League, and other philanthropic and industry partners. TRACK-TBI has enrolled >3000 TBI subjects across the injury spectrum, and controls, at 18 US Level 1 Trauma Centers. Our effort has established the world's largest collection of TBI imaging studies and biospecimens and our study results are already being adopted into clinical research and bedside practice. The TRACK-TBI Consortium is now primed to deliver on critical military and public health knowledge gaps and needs: objective classification of TBI based on what we term "mechanistic" endophenotypes, e.g., diffuse axonal injury (DAI), microvascular injury (MVI), and neuroinflammation. An endophenotype is an internal phenotype discoverable by biochemical, physiological, radiological, pathological, or other techniques, which is intermediate between a complex phenotype and the presumptive genetic or environmental contribution to a disease.[9] Endophenotypes are quantitative, continuous variables, unlike a phenotype which is usually a binary, categorical variable. These mechanistic endophenotypes, defined by imaging and blood-based biomarkers, will direct targeted treatments based on mechanism, providing the tools needed for successful execution of precision medicine clinical trials. To achieve the goal of precision medicine in TBI, it is necessary to identify subgroups of TBI patients that will respond to a targeted therapy.

2. TRACK-TBI PRECISION MEDICINE RATIONALE, SPECIFIC AIMS, AND OBJECTIVES FROM THE ORIGINAL GRANT SUBMISSION

2.1 Rationale

In Phase I of this study, we will assess putative blood-based and neuroimaging biomarkers for DAI, MVI, and neuroinflammation (**Table 1**). Fluid biomarkers complement imaging markers and may provide important tools for precision medicine clinical trials. In Phase 2 of this study, we will collect acute data (early and ultra-early i.e., hours-days following injury), to validate the utility of these biomarkers identified during Phase I in defining TBI mechanistic endophenotypes for use in clinical trials.

***Table 1**. Proposed TBI Biomarkers and their Relationship to TBI Mechanistic Endophenotypes*

Mechanistic Endophenotype	Blood-Based Biomarkers	Neuroimaging Biomarkers
Axonal injury	pNF-H, NF-L, Tau, P-Tau	MRI (DW, DTI, rs-fMRI)
Microvascular injury	vWF, c-fibronectin, ICAM-1, VCAM-1	MRI (SWI; ASL perfusion)
Neuroinflammation	IL-6, IL-10, IL-17, TNFa, HMGB-1 AutoAb[GFAP]-IgM, IgG	MRI (free water imaging) - (FISO) from NODDI
Neuronal Injury	*UCH-L1*	*(as benchmark in Aims 2-3)*
Astroglial Injury	*GFAP*	*(as benchmark in Aims 2-3)*

2.2 Specific Aims

- SPECIFIC AIM 1: To validate biomarkers of Diffuse Axonal Injury (DAI), Microvascular Injury (MVI), and Neuroinflammation using advanced blood-based assay platforms and imaging sequences.
  Study activities conducted in support of this Aim are reviewed under separate IRB protocols:
  - *University of California, San Francisco IRB # 18-26754*
  - *University of Florida IRB # IRB201802961*
  - *University of Pennsylvania IRB # 832422*

- SPECIFIC AIM 2: To validate early and ultra-early blood-based and novel imaging biomarkers of DAI, MVI, and neuroinflammation that may serve as predictive and pharmacodynamic biomarkers in a new cohort of moderate-severe subjects.
  Study activities conducted in support of this Aim are reviewed under this IRB protocol.

- SPECIFIC AIM 3: Conduct a multicenter double-blind, placebo controlled exploratory clinical trial comparing the impact of Cyclosporine A (CsA) on blood-based and imaging biomarkers of DAI, MVI, and neuroinflammation in moderate-severe TBI patients admitted to the ICU.
  Study activities conducted in support of this Aim will be reviewed under a separate IRB protocol.

2.3 Study Objectives

Phase 1-Base (Year 1): Validate biomarkers of Diffuse Axonal Injury (DAI), Microvascular Injury (MVI), and Neuroinflammation using advanced blood-based assay platforms and imaging sequences.

- Phase I-Base analyses are reviewed under a separate IRB protocol.

Phase 2-Option I (Year 2): Validate early and ultra-early blood-based and novel imaging biomarkers of DAI, MVI, and neuroinflammation that may serve as predictive and pharmacodynamic biomarkers in a new cohort of moderate-severe TRACK-TBI subjects.

- In Phase 2-Option 1 (study activities reviewed under this protocol), we will enroll a cohort of moderate to severe TBI subjects (N=50), stratified according to VA/DoD criteria for these injury severities through the existing TRACK-TBI network sites to obtain novel advanced neuroimaging and more frequent biomarker sampling. Subjects will be assessed according to the existing TRACK-TBI outcomes protocol over 3 months.

Phase 3-Option II (Year 3): Conduct a multicenter double-blind, placebo controlled exploratory clinical trial comparing the impact of Cyclosporine A (CsA) on blood-based and imaging biomarkers of DAI, MVI, and neuroinflammation in moderate-severe TBI patients admitted to the ICU.

- Phase 3-Option II will be reviewed under a separate IRB protocol.

3 STUDY DESIGN

3.1 Participating Sites

1. University of California, San Francisco (UCSF)
    a. PI Geoffrey Manley
2. University of Pittsburgh (UPitt)
    a. PI David Okonkwo
3. University of Pennsylvania (UPenn)
    a. PI Ramon Diaz-Arrastia
4. Medical College of Wisconsin (MCW)
    a. PI Michael McCrea
5. University of Utah
    a. PI Ramesh Grandhi

3.2 Participants

Subjects will be recruited among patients with TBI admitted to the emergency department, trauma, or neurosurgical services at 5 participating TRACK-TBI Clinical Sites. Each site has a system for identification and early notification of potential patients who qualify for the study. The early notification system will result in timely arrival of the study coordinator or other trained study personnel, who will evaluate a participant's eligibility. Individuals notifying study personnel of potential patients may include ambulance coordinating system personnel, neurosurgery residents, emergency room physicians, or other hospital personnel who are likely to see brain injured patients shortly after their arrival.

Once notified, study personnel will review the potential patient's information and screen the patient according to the study inclusion and exclusion criteria (Table 3). Upon determining that the patient is potentially eligible for the study, consent will be obtained from the patient or the legally authorized representative (LAR) according to local IRB guidelines. If the patient is determined to have capacity to provide his or her own consent, the patient will be asked to provide informed consent. For participants whose LAR originally gave consent, an informed consent will be obtained from the participant once they have the capacity to do so.

The target enrollment for this study is 50 participants.

3.3 Study Procedures

Table 2*. Study Procedures*

Study Procedures	*Screening/ Enrollment*	*<6 hr*	*12 hr*	*24 hr*	*Day 2*	*Day 3*	*Day 5*	*Day 14*	*Day 42*	*Day 90*
Screening and Eligibility	X									
Inclusion/Exclusion criteria	X									
Informed consent	X									
Eligibility CT reading	X									
Blood collected		X	X	X	X	X	X	X	X	X
MRI scan				(X)				X		X
*Clinical Data Collection	X									
TRACK-TBI Outcome Enrollment Battery				X						
TRACK-TBI Follow –up Outcome Battery								X	X	X

(X)—MRI will be collected on either Day 1 or Day 2

* Clinical Data will be collected daily until the subject is discharged from hospital

3.4 Milestone Plan

Our target follow-up rate for the 3-month duration of the study is 80%. The Clinical Core will monitor this rate at the overall study level as well as the individual site level. Women and minorities will be included.

4 SUBJECT ELIGIBILITY

4.1. Assessment of Eligibility

We will enroll adult patients (age 18-65y inclusive) presenting to the Emergency Department (ED) with a history of acute TBI as per American Congress of Rehabilitation Medicine (**ACRM) Criteria**, in which the patient has sustained a traumatically induced* physiological disruption of brain function, as manifested by ≥ one of the following:

- Any period of loss of consciousness (LOC)
- Any loss of memory for events (e.g., amnesia) immediately before or after the accident (PTA)
- Any alteration of consciousness/mental state at the time of the accident (feeling dazed, disoriented, and/or confused) (AOC)
- Focal neurologic deficits that may or may not be permanent

* Traumatically induced includes the head being struck, the head striking an object, or the brain undergoing an acceleration/deceleration movement (e.g., whiplash) without direct external trauma to the head.

<u>Screening questions for LOC</u>

Did you have a period of time after the event when you were completely unconscious? That means you had no ability to think, speak, or move and were completely unaware of the world around you.

<u>Screening questions for PTA</u>

Was there a period of time after the injury for which you have no memory? If so, how long did it take for your memory to return to normal or become consistent (e.g., who you saw, conversations, what you ate, etc. (Walk them through the post-injury events if and as necessary).

<u>Screening questions for AOC</u>

Right after the event, did you feel dazed or confused or in a fog? Did you have trouble knowing where you were or what happened to you? Did you keep asking the same question over and over? Did you insist you could do things that you could or should not do?

<u>Suggested prioritization for AOC and LOC:</u>

1st- EMS run report
2nd- Witness report
3rd- ED records (if positive)
4th- Participant

In general:

- **AOC**: should be recorded as "positive" if present in any of these sources. Only record AOC as negative if available sources (especially the participant) state it did not occur.
- **LOC:** Subject's recall is unreliable unless the subject explicitly states that a witness told informed the subject that the subject was knocked out cold.
- **PTA:** Use the participant report for mild cases. Use EMS or hospital medical records for more severe cases.

4.2 Inclusion/Exclusion Criteria

Table 3 summarizes study inclusion and exclusion criteria. These criteria are informed by the experience of the TRACK-TBI U01 study, and are designed to mirror criteria appropriate for future trials of neuroprotective or neurorestorative therapies. These clinical and imaging criteria were identified through the TRACK-TBI U01 study, and include select subjects with TBI who are at high risk for incomplete recovery (GOSE < 8) out to 6 months after injury. The criteria also exclude participants with very severe TBI who stand a low chance of survival.

