

TRACK-TBI: CLINICAL PROTOCOL CHANGE LOG

CHANGE LOG V13 to V14 (July 6, 2016)

New text in red

5.1 SUBJECT GROUPS

The Controls will be adult orthopedic trauma patients who meet the following criteria:

1. An Abbreviated Injury Score of ≤ 4 (not life threatening **extremity**) for their extremity and/or pelvis injury **and/or rib fracture**.
2. Meet the same inclusion and exclusion criteria as the TBI subjects (Section 6.1) except that the criterion of having undergone a CT or MRI in the ED for suspected head injury does not apply. TBI will be ruled out for the current injury by interviewing potential controls about LOC, disturbance of consciousness, and PTA/RA.
3. Each site will be provided a plan in Appendix 8 for the number of controls to target according to age and gender distributions derived from the TBI Cohort.
4. Controls will be enrolled into the CA-MRI cohort for follow-up (Section 5.4) and drop to CA at 2-weeks if unable to complete the MRI visit.

7.3 NEUROIMAGING

CT or initial MRI will be obtained as part of clinical care. 3T MRI will be obtained at 2 weeks and 6 months from CA+MRI subjects only. All initial and follow-up brain CT scans, and any brain MRI scans that are done for clinical care and their reports will be collected. Images will be read and coded by the Neuroimaging Core radiologist in accordance to the Neuroimaging TBI-CDEs. **Only** Sites with a Siemens scanner participating in the HDFT protocol will enroll new TBI patients into the CA+MRI cohort. Non-HDFT sites will finish out their 6 month imaging visits on the Phase 1 protocol. All control subjects will complete their 2 week and 6 month imaging visits on the Phase 1 protocol. **Sites with the capability to collect the Phase 1 3T MRI on inpatients may continue to enroll into the CA+MRI cohort. The Phase 1 protocol can be completed at 2 weeks on patients who are still in the hospital who presented with a moderate-severe TBI (ED Arrival GCS 3-12). The follow up scan at 6 months will be on the Phase 1 protocol as well.**

CHANGE LOG V12 to V13 (April 28, 2016)

New text in red

5.1 SUBJECT GROUPS

A total of 2,700 TBI patients will be enrolled evenly across 3 clinical groups, differentiated by clinical care path:

1. Patients evaluated in the ED and discharged (ED)
 - a. **After May 5, 2016 patients in this clinical care path will only be enrolled as controls and as TBI subjects at the sites participating in the HDFT imaging protocol.**
2. Patients admitted to the hospital, but not to ICU (ADM)
3. Patients admitted to the ICU (ICU)

5.3 PATIENT COHORT SELECTION FOR MRI

The goal is to enroll a minimum of 600 patients in the Phase 1 CA+MRI cohort that have completed both the 2-week and 6-month visits. After that goal is met sites with a Siemens scanner participating in the high diffusion fiber tracking (HDFT) protocol will continue to enroll into this imaging Phase 2 protocol. Based on the TRACK-TBI Pilot study and others in the field, the 2-week MRI is a challenge for both the TBI patient schedule as well as hospital research resources including scheduling, personnel time, and resources. As we seek to enroll a total of 1800 patients in the Comprehensive Assessment, an achievement of 33% with MRI completed at 2 weeks and 6 months was set as a feasible initial threshold. Given the resource value of the MRI and the known challenges for its completion all patients approached for the study will be enrolled initially into the CA+MRI group. Patients who are unable to complete the MRI at 2 weeks due to contraindications, scheduling, or loss to follow-up will be placed in the CA cohort with all follow-up timepoints identical to the CA+MRI cohort. Completion rates of 2-week and 6-month MRI will be assessed quarterly by the Clinical Core. Should TRACK-TBI be on a trajectory to exceed the initial threshold of 33% MRI completion rate, the Clinical Core will evaluate pacing, enrollment strategies, and potential resource needs for an increased total number of MRIs achieved, and report such recommendations to the Steering and Executive Committees for appropriate modifications to the enrollment target.