***Table 3**. Enrollment Inclusion and Exclusion Criteria*

Criteria	Data Source	Comments
Inclusion Criteria		
1. Age 18 – 65y inclusive	Chart, Interview	
2. History or evidence of TBI, according to DoD-VA criteria	Chart, Interview	
3. GCS 3 – 15 after resuscitation in the ED	Chart	
4. Cranial CT with evidence of trauma-related abnormality (i.e., CT positive except for isolated epidural hematoma (EDH))	Chart	Based on radiologist's read
5. Ability to undergo MRI	Chart, Interview	
6. Ability to obtain informed consent from participant or LAR	Interview	
7. Fluency in English or Spanish	Interview	Based on test battery and available personnel
Exclusion Criteria		
1. Unstable respiratory or hemodynamic status	Chart	
2. Evidence of penetrating brain injury	Chart	
3. Isolated EDH as only trauma-related CT abnormality	Chart	Favorable natural history
4. Systemic traumatic injury that would preclude participation in study, which is expected to result in long-term disability not related to TBI	Chart	
5. Evidence of serious infectious complications (sepsis, bacteremia, multilobar pneumonia)	Chart	
6. Acute ischemic heart disease (myocardial infarction or unstable angina)	Chart, Interview	
7. History of syncope or hypotension	Chart, Interview	
8. SBP < 90 mm Hg, DBP < 40 mm Hg for longer than 5minutes	Chart	Hypoxic brain injury has very poor prognosis
9. History or evidence of active malignancy	Chart, Interview	
10. History of pre-existing neurologic disorder, such as dementia, mild cognitive impairment, uncontrolled epilepsy, multiple sclerosis, strokes, brain tumors, prior severe TBI, or other disorder that may confound interpretation of MRI or neuropsychological results	Chart, Interview	May confound interpretation of MRI or neuropsychological results
11. History of pre-existing disabling mental illness, such as major depression or schizophrenia	Chart, Interview	Disabling psychiatric conditions confound outcome measures and reduce FU rate
12. History or evidence of chronic heart failure or chronic renal failure	Chart, Interview	

13. Low likelihood of follow-up (e.g., participant or family indicating low interest, residence in another state or country, unhoused or lack of reliable contacts)	Chart, Interview	Makes FU visits difficult
13. Women who are pregnant or breast-feeding	Chart, Interview	
14. Prisoners or patients in custody	Chart, Interview	
15. Patients on psychiatric hold (e.g. 5150, 5250)	Chart, Interview	

5 SUBJECT RECRUITMENT AND SCREENING

5.1 Subject Identification

Study personnel will identify potential subjects in the ED, hospital, and ICU during "peak hours" as appropriate for their study site by review of medical records, trauma logs, and triage notes as well as by conferring with on-duty doctors and nurses to identify potential subjects. Many of the inclusion/exclusion criteria can be evaluated by a review of the potential subject's medical records, such as mechanism of injury, extent of non-head injuries, prior medical history, and prior clinical visits at the center of care. As all eligible patients must receive an acute clinical brain CT due to external force trauma to the head, the ideal place to begin screening is scanning for acute scheduled CT brain studies in the radiology department. When a potential subject is identified and has been screened against the primary set of inclusion/exclusion criteria, they will be approached about the study.

5.2 Screening Process

Due to the vulnerability of the subjects and the complexity of the protocol, we envision a three-stage screening process. These stages are: 1) review of medical records and test results to determine eligibility, 2) subject completion of a screening evaluation to determine competency to provide informed consent, and 3) subject interview to present and discuss this research participation opportunity. Only after all three of these phases have been completed would the subject be asked to participate and provide formal signed informed consent.

Prior to enrolling a subject, the research personnel will screen the subject for competency to provide informed consent. This is necessary because TBI may result in a period of posttraumatic amnesia (PTA) characterized by confusion, disorientation, and impaired memory for ongoing events. The Galveston Orientation and Amnesia Test (GOAT) will be used as the standard assessment instrument for this screening. A score of ≥75 on the GOAT would indicate that the subject is competent to provide informed consent. If the subject scores <75 on the GOAT, consent must be provided by a Legally Authorized Representative (LAR).

To accomplish the competency evaluation part of the screening process, the research personnel will approach the subject and introduce the study, explaining that the subject may be a candidate but that additional information is required to determine this. It takes approximately 5 minutes for the subject to answer the test questions contained in the GOAT. The research personnel will then score the test as described. If the subject qualifies and wishes to proceed, then the research personnel will move to the third stage of this process. If the subject is not interested in participation in the protocol, the subject will be thanked for their time and any data collected up to this point will be destroyed.

5.3 Participation Requirements

An important part of the screening and enrollment process is an interview with the subject, where the research personnel explains the project in detail, presents the consent forms, and responds to all patient questions and concerns. Key points that will be explained during this interview process are:

- Participation in the project is immediate and for all components (clinical, biospecimens, MRI, outcomes), unless contraindicated for MRI.

- Potential subjects will be given time to read the Consent Form(s) and to consult with family members who may be present or by phone. If the subject agrees to participate, then they will sign the appropriate forms. A copy of the form(s) will be given to the subject.
- Upon enrollment, data collection will begin in the hospital. Participation in follow-up activities must be completed within given follow-up assessment windows as specified below (Table 4), but will be scheduled to accommodate the patient:

***Table 4**. Schedule for Follow-Up (FU) Assessment Windows*

In-person 2 Week Follow-up Assessment Windows	
2 Week FU	MRI: 14 days post-injury ± 4 days
	Outcomes + blood collection: ± 3 days of 2-week MRI

In-person 6 Week Follow-up Assessment Window	
6 Week FU	Outcomes + blood collection: 42 days post-injury ± 4 days

In-person 3 Month Assessment Window	
3 Month FU	MRI: 90 days post-injury ± 14 days
	Outcomes + blood collection: ± 3 days of 3 month MRI

- All efforts should be made to schedule patient return within the specified window for each time point. Patients who are reached and scheduled but fall outside the window for any outcomes testing time point should still have their outcomes assessment completed during the next scheduled follow-up time point. The number of days from date of injury, and the number of days outside of the exact 2-week, 6-week, and 3-month, window will be documented in the QuesGen database.
- Compensation is provided for participation in each study activity. See section 5.4 Subject Compensation for further information.

5.4 Subject Compensation

Participants in study activities will receive financial compensation in recognition of the time required by the study. The suggested compensation is in **Table 5** 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 local IRB.

***Table 5**. Patient Reimbursements*

Time point	Study Milestone	Subject Reimbursement
< 6 hours	Blood Draw	$20
12 hours	Blood Draw	$20
24 hours	Blood Draw	$20
< 24 hours	Enrollment Outcome Battery	$25
2-Day	Blood Draw	$20
< 48 hours	MRI	$120
3-Day	Blood Draw	$20
5-Day	Blood Draw	$20
14-Day	MRI	$120
14-Day	Blood Draw	$20
14-Day	Outcome Battery	$70
42-Day	Blood Draw	$20
42-Day	Outcome Battery	$70
90-Day	MRI	$120
90-Day	Blood Draw	$20

90-Day	Outcome Battery	$70
Patient travel stipend (Maximum amount per subject)		$150 ($50/in-person visit)
Maximum amount per subject costs		**$775 + up to $150 for travel**

Compensation will be disbursed at the end of each visit. Subjects must provide a social security number or other form of tax identification to receive these funds.

6 INFORMED CONSENT

6.1 Study Personnel Obtaining Informed Consent

The individuals responsible for identifying potential subjects, explaining the studies, answering questions, and obtaining informed consent will be study research personnel who are healthcare professionals, including MD, RN, Research Coordinators, and Research Associates (RAs). Qualifications for these positions include clinical experience with TBI patients, patient teaching skills related to home medication administration, excellent interpersonal and problem-solving skills, and knowledge of the clinical research process.

Based on sites' local IRB policies, sites may include language in their informed consent, which will ask patients if they wish to be contacted for future research after the completion of this study.

> Suggested IRB language: *In the future, other studies involving traumatic brain injury may become available. If you agree, then someone from the [site name] Neurosurgery team may contact you in the future about additional research that you may be interested in participating in. You agree to allow someone to contact you about research in the future. _yes _no*

6.2 Location and Privacy

Potential subjects will be approached in the ED, hospital wards, or ICU at each IRB-approved enrollment site. All sites have implemented electronic medical records in their hospitals and much of the screening process can be completed via utilizing these resources. Interested subjects are offered the opportunity to participate on-site during their emergency hospital visits or contacted by phone after hospital discharge.

If potential subjects are approached in the ED, all means of ensuring privacy will be undertaken. If the potential subject approaches their time of discharge, then the research personnel will escort the subject and family to a private area to discuss the study and conduct the informed consent process. The approach to potential subjects in the ED will not be made in such a way that it interferes with or delays the diagnosis and treatment process in the ED. Potential subjects will be given as much time as needed to read the informed consent document, discuss it with family members if they choose, and to ask questions of the research personnel.

6.3 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 local practices/guidance regarding informed consent procedures. If informed consent can be obtained remotely (i.e., by eConsent) through a secure and locally approved platform (e.g., RedCap, Docusign, etc.), sites should get IRB approval to do so. All eConsent procedures should be documented according to local procedures, and included in the participant's study record in the TRACK-TBI electronic database (i.e., QuesGen).

6.4 Competency Screening and Legally Authorized Representatives

TBI often results in a period of posttraumatic amnesia (PTA) characterized by confusion, disorientation, and impaired memory for ongoing events. Thus, TBI patients will be screened for competency using the Galveston Orientation and Amnesia Test (GOAT) to determine whether they are competent to provide informed consent

or whether this must be done by a Legally Authorized Representative (LAR). This competency screening will be performed prior to inviting the subject to participate in the study and while the subject is in the ED or hospital.