7.3 NEUROIMAGING

CT or initial MRI will be obtained as part of clinical care. 3T MRI will be obtained at 2 weeks and 6 months from CA+MRI subjects only. All initial and follow-up brain CT scans, and any brain MRI scans that are done for clinical care and their reports will be collected. Images will be read and coded by the Neuroimaging Core radiologist in accordance to the Neuroimaging TBI-CDEs. Only sites with a Siemens scanner participating in the HDFT protocol will enroll new TBI patients into the CA+MRI cohort. Non-HDFT sites will finish out their 6 month imaging visits on the Phase 1 protocol. All control subjects will complete their 2 week and 6 month imaging visits on the Phase 1 protocol.

12.2 BIOSPECIMENS

Biospecimens collection. Study sites will collect, process, and ship blood 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. The UP biorepository will aliquot and ship serum and plasma specimens to Abbott Laboratories to conduct research assays on potential diagnostic biomarkers for TBI. Formalized QC/QA policies for collection, processing and storage were developed and validated for TRACK-TBI Pilot. Refer to the full Biospecimens Protocol (Appendix 4) for detailed information regarding control of collection supplies (disposables and reagents), identification (using Study ID) and 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 Repository. The Biospecimens Core will review the efficiency of existing processes and procedures on a quarterly basis.

CHANGE LOG V11 to V12 (March 3, 2016)

New text in red

Section 5.1 (Pg. 30) Subject Groups

The Controls will be adult orthopedic trauma patients who meet the following criteria:

5. An Abbreviated Injury Score of ≤ 4 (not life threatening extremity) for their extremity and/or pelvis injury.
6. Meet the same inclusion and exclusion criteria as the TBI subjects (Section 6.1) **except that the criterion of having undergone a CT or MRI in the ED for suspected head injury does not apply.** TBI will be ruled out for the current injury by interviewing potential controls about LOC, disturbance of consciousness, and PTA/RA.
7. Each site will be provided a plan in Appendix 8 for the number of controls to target according to age and gender distributions derived from the TBI Cohort.
8. Controls will be enrolled into the CA-MRI cohort for follow-up (Section 5.4) and drop to CA at 2-weeks if unable to complete the MRI visit.

CHANGE LOG V10 to V11 (January 5, 2016)

New text in red.

Section 5.1 (Pg. 30) Subject Groups

Directions for sites for selection of controls

An additional 100 patients per clinical group (n=300) with extracranial trauma but no TBI will be enrolled as controls for a total enrollment of 3000 patients. This stratification plan into 3 clinical groups, developed and adopted by InTBIR working groups, facilitates CER analyses and is not constrained by traditional differentiation into "Mild/Moderate/Severe" TBI. Data collection is dependent on the clinical care path (ED, ADM, ICU) and requirements of each Aim. Patients in each group will be stratified into 3 cohorts that define the extent of data to be collected. Cohort distribution, data components, and time points appear in the Clinical Protocol Grid and Flexible Outcome Assessment Table.

The Controls will be adult orthopedic trauma patients who meet the following criteria:

9. An Abbreviated Injury Score of ≤ 4 (not life threatening extremity) for their extremity and/or pelvis injury.
10. Meet the same inclusion and exclusion criteria as the TBI subjects (Section 6.1) with the exception of not having undergone a CT or MRI in the ED for suspected head injury. TBI will be ruled out for the current injury by interviewing potential controls about LOC, disturbance of consciousness, and PTA/RA.
11. Each site will be provided a plan in Appendix 8 for the number of controls to target according to age and gender distributions derived from the TBI Cohort.
12. Controls will be enrolled into the CA-MRI cohort for follow-up (Section 5.4) and drop to CA at 2-weeks if unable to complete the MRI visit.

CHANGE LOG V9 to V10 (December 8, 2015)

New text in blue.

Section 1.4 (Pgs. 6-16) Sites and Contacts

Updated site personnel lists.

Section 5.4 (P.32) Clinical Protocol Grid

Revised footnote in clinical protocol grid about holding off on assignment of BA cohort for an indefinite period of time.

BA* n=1200	CA n=1200	CA+MRI n=600	Procedure	Admission	Hospital	2W	3M**	6M	12M
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*Patients in the BA cohort will not be enrolled until a directive has been issued by the Executive Committee to the study sites.