The procedure for this competency screening will be:

1. The subject's ED medical record will be reviewed to determine whether the subject has been diagnosed with post-traumatic amnesia or other cognitive deficits.
2. The subject and family, if present, will be approached and informed about the study.
3. If subject and family agree, the GOAT will be administered according to standard procedures.
    a. If the subject scores ≥75 on the GOAT, the subject will be deemed competent to provide informed consent.
    b. If the subject scores <75 on the GOAT, then informed consent must be provided by a LAR.

6.5 Language and Literacy

Subjects should be fluent in English to be eligible for the study. Sites with research personnel fluent in Spanish may elect to enroll patients who speak Spanish as their primary language. The informed consent documents are available in both English and Spanish. Patients not fluent in English, or Spanish at certain sites, will be ineligible for the study.

6.6 Need for Re-consent

As this is a longitudinal study with multiple assessment time points over the course of 3 months, and knowing that the status of TBI patient cognition may change over this time course, it is likely that subjects may not recall all of the activities or procedures associated with each follow-up visit. To ensure that subjects are still willing to participate, the research personnel will review the Informed Consent document with the subject at the beginning of each follow-up visit.

In the event that a subject was determined incompetent to sign their informed consent document (i.e., GOAT score <75 at time of screening/consent) but later demonstrates competency, then the subject will be asked if they wish to continue participation. If so, then the subject will be asked to sign the Informed Consent Form at that time. If they decline to do so, they will be withdrawn from the protocol.

6.7 Storage of Consent Documents

Signed paper consent forms will be stored in a locked file cabinet located in the study office behind locked doors at each site. These documents will be stored for a minimum of 5 years after the conclusion of the study. These documents will be made available, as needed, for review for quality monitoring purposes.

6.8 Waiver of Consent

Sites may elect to enroll qualifying patients initially incapable of informed consent who have no legally authorized representative available for LAR consent. This can be done under a "waiver of consent" rule in the emergency setting in order to procure and process all study blood collections. While UCSF will serve as the single IRB (sIRB) for this study (further details about this below), each site who signs on to the study will be able to determine, independently, if they will implement the Waiver of Consent at their local site.
This protocol meets all "Waiver of Consent" criteria under 45 CFR 46.116(f) (3):

(i) The research involves no more than minimal risk to the subjects;

(ii) The research could not practicably be carried out without the requested waiver or alteration. Our research team has extensive experience conducting research in this population; TBI patients very frequently present alone (without a LAR) and with alteration of mental status (ranging from mild disorientation to coma) limiting capacity for self-consent due either to their acute injury or other contraindications.

(iii) The research could not practicably be carried out without using information or biospecimens in an identifiable format. We need to collect identifiable private information (such as patient name, medical record number, and contact information) from patients under waiver so that we can extract data from the EMR, contact a LAR to provide consent as soon as possible, and so that we can complete additional longitudinal follow-up timepoints with the patient/LAR and link this data to previously collected data) in the event that informed consent is obtained;
(iv) The waiver or alteration will not adversely affect the rights and welfare of the subjects. The primary risks of this observational study is loss of privacy and standard risks associated with a blood draw. We have taken steps to ensure the privacy of subjects. In most cases, blood draws will be collected through already placed arterial lines and/or at the same time of clinically indicated blood draws, and thus, there will be minimal to no additional risks associated with these blood draws. Furthermore, in the event that patient or LAR consent cannot be obtained by the time of the 2 week study visit, all data collected on the patient, including blood collected and processed, will be discarded (will not be analyzed, banked, or shared with collaborators);
(v) Whenever appropriate, the subjects or LAR will be provided with additional pertinent information after participation. We will make every effort to obtain patient or LAR consent as soon as possible after enrollment under waiver. A copy of the consent form as well as a study summary document that summarizes the pertinent details about the study will be left at the bedside of a patient enrolled under Waiver of Consent, and study staff will stay in touch with hospital staff to monitor the patient's status while inpatient. If a patient is discharged while still under waiver, then the patient will be discharged with a copy of the consent form, a study summary document that summarizes the pertinent details about the study, and contact information for study staff. Study staff will approach in-person (if the patient remains inpatient/the LAR presents to the bedside) or by phone (if the patient is discharged/a LAR is identified who is off-site) to complete the informed consent process as soon as the patient may be able to consent for her/himself and/or a LAR presents her/himself. If self or LAR consent is not obtained by the time of the 2 week study visit, then all data and blood collected under waiver will be destroyed/discarded.

Suggested IRB language: *If an eligible TBI patient presents to our hospital who is not capable of self-consent, and there is no LAR identified, then a 'Waiver of Consent' will be used to collect baseline clinical data and study blood draws (most critically, the baseline blood draw must be within 6 hours of injury and ideally as soon as possible after injury). Specifically, we will complete study blood draws, blood processing and freezing in our local freezer, and collection of baseline clinical data (including data from the EMR and head CT imaging that was obtained as part of routine clinical care) without consent if the subject does not have the capacity to provide consent and there is no LAR identified. The blood taken under waiver could be the 6-hour, 12-hour, and 24-hour blood draws. Each blood draw is 16.0 mL and this will total 48 mL of blood taken under waiver. If the patient cannot provide consent or an LAR has not been identified to provide consent by the two week timepoint then the patient will be removed from the study. We anticipate that most of the patients we enroll will have a line placed and we will ask for the draw through this. If unavailable, we will ask the nurse to complete the blood draw with a stick. The collected blood will NOT be analyzed in any way (either proteomic or genetic analyses), shared with collaborators, or sent to the National TBI Biorepository (NTBI-BR) at the University of Pittsburgh Medical Center without informed consent from the patient or LAR. Research MRIs will not be completed without consent. If an MRI is not completed within the first 48 hours, the patient will be eligible to remain in the study. In the event that the patient remains incapable of self-consent or a LAR is not identified by the time of the 2 week visit, then all clinical data will be destroyed and all collected blood samples will be discarded. If the patient regains capacity to consent or a LAR is identified before the time of the first follow-up and s/he declines future participation in the study, then the patient/LAR will then be given the opportunity to provide informed consent to permit the use of any already-collected clinical data and/or blood (that was collected under waiver) for research purposes. If the patient/LAR consents to the use of already collected data, then s/he will sign the informed consent form but will then be documented as electively withdrawing from future participation in any additional*

follow-up data collection. If consent is not obtained prior to the patient's discharge, they can be contacted with the Verbal Consent Script to describe the study objective and voluntary nature. If they are interested in the study, the research staff will explain the study in full over the phone. If they agree to participate, they will be mailed hard copies of the informed consent packet, emailed the informed consent packet, and/or asked to sign the informed consent using DocuSign.

6.9 Single Institutional Review Board (sIRB) and Human Research Protections Office

As of January 2020, all federally-funded studies are now required to use a Single Institutional Review Board (sIRB). UCSF will serve as the sIRB for this TRACK-TBI Precision Medicine protocol. Participating sites will rely on UCSF as the IRB of Record for this protocol. The UCSF Lead Coordinating Site Study Team is responsible for securing initial IRB approval from UCSF for this MSP (Master Study Protocol) and all other study documents such as the Informed Consent Form, any recruitment materials, and all study Standard Operating Procedures (SOPs) that describe the procedures and operations of the study as they pertain to enrolled subjects. Other sites cannot be added to the protocol until UCSF has initial approval for the study. The UCSF Lead Coordinating Site Study Team will utilize the online SMART IRB system to request, track, and document reliance on UCSF IRB for each Relying Site under the SMART IRB Agreement.

All relying sites' Study Teams will use the Informed Consent Form template(s) provided by the UCSF Lead Coordinating Site Study Team. Site Study Teams will provide any site-specific informed consent form language required for local study team contact details, compensation for injury, study participant reimbursement, etc. The Site Study Team will incorporate these site-specific changes to the Informed Consent with tracked changes, and will provide this form to the UCSF Lead Coordinating Site Study Team for submission to UCSF IRB.

The UCSF Lead Coordinating Site Study Team will be responsible for submitting amendments to the MSP as well as any unanticipated events, protocol deviations, adverse events, and annual continuing reviews, in accordance with UCSF IRB's established procedures and policies. The UCSF Lead Coordinating Site Study Team and participating relying Site Study Teams will follow the procedures as set forth in the UCSF sIRB Standard Operations Procedures (See "sIRB SOP for sites v2.2" on the Study Shared BOX folder at "Box\TRACK-TBI Precision Medicine Study Documents\Regulatory\IRB\sIRB SOP for all sites).

After IRB approval is obtained, the approved master study protocol (MSP) and supporting documents will be submitted to the Department of Defense Human Research Protection Office for review. Human subjects research cannot begin at a site until HRPO approval has been obtained.

7 SUBJECT PROCEDURES BY CORE

7.1 Clinical

The following broad categories of clinical data variable types will be collected from all enrolled patients through medical record and personal interview:

- Baseline demographics e.g., age, gender, race, ethnicity, handedness
- Baseline socioeconomics e.g., education, employment, living situation, types of support
- Baseline medical history by system including substance abuse, prior TBI, and medications
- Mechanism of injury, location, and surrounding circumstances
- Pre-hospital clinical course variables e.g., vital signs, transport times, GCS score
- Brain CT report including presence of skull fracture and intracranial abnormalities
- Emergency department clinical course e.g., vital signs, GCS, fluids, labs, toxicology, complications
- Hospital admission clinical course e.g., complications, surgeries, neuromonitoring

- Hospital daily therapeutic intensity level for ICU patients with neuromonitoring
- Admit and discharge dates and times throughout full clinical course
- Abbreviated Injury Scale (AIS) score and Injury Severity Score (ISS)
- Discharge destination and acute care outcome evaluation

7.2 Biospecimens Procedures.

We will obtain 12.0 ml of blood at each of the following time points: within 6 hours of injury, and again at 12h, 24h, 2d, 3d, 5day, 2w, 6w and 3m post-injury (See **Table 6**: Biospecimen Sample Collection Schedule below). Every blood draw will be optional. The TRACK-TBI Precision Medicine procedures around collection, processing, storage, and shipping of biospecimens collected during the in-person assessment will align with the TRACK-TBI U01 procedures (see Appendix 2: TRACK-Precision Medicine_Biospecimen Protocol_MOP_v1.5_APR062021, also saved on the Study Shared BOX folder at: TRACK-TBI Precision Medicine Study Documents\Biospecimens core\Biospecimens MOP).

- Collection at each time point will consist of one 6.0 ml lavender EDTA tube (plasma and buffy coat) and one 6.0 ml red top tube (serum).
- Whole blood will be processed for serum, plasma, and buffy coat. Serum and plasma will be stored in 500 μl aliquots for future analyses.

Table 6*. Biospecimen Sample Collection Schedule*

Schedule of blood sample Collection (From the time of traumatic brain injury)	*<6 hr*	*12 hr*	*24 hr*	*Day 2*	*Day 3*	*Day 5*	*Day 14*	*Day 42*	*Day 90*
Blood volume to be collected at each time point	12 mL	12 mL	12 mL	12 mL	12 mL	12 mL	12 mL	12 mL	12 mL
Total blood volume that may be collected in 3 month period=108 ml									

- At some sites (subject to IRB approval), cerebrospinal fluid (CSF) will be drawn for patients with ventricular catheters. The CSF collection protocol is detailed in TRACK TBI Precision Medicine Manual Of Procedures (see Appendix 2: Section 6 of TRACK_Precision Medicine_Biospecimen Protocol_MOP_v1.5_APR062021, also saved on the Study Shared BOX folder at: TRACK-TBI Precision Medicine Study Document\Biospecimens Core\Biospecimens MOP). *This is a site-specific protocol item.*
- Specimens will be kept indefinitely until they are used up or destroyed, and may be used in future research unrelated to this study.

Analysis.

A subset of the most promising DAI, MVI, and neuroinflammation blood-based markers identified previously in Phase 1-Base (under a separate IRB protocol) will be analyzed in this cohort. In addition, neuronal injury (UCH-L-1) and astroglial injury (GFAP) biomarkers will also be assayed in these subjects.

7.3 Neuroimaging

Clinical Care Neuroimaging Acquisition

CT or initial MRI will be obtained as part of clinical care. The subject may be transferred to the study hospital from another hospital at which an initial CT/MRI was already performed. In this case, the site must have the initial image available for collection in order to enroll. All initial and follow-up brain CT scans, and any brain MRI scans that are collected for clinical care will be acquired along with the radiology reports. Images will be read and coded by the Neuroimaging Core radiologist in accordance with the NINDS Neuroimaging TBI-CDEs.

MRI Procedures

In this cohort, we will obtain 3T MRIs within 2 week of injury (early), and for a subset of 20% of patients, an additional ultra-early MRI within 48 hours of injury. All patients will also receive a follow-up MRI at 3m post-injury. The overall MRI protocol is based on established TRACK-TBI standards for structural imaging, DTI and rs-fMRI that have been harmonized across 3T scanners from all 3 MR vendor platforms. Standard operating procedures for acquisition, QA, QC, and data management of this 3T MRI protocol will align with the TRACK-TBI U01 procedures. Participants will undergo the same MRI procedures as set forth in the TRACK U01 study (See Appendix 1: Precision Medicine-Neuroimaging MOP v1.1-03102021.docx, also saved on Study Shared BOX folder at: TRACK-TBI Precision Medicine Study Documents\Neuroimaging Core\ Neuroimaging MOP) with a few modifications. In addition to volumetrics, DTI and rs-fMRI, the new MRI protocol will incorporate novel imaging measures of axonal density (using neurite density index (NDI) from NODDI analysis of multishell diffusion MRI), cerebral blood flow (using ASL perfusion), and neuroinflammation (using free water content (FISO) from NODDI analysis of multishell diffusion MRI), which will all be standardized across sites and MRI vendors prior to participant enrollment.

The proposed MRI protocol includes one additional sequence not represented in the original TRACK-TBI protocol: ASL perfusion imaging of cerebral blood flow (CBF), as well as an additional 64-direction diffusion-weighted shell for the DTI protocol at b=3000 s/mm2 to create the multishell diffusion MRI sequence.

Arterial Spin Labeled Perfusion MRI Protocol: The ASL perfusion protocol is adopted from the new Alzheimer Disease Neuroimaging Initiative 3 (ADNI3) standards for all 3 MR vendors. In brief, the 5-minute sequence consists of 3D pseudo-continuous ASL (PCASL) on 3T GE scanners and 2D pulsed ASL (PASL) on Siemens and Philips scanners, with an additional proton density reference scan using the same ASL readout at a longer TR. These ASL acquisitions for all 3 MR vendor platforms conform to the most recent best practice guidelines for ASL perfusion imaging reported by the International Society for Magnetic Resonance in Medicine.44

The entire proposed MRI protocol can be acquired in 60 minutes. The de-identified neuroimages from each site will be uploaded to the neuroimaging core repository at UCSF.

MRI Analysis

We will incorporate axonal density from NODDI analysis of multishell diffusion MRI as an advanced microstructural imaging biomarker of both acute DAI and long-term white matter degeneration. Axonal density, measured as the neurite density index (NDI) of white matter from NODDI, is a metric of the intracellular volume fraction and is not affected by changes in the free water fraction. Therefore, it is a more specific biomarker of axonal loss than any DTI metric such as FA, MD, AD, or RD. In addition, we will incorporate a quantitative imaging biomarker of MVI, specifically, CBF using ASL perfusion MRI.

MRI Statistical Considerations

We will calculate Pearson's correlation of each of the baseline early (<6 hours to 1 week) blood-based biomarkers, with the corresponding MRI markers that look promising based on Phase 1 results. There will be no adjustment for multiple comparisons as these comparisons are exploratory given the paucity of information about the time-course of these markers in people with TBI. ROC analysis will be performed to determine the discriminative ability of the blood-based and imaging biomarkers in predicting outcomes. AUC will be calculated and reported along with 95% confidence intervals. Prediction increment will be measured by change in AUCs calculated based on logistic regression models.

Adequacy of sample size: With 50 participants, using correlation power analysis, we have at least 80% power to detect a correlation of .38 or greater.

7.4 Outcomes

All clinical outcome assessment (COA) measures will be obtained from the patient, or if cognitively unable, the surrogate (i.e., caregiver). The enrollment outcome assessment battery will be obtained at consent or by

phone within 24 hours of injury. It will be administered only to participants who score ≥75 on the Galveston Orientation and Amnesia Test (GOAT). At subsequent follow-up visits, the participants will undergo in-person outcomes testing according to the Flexible Outcome Assessment Battery Decision Workflow (see **Figure 1**) at 2 weeks, 6 weeks, and 3 months from the time of injury. All measures that can be collected by phone will be collected by phone (see Section 8 TRACK-TBI PRECISION MEDICINE ASSESSMENT BATTERY AND ORDER OF ADMINISTRATION tables below), if study staff cannot administer in person.

Flexible Clinical Outcome Assessment (COA) Battery Framework

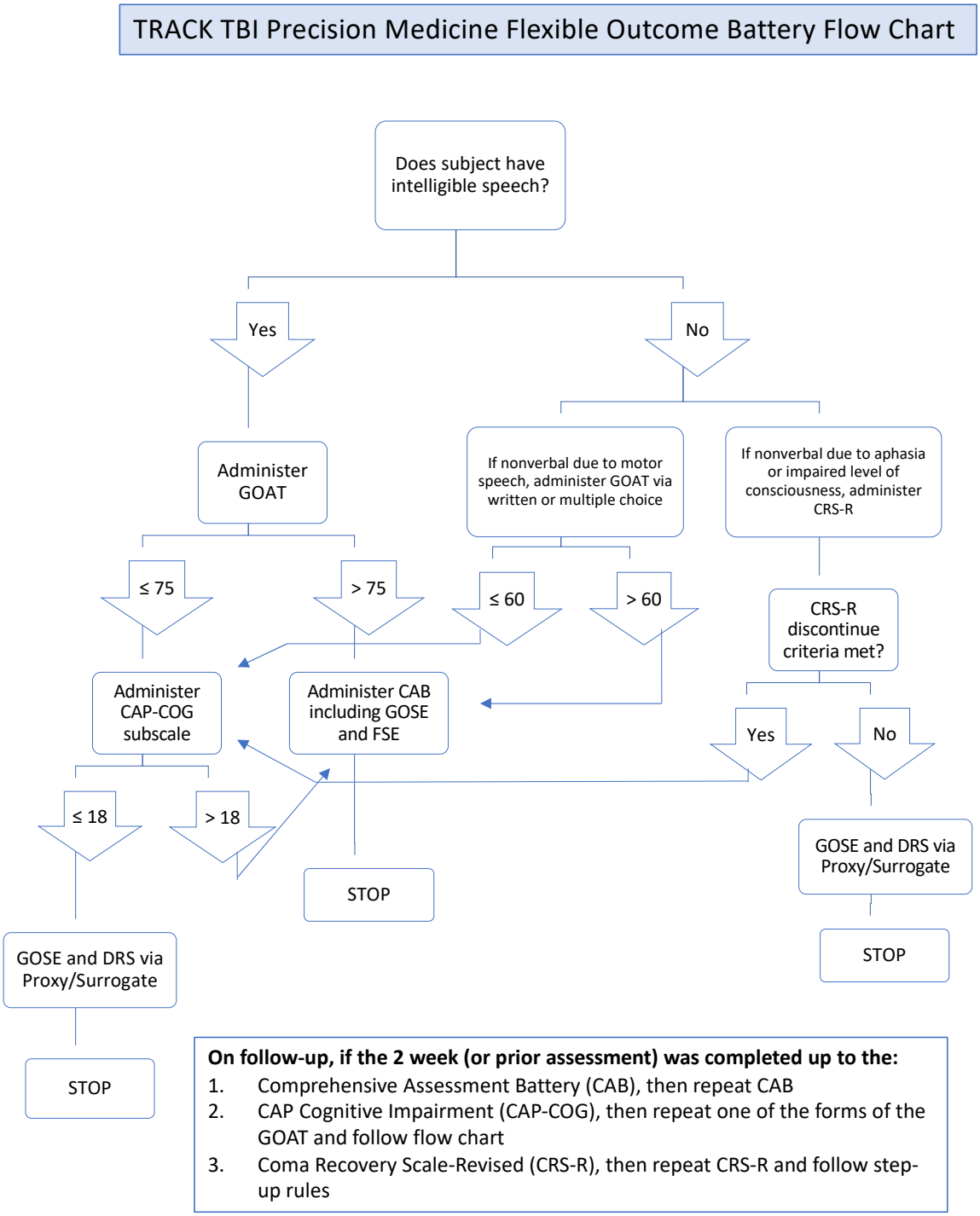
The Flexible Outcome Assessment Battery is designed to assess multiple outcome domains across all phases of recovery in patients at all levels of TBI severity. The battery comprises the original Core CDE measures (TBI-CDE Version 1.0) administered in the TRACK-TBI Pilot study, and additional Basic and Supplemental CDEs (TBI-CDE Version 2.0) that further assess psychological health and cognition. The combined TBI-CDE versions constitute the Comprehensive Assessment Battery (detailed in section 8.2 below). Patients who are too impaired to tolerate the Comprehensive Assessment Battery will undergo assessment on the Abbreviated Assessment Battery (detailed in section 8.3 below), which consists of standardized measures of basic neurobehavioral (e.g., Coma Recovery Scale-Revised [CRSR]) and cognitive (e.g., Confusion Assessment Protocol [CAP]) function. See **Figure 1** for the Flexible Outcomes Assessment Battery Framework Decision Workflow.