Section 8.3 (p.40) Participation Requirements

Revision of language to conform with Section 15.2 Protocol Deviations and the June 16, 2015 revision where outcome visits outside of the window are considered exceptions when Executive Committee approval obtained.

All efforts should be made to schedule patient return within the specified window for each timepoint. Patients who are reached and scheduled but fall outside the window for any outcomes testing timepoint should still have their outcomes assessment completed in person, or over the phone at 3 months (refer to Section 15.2 for guidance). The number of days from date of injury, and the number of days outside of the exact 2-week, 3-month, 6-month, and 12-month window will be documented in the QuesGen database.

Section 10.4 (P.46) Potential Benefits of Proposed Research

Revised guidance for sites to respond to request for results of 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 their respective 2-week and 6-month timepoints. If requested, subjects will receive a CD of their conventional MR imaging data and a viewer application tool. The study ID will be stripped from the MRI scan.

Release of outcomes testing results is a site-by-site issue to be addressed in accordance with local IRB and Risk Management policies with the following guidance:

- Information will be released only to the subject or the guardian
- Information will 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)
- Upon request, sites that agree to provide results to subjects can do so ~~subjects~~ after completion of their 12-month outcomes, as to minimize the feedback and undue influence of test results on the subjective perception from the research subjects during the study.
- All participants may share their study information with their care providers or others as they choose. Investigators will also be available for consultation with subject’s care providers to interpret these findings with the subject. All outcomes data provided to subjects will be stripped of Study ID.

Section 11 (p.47) Subject Compliance and Retention

Revision of language for cohort assignments for subjects who miss milestones or are lost to follow-up and efforts to be made to obtain telephone measures for patients who can't return for in-person assessments.

In the event that a CA+MRI subject does not or cannot return for the 2-week MRI, every effort should be made to schedule participation in the in-person CA visits [for outcomes and blood draws](#).

- [Subjects initially enrolled into the CA+MRI cohort that do not complete the MRI but are able to complete the 2-week in-person outcomes assessment and blood draw will be reassigned to the CA cohort as their final cohort at 2-weeks and this will be documented in the QuesGen patient management form. The cohort does not change after 2-weeks.](#)
- [If the 2-week MRI is missed, subjects will not be asked to come back for a 6-month MRI.](#)
- [If the CA subject who has completed the 2-week visit doesn't or can't return for the 6 and 12-months visits then always attempt telephone interview with those tests that are suitable.](#)
- [If a CA subject can't be scheduled for the 2-week in-person visit then an attempt should be made to obtain the telephone assessment battery and the subject will be assigned to the CA cohort as their final cohort at 2-weeks and this will be documented in the QuesGen patient management form. The cohort does not change after 2-weeks.](#)
- [If a subject does not complete the 2-week in-person or telephone CA visit then the final cohort at 2-weeks remains as CA and it's reported as a missed milestone.](#)
- [If a CA subject misses the 2-week appointment entirely, the subject should still be contacted for their 3-month follow-up and a protocol deviation will be recorded for the 2-week timepoint. If the 3-month follow-up is missed, then the subject will be recorded as "lost to follow-up" \[in the contact log\]\(#\) and no more contact for study purposes will be necessary. In the event that the subject has never shown up for \[in-person or via telephone for 2-week, 3-month -6-month or 12-month\]\(#\) follow-up but self presents and contacts the study coordinator during the 3, 6 or 12-month windows then attempt to obtain the GOSE \[and then as much as the interview as possible over the phone.\]\(#\)](#)
- [Assignment to the BA cohort is not being used for enrollment or as a drop-down at 2 weeks. Assignment to the BA cohort will be upon notification to sites by the Executive Committee at such time that a site has fulfilled their CA-MRI and CA enrollment quotas during the study year. It is possible that sites completing the CA-MRI and CA quotas will be asked to do additional CA-MRI or CA enrollments if other sites are not meeting the quotas.](#)

Section 15.2 (P.54) PROTOCOL DEVIATIONS

Revisions to clarify between what is considered a protocol deviation and what is an exception for the outcome, MRI and blood draw assessments.