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

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 UCSF if they require further guidance on completion of TRACK-TBI-related study activities. The utility and necessity of these procedures will be evaluated over time to see if they need to be modified due to COVID-19, or kept in place after COVID-19 restrictions are lifted.

- **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 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).
- **Performance 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**: MRI and blood collection procedures 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**.

***Figure 1**: Flexible Outcomes Assessment Battery Framework: Decision Workflow*



8 TRACK-TBI PRECISION MEDICINE FLEXIBLE OUTCOME ASSESSMENT BATTERY AND ORDER OF ADMINISTRATION

8.1 Enrollment Battery (at consent or by phone within 24 hours of injury): ~11 minutes

1. Rivermead Post Concussion Symptoms Questionnaire (RPQ): 3 mins
2. Brief Symptom Inventory 18 (BSI-18): 3 min
3. Standard Assessment of Concussion* (SAC): 5 min

The enrollment outcome assessment battery will be administered only to participants who score ≥75 on the Galveston Orientation and Amnesia Test (GOAT).

*The SAC can only be collected in-person, and cannot be collected by telephone.

8.2 Comprehensive Assessment Battery (CAB) (2 W, 6 W, 3 M) 91-108 minutes

Domain	Subdomain	Instrument	Administration Time	Order of Administration In person (~98 min)
Screening	Screening	Assessment of Speech Intelligibility*	2 min	1, and as needed
		Galveston Orientation and Amnesia Test (GOAT)*	5 min	2, and as needed
History	Participant Interview	Interview to update occupational status; living situation; medical history (e.g., known neurologic, cognitive, psychiatric conditions)*	10 min#	3
Daily/Global Function	Global Outcomes	Glasgow Outcome Scale Extended (GOSE)*	15 min	5
		Functional Status Exam (FSE)*	10 min	4
Psychological Health/ Neurobehavioral Symptoms	Depression, Anxiety, Somatic	Brief Symptom Inventory-18 (BSI-18)*	3 min	13
	TBI-Related Symptoms	Rivermead Post Concussion Symptoms Questionnaire (RPQ)*	3 min	11
	Post-traumatic stress	PTSD Checklist for DSM-5 (PCL-5)*	3 min	12
	Suicide	Columbia Suicide Severity Rating Scale Screening Version+ (C-SSRS)*	5 min	As needed
	Life Quality (Brain)	Quality of Life after Brain Injury Overall Scale (QoLIBRI-OS)*	3 min	7
Symptom Validity	Symptom Validity	Structured Inventory of Malingered Symptomatology (SIMS)*	10 min	6
Cognitive Performance	Episodic Memory	Rey Auditory Verbal Learning Test (RAVLT)	15 min	8 (delay after BSI-18)
	Executive Function	Trail Making Test A+B	5 min	9
	Processing Speed	Wechsler Adult Intelligence Scale – 4th Edition Processing Speed Index (WAIS-IV) PSI	4 min	10
Motor	Fine motor (Bradykinesia)	Finger tapping	5 min	14
	Gross motor/mobility	Short Physical Performance Battery (SPPB)	5 min	15

+Triggered by /BSI-18

*Measures that should be collected over the phone

8.3 Abbreviated Assessment Battery (AAB) (2 W, 6 W, 3 M) 60-67 minutes

Domain	Subdomain	Instrument	Administration Time	Order of Administration In person (~72 min)
Screening	Screening	Assessment of Speech Intelligibility*	2 min	1, and as needed
		Galveston Orientation and Amnesia Test*	5 min	2, and as needed
Consciousness and Basic Cognition	Confusion	Confusion Assessment Protocol (CAP)	15 min	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	
Daily/Global Function	Global Outcomes	Glasgow Outcome Scale Extended (GOSE)*	15 min#	3
		Disability Rating Scale (DRS)*	10 min#	4

*Measures that should be collected over the phone

9 TRACK-TBI PRECISION MEDICINE ASSESSMENT BATTERY: DESCRIPTION OF MEASURES

9.1 Measures to Screen Competency and Selection of 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 at the beginning of the assessment to determine if the Abbreviated Assessment Battery should be administered and whether to administer the CAP and/or CRS-R. This measure can also be administered at any point during a phone 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 at the beginning of the assessment to determine if the Abbreviated Assessment Battery should be administered and whether to administer the CAP and/or CRS-R. This measure can also be administered at any point during the phone or in-person assessment, if the study coordinator has any concerns about the participant's capacity to consent and complete an assessment.

9.2 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 Precision Medicine participant interview is based on the TRACK-TBI 3M follow-up Participant Interview and adds a neurologic screen for epilepsy as well as questions pertaining to 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 should be administered by telephone but can also be administered in-person if permitted by local policy and acceptable to the subject or LAR.

9.3 Measures of Daily/Global Function

Functional Status Exam (FSE)

The FSE[47] 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 non-performance 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 surrogate. The FSE measure should be administered by telephone but can also be administered in-person if permitted by local policy and acceptable to the subject or LAR.

Additional information regarding the administration of the FSE can be found in the pdf "Functional Status Examination Manual" saved on the Study Shared BOX folder at "Box\TRACK-TBI Precision Medicine Study Documents\Outcomes Core\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. A "TBI" score will be collected for the purposes of TRACK-TBI Precision Medicine. The GOSE should be administered by telephone but can also be administered in-person if permitted by local policy and acceptable to the subject or LAR.

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 areas, information obtained during the FSE interview that relates to a specific GOSE area can be directly applied to the GOSE rating. This approach will minimize subject burden and help reduce the completion time of the TRACK-TBI Precision Medicine battery.

Standard Assessment of Concussion (SAC)

The Standardized Assessment of Concussion (SAC)[48] is a brief screening instrument designed for the neurocognitive assessment of concussion by a non-neuropsychologist without prior expertise in psychometric testing. The SAC requires approximately 5-10 minutes to administer and includes measures of orientation, immediate memory, concentration, and delayed recall, summing to a total composite score of 30 points, with a higher score indicating better cognitive functioning. The SAC will be obtained only at enrollment and must be collected in-person; the SAC cannot be collected by telephone.

Disability Rating Scale (DRS)

This measure is administered and scored in the same way as described in the TRACK-TBI Outcomes Assessment SOP. The DRS measure will be administered during the in-person assessments but can be collected by phone. Only the DRS Caregiver version will be collected in this study.

9.4 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 measure should be administered by telephone but can also be administered in-person if permitted by local policy and acceptable to the subject or LAR.

Rivermead Post Concussion Symptoms Questionnaire (RPQ)

This measure is administered and scored in the same way as described in the TRACK-TBI Outcomes Assessment SOP. The RPQ measure should be administered by telephone but can also be administered in-person if permitted by local policy and acceptable to the subject or LAR.

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 should be administered by telephone but can also be administered in-person if

permitted by local policy and acceptable to the subject or LAR.

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 should be administered by telephone but can also be administered in-person if permitted by local policy and acceptable to the subject or LAR.

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

The Screening Version of the Columbia will be administered if the participant answers >1 on Q#17 of the BSI-18 (this is the same triggering criteria in 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** (saved on the Study Shared BOX folder at "Box\TRACK-TBI Precision Medicine Study Document\Outcomes Core\Outcomes Core SOP"). The C-SSRS measure will be administered during the in-person assessments but can be collected by phone.

9.5 Measure of Symptom Validity

Structured Inventory of Malingered Symptomatology (SIMS)

The Structured Inventory of Malingered Symptomatology™ (SIMS™)[49] is a 75-item, true-or-false screening instrument that assesses both malingered psychopathology and neuropsychological symptoms. It 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), as well as five nonoverlapping scales that reflect theoretical and statistical considerations of the more commonly feigned or exaggerated disorders: (a) Psychosis, (b) Neurologic Impairment, (c) Amnestic Disorders, (d) Low Intelligence, and (e) Affective Disorders. The SIMS is intended to serve multiple functions as (a) an initial screening tool for individuals who may not otherwise be referred for specific evaluation of potential feigning within a forensic or medico-legal context or setting; (b) an initial screening tool for individuals suspected of feigning to determine the need for more extensive evaluation; and (c) convergent data in a comprehensive evaluation for potential feigning. The SIMS' brief, easily administered self-report format and fifth-grade reading level reduce clinician burden and allow for completion by a wide range of individuals at varying educational/cognitive levels. The SIMS measure should be administered by telephone but can also be administered in-person if permitted by local policy and acceptable to the subject or LAR.

9.6 Measures of Cognitive Performance

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, and can only be collected at an in-person assessment. The Delayed Recall trial will be administered after the BSI-18.

Trail Making Test

This measure is administered and scored in the same way as described in the TRACK-TBI Outcomes Assessment SOP, and can only be collected at an 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, and can only be collected at an in-person assessment.

9.7 Measures of Motor Function

Finger tapping

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)[50]. 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. 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 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 won't 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 stop watch 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. So, 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."

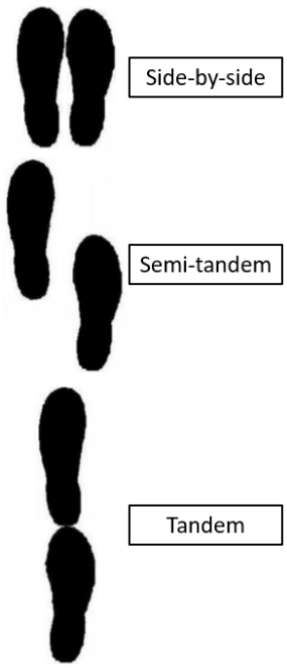
*When demonstrating speed for a significantly impaired participant, it is not necessary to go as fast as you can. Instead, demonstrate a moderated speed.

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, and can only be administered in person.

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.)

"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.)

9.8 Measures of 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. The CAP measure can only be collected during an in-person assessment.

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, and can only be collected during an in-person assessment.

10 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 Precision Medicine 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 Precision Medicine 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 Patient Number.

11 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 Precision Medicine 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 the Study Shared BOX folder (Box\TRACK-TBI Precision Medicine Study Documents\Outcomes Core\Outcomes training and administration guidance). Competency in administration and scoring of the Precision Medicine 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 Precision Medicine 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 publicly accessible websites such as YouTube.**

12 SUBJECT RISKS AND BENEFITS

12.1 Foreseeable Risks By Core

The potential risks to the subject are minimal across all domains of data collection. The subject's signed consent form may become part of their medical record, but no research data collected as part of this study will become part of the subject's medical record.

Clinical. The TBI event will already be part of the subject's medical record, so involvement in this study will not have any effect on obtaining care or coverage under insurance. The risks involve some degree of loss of privacy. This will be minimized as much as possible. All data will be confidential and stored in locked areas to which only authorized study personnel have access. Records will be coded with a Patient Number as soon as the patient is enrolled so that names and other identifying information will not be linked to personal or sensitive data, in compliance with federal regulations of the Health Insurance Portability and Accountability Act (HIPAA). The Patient Number is automatically generated by the QuesGen System as soon as the patient is entered into the database. In addition, subjects and their families will be informed that participation is completely voluntary, that they may decline response to any questions, and that they may withdraw from the study at any time, all without jeopardizing medical treatment to which they are otherwise entitled. Subjects and their families will not be required to answer any interview or assessment questions that they find distressing or sensitive in nature.

Biospecimens. The blood sample will be drawn from an arterial or central venous catheter placed as a part of standard care for those patients consented while in the ICU. Those patients consented on the ward or in the emergency room will need to undergo phlebotomy, but every attempt will be made to collect the blood sample at the same time a clinical sample is drawn to reduce needle sticks. The subject may experience the discomfort associated with a needle stick and may suffer bruising at the site of the needle stick. No more than two venipuncture attempts will take place.

Genetic Research. There is a possibility that, if the results of a research study involving genetic material were to become generally known, this information could affect one's ability to be insured, employed, future decisions regarding children, or family relationships. As noted, all data will be de-identified and linked by Patient Number. Data will be stored in locked areas to which only authorized study personnel have access.

The Genetic Information Nondiscrimination Act of 2008 (GINA) prevents employers and health insurers from discriminating based on genetic information. Below GINA language will be included in the informed consent form for this study:

A new Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- *Health insurance companies and group health plans may not request your genetic information that we get from this research.*
- *Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.*
- *Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.*

Be aware that this new Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Neuroimaging. Participants will undergo noninvasive brain imaging using FDA-approved 3 Tesla MR scanners within 48hr, at 2 weeks and at 3 months post-injury. No exogenous contrast agents and no sedation will be used. The MRI procedures are noninvasive and painless. The MRI does require the subject to lie still with the head and part of the body confined in a tunnel-like device for a considerable length of time (total scan time of approximately 60 minutes). The subject will have frequent communications with the MRI technologist and study staff, and will be able to stop the MRI scan at any time. Contraindications for the MRI examination include those who have cardiac pacemakers, neural pacemakers, surgical clips in the brain or blood vessels, surgically implanted steel plates, screws or pins, cochlear implants, intrauterine devices, or non-MRI compatible metal objects in their body, especially in the eye. Subjects will be required to remove all ferromagnetic items (e.g., keys, phones, credit cards, belts, loose change, and others) before entering the MRI examination room. Claustrophobia may also preclude successful MR imaging. Careful screening will prevent such individuals from participating in this study, as well as preventing the introduction of any ferromagnetic objects into the scanner room. Dental fillings do not present a problem.

The FDA has set recommendations for exposure in MRI studies and the proposed 3T examinations satisfy those criteria. The guidelines from the Bureau of Radiological Health of the FDA will be followed in regard to specific absorption rate (SAR) of radiofrequency energy and time varying magnetic fields (dB/dt). Precautions will be maintained so that SAR will be less than 8 watts per kilogram in any 1 gram of tissue. This is the estimated power required to raise the temperature 1 degree centigrade. The maximum dB/dt will be set at 20T/sec for > 120usec or 200T/sec for < 12usec. These levels are well below peripheral nerve stimulation threshold in humans, both children and adults. In rare cases, subjects may still experience some peripheral nerve stimulation during portions of the MRI procedure. These experiences are transient and harmless. MRI participants will be instructed prior to examination to refrain from skin-on-skin contact of their extremities (e.g., clasping hands or legs) to further reduce this risk. The MRI will produce loud noises during image acquisition. The decibel intensity of these noises is not considered harmful per FDA regulations, and is below FDA guidelines of 140 dB peak referenced to 20 micropascals. Subject will be provided with earplugs and noise-cancelling headphones/earpads to minimize discomfort.

Subjects will always be in communication with the MRI technologist and will be given a squeeze ball that triggers an alarm. If the subject indicates at any point that they have a desire to stop the procedure, the exam will be terminated immediately and without any penalties to the subject in any way.

If any unexpected findings are identified that may be clinically significant, the participant will be counseled by the Site PI and recommended to seek medical care from their primary care physician.

Outcomes. Some of the questionnaires and interviews used in this research ask about personal and potentially sensitive information. This will be explained to subjects both orally and in the consent document. Further, only trained study personnel who are sensitive to these issues will administer such interviews and questionnaires. If a subject endorses any of the questions regarding suicide, it will be documented in the research record and the study staff will follow the **TRACK-TBI Suicide Protocol and Safety Plan** (saved on the Study Shared Box folder at: BoxTRACK-TBI Precision Medicine Study Documents\Outcomes Core\Outcomes Core SOP).

12.2 Protections Against Subject Risks

Recruitment and Informed Consent. All study sites are experienced with recruiting TBI subjects. All sites will obtain IRB approval through a central UCSF IRB to enroll patients into TRACK-TBI Precision Medicine. Research staff will locate eligible patients in the hospital (emergency department, hospital wards, intensive care unit), explain the research study, review the consent form, ask the subject or LAR if s/he voluntarily agrees to participate, and obtain consent. Prospective subjects will be given as much time as needed to consider study participation. If the subject is not capable of self-consent, all efforts will be made to locate a LAR to sign in person or via fax.

Clinical. The potential risk to subjects is minimal. We will take all necessary steps to reduce risk for all study participants. We will inform subjects of the potentially sensitive nature of some of the research questions and create an atmosphere of security and trust prior to collecting data. We carefully explain the steps taken to assure the confidentiality of all participant data. Subjects are always given permission to not answer questions with which they feel uncomfortable. In our experience with TRACK-TBI Pilot and TRACK-TBI U01, with the establishment of rapport by a sensitive, experienced research team, the majority of subjects welcome the opportunity to participate in research. Following initial consent, subjects will be reminded before every procedure that participation is completely voluntary, that they may decline to respond to any questions, and that they may withdraw from the study at any time without jeopardizing medical treatment to which they are otherwise entitled.

To protect confidentiality, no paper copies of study forms will include subjects' names, but instead will contain a Patient Number as the identification key to match subjects over the repeated measures. The subject names will be entered into the QuesGen web-based eCRFs in order for study personnel to contact patients and conduct follow-up visits. However, only designated study site personnel will be able to view the subject name fields in QuesGen. All data communication between the QuesGen browser and secure servers is through an encrypted secure socket layer connection. Servers are located in a Statement on Auditing Standards-70 compliant data center behind a dedicated firewall. QuesGen has procedures in place for full compliance with HIPAA security standards for protection of PHI. User password accounts are assigned according to user types and access roles which allow or restrict the viewing of any PHI fields. An algorithm is applied to each data element to determine if it should be considered PHI. The default determinations can be overridden if incorrectly classified as PHI. Administrative users can set up accounts for users to only view the data or set filters that limit viewing of records according to their study site. Every data modification is tracked and all views and deletions are logged so that data tampering is not possible. Study sites that are not covered entities by their institution will be required to establish Business Associate Agreements with QuesGen Systems, Inc.

Study data will be entered into eCRFs using designated laptop and desktop study computers with secure, encrypted connections to the eCRF data. No PHI will be stored on the hard drives of any study computers. Study computers will have encrypted drives conforming to IT standards at each respective site. Study computers will be password-protected and securely maintained with virus protection software installed to automatically update and scan the drives. Only research personnel responsible for data entry or review will have password access for study computers. Paper copies of surveys will be filed by their Patient Number in locked file cabinets behind locked doors at each study site. A list linking the Patient Number and names will be kept in a separate locked file cabinet behind locked doors at each study site. Once the final outcome

assessments are completed and checking for data quality monitoring purposes is completed, PHI for the subject will no longer be accessible to previously authorized personnel except the study site PI. At project conclusion, PHI data will be stored in a password protected PDF file and given to the site PI for long-term protected storage. The QuesGen Data Manager will then remove the PHI data from all server hard drives and all backup devices. QuesGen will not retain any copies of the PHI data long-term. These identifiers will then be accessible only by the study site PI and would be used at a later time only if it becomes necessary to contact the subject for additional studies or for regulatory purposes.

Biospecimens. For the blood draw, no more than two venipuncture attempts will be performed and specimens will be coded when the draw is complete.

Neuroimaging. As noted, the total scan time is approximately 60-75 minutes during which time the subject will have continuous communication with the experimenter. Some patients find the loudness of the oscillating gradients during image acquisition to be discomforting, but the acoustical noise level is below FDA guidelines of 140 dB peak referenced to 20 micropascals. In addition, all patients are provided with earplugs to reduce the noise. There is no evidence for long-term negative effects of MRI procedures on the body. The 3T scanner is an FDA-approved system. For patients' safety, only MRI-compatible monitoring equipment will be used in the scanner suite for any patients requiring that for the ultra-early MRI.

Outcomes. An experienced outcomes team designated by the Outcomes Core will train all outcomes personnel for TRACK-TBI. Only trained study personnel sensitive to the inherent issues across cognitive, mental health, psychological, and quality of life domains will administer the outcome instruments for the study. Subjects will be re-introduced to the study at each outcomes time point for understanding and approval to continue participation. Subjects are informed that they are free to not answer any question that may be uncomfortable for them. If a subject endorses any of the questions regarding suicide, it will be documented in the research record and the research personnel will notify the Site PI and activate local suicidality protocols.

12.3 Certificate of Confidentiality

As an additional level of safeguard for study participants, we have obtained a Certificate of Confidentiality from the NIH. Having this Certificate means that investigators and study personnel cannot be forced to disclose research information that might identify the subject in any federal, state, or local criminal, civil, administrative, legislative, or other proceedings. This is important because TBI patients are often involved in high-risk behaviors that result in their injuries.

12.4 Potential Benefits of Proposed Research

There is no direct benefit to study participants. The results will be directly relevant to society in general and to future patients who suffer TBI. Tokens of thanks for study participants are especially important in longitudinal studies, where the burden on the respondent, even if small, tends to multiply over time. Each site will establish a reimbursement schedule for each of the time-consuming components of the study, including travel, MRI, telephone and in-person outcomes testing.

TRACK-TBI subjects will undergo extensive neuropsychological testing and brain imaging. These procedures are not part of the standard of care for mild TBI.

- All subjects will have access to the results of their research MRI results within 2 weeks of the MRI collection. If requested, subjects will receive a CD of their conventional MR imaging data and a viewer application tool. The Patient Number will be stripped from the MRI scan.

For details regarding the release of outcomes testing results to the participants refer to the section '10 Protocol for Sharing Outcome Data with Participants'.

13 SUBJECT COMPLIANCE AND RETENTION

We will monitor subject compliance with the observational portion of the protocol, and research personnel will maintain scheduled contact with the subjects and their family members to ensure on-going compliance through the 3-month study duration. Upon consent and enrollment, participants will be asked to provide multiple forms of contact information including phone, address, and email. Upon their permission, participants will be asked to provide one or more alternate contacts. The Site will maintain a schedule of contacts to maximize the chance of successful communication and scheduling for follow-up time points as soon as their window of return opens for that time point. This will involve training Research Coordinators to monitor their own site progress, which will be supplemented by automated reminders of upcoming windows for follow-up generated by QuesGen Systems and emailed to each site coordinator weekly. Every effort will be made to schedule return visits at the subject's convenience, and multiple procedures for that time point will be scheduled on the same day. When subjects return for their follow-up, they will be met by research personnel who will escort them to the various testing locations. Subjects will have full opportunity to ask any questions before, during, and at the end of the follow-up appointment. Site Coordinators will be encouraged to have relevant resource packets and materials for TBI assembled to provide to study patients.

In the event that a participant misses a follow-up time point, every effort should be made to schedule subsequent visits for outcome assessment, neuroimaging, and blood draws.

- If an in-person assessment cannot be scheduled despite multiple attempts, outcome assessments at that time point should be collected by phone.

14 DATA MANAGEMENT AND COMPLIANCE

14.1 Clinical database

Upon study enrollment, the subject will be entered onto the QuesGen System, which will automatically generate a Patient Number. This Patient Number is not generated from personally identifiable information (PII). Patient Numbers in this study will be assigned as follows: each site will start with subject "PM-XX-3001" for the Patient Number where PM = Study Name, XX = Site ID (see Site IDs for the 5 participating study sites below), and the last four digits will start at "3001" and increase consecutively with each enrollment at the site. MRI scans will have an additional label at the end to distinguish the time point and whether the scan is a patient or phantom. The additional labels are as follows: (PM-XX-XXXX_Ultra-early for MRI within 48 hours, _2WK for 2-week MRI, _3MO for 3-month MRI and _PHA for phantom). Clinical data will be entered into eCRFs via a web-based portal to the secure, fully HIPAA-compliant QuesGen clinical database.

Site IDs for participating sites are as follows:

Site Name	Site IDs
UCSF	03
Univ. of Pittsburgh	07
Univ. Pennsylvania	12
MCW	14
Univ. of Utah	15

Automated data integrity monitoring. All clinical data will be entered into electronic Case Report Forms (eCRFs) and managed by the QuesGen data management platform. As data is entered into each form, the system will run data validation checks that include conditionally required data, validation across fields, and validation requirements based on subject type. If any validation check fails, the user is alerted immediately that the data does not meet QA criteria and the issue can be addressed and corrected at that point. If a data

element fails a validation check, yet the value entered is correct, the user can enter an exception to the problem and provide a notation as to why the out-of-range data is actually correct.

- **Date/time value checks:** all dates and times entered into the database are checked to ensure that events recorded are accurate and in sequence.
- **Range value checks:** all numeric, non-date fields have range values specified to minimize data entry errors.
- **Selection lists:** all categorical data fields have predetermined drop-down lists, check boxes, or resettable radio buttons instead of free text to ensure accuracy.
- **Logic checks:** data fields from different sections of the eCRF will be compared to pass logical integrity
- **Required fields:** the eCRF will be programmed to require input into fields when appropriate to minimize missing information.
- **Score calculation** will be performed and programmed into eCRFs for tests and measures with numerical score summations or norming to avoid mathematical errors by the examiner. All automated scoring computations will be fully documented and validated by QuesGen and the Clinical Core, and must pass User Acceptance Testing.
- **Electronic data audits** will be automated in the QuesGen database through a series of pre-determined queries against the study database at regular intervals. These queries will be designed for the Clinical Core to monitor data quality and completeness and identify protocol variations/deviations/violations.
- **Data audits against source documents**, where available, will be conducted prior to the final "lock" of each subject's data set. Errors found will be corrected at this time.

All investigators and designated study personnel will have unique and confidential password access to the QuesGen database. All access to the database and to study data will be logged in an audit trail and monitored. Any indication of inappropriate access will be reported immediately to the Clinical Core.

The QuesGen system will also provide checks for form completion based on the subject type. Validation rules will establish when forms for a particular subject should be entered, and any missing forms can be tracked by the Study Site and Clinical Core immediate follow-up. Once subject forms are marked complete, a dataset for sharing can be created. The QuesGen platform stores the exact dataset that is shared for future reference.

Due dates for eCRF completion windows are set by the Clinical Core. The Subject and Presentation eCRFs need to be initiated as soon as possible following enrollment in order to assign subject IDs for the biospecimen vials. In general, every effort should be made to complete eCRFs within 2 business days of enrollments, inpatient stays, follow-up milestones and discharges. It is understood that some forms and fields within forms may not yet have complete information available to report (e.g., Hospital Admission/Discharge, AIS/ISS, Surgeries, Concomitant Medications, etc.). The QuesGen System will automatically generate reminders to complete eCRFs for enrolled patients. Monthly reports of enrollment, timeliness of eCRF completion and error correction will be monitored and adjudicated by the Clinical Core.

Integration with analytics platforms. All de-identified electronic study data in the TRACK-TBI database will be maintained in secure storage by QuesGen Systems for the duration of subject enrollment and follow-up and for a period afterwards for data analysis and preparation of publications. We estimate that the analysis and publication period will last for several years after the conclusion of subject enrollment.

Together with QuesGen Systems, the Clinical Core will ensure that data standards are established for the data model e.g., conformity of field formats, field codes and names to ensure consistency across all datasets. After the initial approval of the data model and eCRFs, any proposed changes to the database will be reviewed by QuesGen and the Clinical Core for impact upon the existing data in the repository. Approved changes will be fully documented with dataset updates to maintain data quality and accuracy.

14.2 Biospecimens (See Appendix 2: TRACK-TBI Precision Medicine Biospecimen MOP for detailed biospecimen procedures)

Biospecimens collection. Study sites will collect, process, and ship blood and CSF (if collected) biospecimens according to the NINDS TBI-CDE Biospecimens Protocol, to a central biorepository at University of Pittsburgh. Each site will batch and ship biospecimens to the central repository on a quarterly basis. Formalized QC/QA policies for collection, processing and storage were developed and validated for TRACK-TBI Pilot. Refer to Appendix 2: TRACK-Precision Medicine_Biospecimen Protocol_MOP_v1.5_APR062021 (also saved on the Study Shared Box folder at: TRACK-TBI Precision Medicine Study Documents\Biospecimens Core\ Biospecimens MOP) for detailed information regarding management of collection supplies (disposables and reagents), identification (using Patient Number), labeling conventions, collection and processing methods, storage and retrieval, shipping and receiving, training, and security. Together these pre-analytic QC/QA policies minimize circumstances that could adversely affect scientific results, ensure the safety of research personnel, and aid in the efficient operation of the TRACK-TBI Biospecimen Core. The Biospecimen Core will review the efficiency of existing processes and procedures on a quarterly basis.

Biospecimen Repository. The NTBI-BR at the University of Pittsburgh will manage receiving biospecimen shipments from all participating sites, inventory of those shipments, storage of all study biospecimens, and shipment of study biospecimens to relevant analytic partners, where genomic and proteomic analyses will be used to discover new TBI biomarkers. See Appendix 2: TRACK-Precision Medicine_Biospecimen Protocol_MOP_v1.5_APR062021 for more details (also saved on the Study Shared BOX folder at: Box\TRACK-TBI Precision Medicine Study Documents\Biospecimens Core\ Biospecimens MOP)

14.3 Neuroimaging (See Appendix 1: TRACK-TBI Precision Medicine Neuroimaging MOP for detailed neuroimaging procedures)

Standardization of MR across sites. All study MR systems will initially be characterized with the Magphan® Quantitative Imaging Phantom (Phantom Laboratory, Salem, NY) designed to measure signal-to-noise ratio, object size scaling, and spatial distortion. The Magphan® Phantom has been extensively used for high-resolution structural brain imaging in numerous trials, including ADNI, as follows:

1. Serial imaging of the phantom will track scanner performance over the study enrollment period using an online MR Distortion and Image Quality service (ImageOwl, Salem, NY) which identifies scanner errors or defects and corrects for scaling errors and gradient non-linearity.
2. Standardization for diffusion MR imaging using an ice water phantom adopted by ACRIN for multi-site diffusion imaging trials.
3. Performance of fMRI will be assessed using the Biomedical Informatics Research Network (BIRN) phantom, with serial data analyzed to assess signal mean and standard deviations, temporal fluctuations, and drift.

Standardized MR protocols will maximize consistency among study sites and across vendor platforms. Within vendors the protocols will be identical and shared via manufacturer-generated tools (e.g. edx files, examcards). Across vendors, protocols will match spatial coverage, voxel dimensions, and primary contrast parameters (e.g. echo time, repetition time). A TRACK-TBI board-certified neuroradiologist will evaluate the test-retest scans from all sites to assure diagnostic image quality and for pathoanatomic analysis of structural MRI sequences.

Neuroimaging Repository. All study neuroimages (CT and MRI) will be de-identified at each study site before uploading to the TRACK-TBI neuroimaging core repository (Flywheel) as DICOM files, utilizing the Neuroimaging Core's de-identification and transport protocol. Image data will then be passed into one of a series of modality-specific semi-automated quality assessment pipelines and evaluated by the Neuroimaging Core for protocol conformance and quality. QA results will be provided to acquisition sites within 48 hours and

the scan repeated if it does not meet QA criteria. Images passing QA will be sent into a modality-specific image analysis pipeline and the resulting processed images and measures will be returned to the neuroimaging repository. The existing image processing provenance collection method will ensure that derived images and data are properly annotated and preserved for future research.

Integration and analysis. The Neuroimaging Core will direct the coding of all TRACK-TBI neuroimages. Final versions of the curated TBI-CDE compliant clinical and outcomes data, neuroimaging, and molecular measures will be integrated within Flywheel. Analytic systems within Flywheel will support real-time inspection of data, hypothesis testing, data subsetting, and data exploration across studies.
See TRACK TBI Precision Medicine Neuroimaging MOP V3_TRACK-TBI_MRI_Manual_27JULY2018 for more details (also saved on the Study Shared BOX folder at: Box\TRACK-TBI Precision Medicine Study Documents\Neuroimaging Core\ Neuroimaging MOP)

15 ADVERSE EVENTS

Events may be categorized as Adverse Events (AEs) if the distress felt by the subject requires termination of testing or procedure (e.g., outcomes testing, MRI). Anticipated AEs in TRACK-TBI include:

- Excessive discomfort, pain, or bruising during venipuncture
- Claustrophobia or severe anxiety in the MRI
- Anxiety during outcomes battery administration due to sensitivity of material discussed
- Anxiety due to fear of legal discovery associated with high-risk/illegal behaviors during interview

15.1 Reporting Procedures. AEs will be documented in the AE section of the QuesGen database. Each Site PI will be informed on a weekly basis regarding the number and nature of the AEs at their site. The Clinical Core will review the number and nature of AEs at each site on a monthly basis. Given that each site must reach the 80% completion of follow-up milestones, if AEs exceed 10% of site enrollment the Clinical Core will contact the site to discuss potential methods for reduction of AE incidence.

15.2 Other Serious Events. Any other serious events that do not meet the above criteria will be reported to the Clinical Core within five working days. These AEs will be recorded for individual subjects during the 3-month study period. In addition to submission as required per IRB regulations, AE data will be analyzed quarterly and reported in the quarterly reports submitted to the Executive Committee.

16 DATA SHARING

TRACK-TBI Precision Medicine internal and external data sharing procedures will align with the TRACK-TBI data sharing procedures (see TRACK-TBI Data Use Agreement/Human Materials Transfer Agreement of TRACK-TBI Research Collaboration Policy_06-19-2020_Final_Current.pdf saved in the Shared Study BOX folder at Box\TRACK-TBI Precision Medicine Study Documents\Data Management\ Data sharing).

UCSF lead team has registered the study on Clinicaltrials.gov under identifier NCT # NCT04602806. The results from this study will be submitted to ClinicalTrials.gov.

17 CLINICAL PROTOCOL MAINTENANCE

17.1 Protocol Modifications

See TRACK TBI U01 protocol-appendix 7 for the procedure for revisions to the Precision Medicine Protocol (Dropbox\1-TRACK TBI Doc Share\clinical core\Clinical Protocol\Clinical Protocol Appendices).

17.2 Protocol Deviations

Protocol compliance and study performance will be monitoring by the Clinical Core using the study reports and dashboards provided by QuesGen Systems. Any protocol deviations should be reported and described in full under the research subject's study record in QuesGen, "Subject → Protocol Deviations" tab.

Protocol deviations may include:

Clinical

- Subject enrolled with unclear time of injury (for assessment of enrollment <24 hours)
- Baseline interview information missed on enrollment
- Other:

Biospecimens

- Blood collected for the baseline sample outside of <6 hour window
- Blood processing times deviated from protocol
- Blood collection was missed at any time point until day 5 only if the patient was still hospitalized
- Blood collected outside of the 2-week, 6-week, or 3-month window without prior approval for exception by the Executive Committee approval.
- Blood collection attempt unsuccessful
- Blood draw missed (i.e., follow up completed by phone, examiner error, subject refused)
- Other:

Neuroimaging

- MRI collected outside of the pre-specified time windows
- Certain MRI sequences were not completed or required separate visits to complete
- MRI missed within 48 hour, at 2 weeks, and 3 months
- Other:

Outcomes

- MRI and Outcomes not completed within 3 days of each other
- Certain outcome measures incomplete
- Certain outcomes measures missed
- Other:

In most instances and especially concerning enrollment, MRI, or outcomes administration dates, protocol deviations must be reported to the Executive Committee for approval before data collection can resume for the subject at the respective time point of deviation. Due to the time sensitivity of blood draws and processing, deviations can proceed at the local level, but must be reported to the Clinical Core within 2 business days. Under circumstances in which the permissible window for outcome assessment cannot be met, with agreement from the subject, data collectors can request permission from the Executive Committee to complete the scheduled follow-up out-of-window. A protocol deviation will need to be reported within the QuesGen database, even if permission is obtained in advance.

In the event that a consistent pattern of poor performance (e.g., not enrolling allotted amount of patients per month, not achieving at or above 80% follow-up rate across all time points) or inadequate compliance (e.g., insufficient blood draw amount, CT or MR imaging, CRF completion without errors, full outcomes battery completion, or any time point completed outside the approved window) is detected, the responsible site investigator will be notified and required to present a plan for improvement and a time line for accomplishing this to the Clinical Core. Failure to meet objectives specified in this plan may result in termination of the project or assignment of the project to another investigator.

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19 ACRONYMS

AEs	Adverse Events
ASL	Arterial Spin Labeled
AUC	Are Under the Curve
BSI-18	Brief Symptom Inventory-18
CBF	Cerebral Blood Flow
CDEs	Common Data Elements
CRF	Case Report Forms
CSF	Cerebrospinal Fluid
DAI	Diffuse Axonal Injury
DoD	U.S. Department of Defense
DTI	Diffusion Tensor Imaging
eCRF	Electronic Case Report Forms
FDA	U.S. Food and Drug Administration
FISO	Free Water Volume Fraction
Fn	Fibronectin
GFAP	Glial Fibrillary Acidic Protein
GOSE	Glasgow Outcome Scale - Extended
ICU	Intensive Care Unit
LAR	Legally Authorized Representative
MD	Elevated Mean Diffusivity
MOP	Manual of Operating Procedures
MRI	Magnetic Resonance Imaging
mod-sTBI	Moderate To Severe TBI
mTBI	Mild Traumatic Brain Injury
MVI	Microvascular Injury
NIH	U.S. National Institutes Of Health
NODDI	Neurite Orientation Dispersion And Density Imaging
PASL	Pulsed ASL
PCASL	Pseudocontinuous ASL
PCL-5	Post Traumatic Stress Disorder Checklist-5
RAVLT	Rey Auditory Verbal Learning Test
RPQ-18	Rivermead Post Concussion Symptoms Questionnaire-18
rs-fMRI	Resting State Functional MRI
SWI	Susceptibility Weighted Imaging
TBI	Traumatic Brain Injury
TMT	Trail Making Test
TRACK-TBI	Transforming Research And Clinical Knowledge In Traumatic Brain Injury Study
UCH-L1	Ubiquitin C-Terminal Hydrolase-L1
WAIS-IV	Wechsler Adult Intelligence Scale-Fourth Edition
SOP	Standard Operating Procedure
DRS	Disability Rating Scale
FSE	Functional Status Exam
SPPB	Short Physical Performance Battery