Biospecimens

- Blood collected for the baseline sample outside of 24 hour window
- Blood processing times deviated from protocol
- Blood collection was missed at any timepoint
- [Blood collected outside of the 2-week or 6-month window without prior approval for exception by the Executive Committee approval.](#)

Neuroimaging

- MRI collected outside of the 2-week ~~or 6-month~~ window
- MRI collected outside of the 6-month window without prior approval for exception by the Executive Committee.
- Certain MRI sequences were not completed or required separate visits to complete
- MRI missed ~~at 2 weeks (drop down to CA Cohort immediately)~~ or at 6 months

Outcomes

- CA+MRI Cohort: MRI and Outcomes not completed within 3 days of each other
- Certain outcome measures were incomplete

In most major 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 timepoint 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 not need to be reported if permission is obtained in advance. Requests made to the Executive Committee to perform 6-month outcomes along with the MRI and blood draws outside of the window will also be considered exceptions and a protocol deviation will not need to be reported if permission is obtained in advance.](#)

CHANGE LOG V8 to V9 (November 30, 2015)

6.1 INCLUSION/EXCLUSION CRITERIA

Criterion	Data Source	Comments
Exclusion Criteria		
10. Current participant in an interventional trial (e.g drug, device, behavioral)	Chart, Interview	Exception to co-enrollment exclusion is made for sites participating in Resuscitation Outcomes Consortium Prehospital Tranexamic Acid for TBI Study.

CHANGE LOG V7 to V8 (September 29, 2015)

Section 5.4 (P.31)

Revised clinical protocol grid for CSF sampling days from 1-5 to 1-7 per revision to Biospecimens SOP.

Section 8.3 (P. 40) Participation Requirements

Revised the window for follow-up at 12 months from ± 14 to ± 30 days

7) Outcomes at 12 months must be completed ± 30 days of 360 days from the date of injury.

CHANGE LOG V6 to V7 (July 28, 2015)

Section 11 (P. 47) SUBJECT COMPLIANCE AND RETENTION

Added guidance on minimum data to collect for patients lost to follow-up who make contact on their own with study site personnel during the 6 or 12 month windows.

In the event that the subject has never shown up for 2-week or 6-month follow-up but self presents and contacts the study coordinator during the 6 or 12 month windows then attempt to obtain the GOSE over the phone.

CHANGE LOG V5 to V6 (June 16, 2015)

Section 15.2 (P. 54)

Added guidance on the scheduling outcome assessments outside of the permissible window.

In most major 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 timepoint 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.**

CLINICAL SOP CHANGE LOG V4 to V5 (December 15, 2014)

Section 3.3 (P. 19)

Changed reference in Biospecimens Core from UCSF to "...central biorepository at UP for storage and analysis."

Section 3.4 (P. 20)

Added Abbott Laboratories to the public-private partner list.

Section 5.2 (P.30)

Added “Repeat blood draw for serum within 3-6 hours of the Day 1 baseline collection (optional for sites to include this component)” to BA, CA, and CA+MRI Cohorts.

Added “Collection of cerebrospinal fluid on days 1 through 5 (optional for sites to include this component)” to CA and CA+MRI Cohorts.

Section 5.4 (Pgs.31-32)

Updated Clinical Protocol Grid to include the 3-6 hour blood draws for BA, Ca and CA+MRI: “X (repeat @ 3-6h).”

Section 7.2 (P.35)

Changed volume of initial blood draw from 17.0 to 24.0 ml and added “Patients from all cohorts (CA+MRI, CA, BA) will have up to 24.0 ml of blood drawn <24 hours of injury and a repeat sample of 14 ml obtained 3 to 6 hours after the initial blood draw.

Under Biospecimens, added following reference: “The CSF collection protocol is detailed in Appendix F of the Biospecimens Full Protocol.”

Section 8.3 (P.40)

Revised BTACT window as follows:

- 6) BTACT should be completed within ± 7 days of Outcomes (but not on the same day and no greater than 201 days from injury).

Section 8.4 (P.40)

Added “For the optional protocol at sites that collect blood at 3 to 6 hours following the baseline blood draw it is suggested that subjects be compensated in the amount of \$50.”

Section 12.2 (Pgs.50-51)

Updated Biospecimen Repository to University of Pittsburgh.

Section 15.2 (P.54)

Revised wording in quotes to reflect that 3-6 hour optional blood draw may be outside of 24 hours and does not require protocol deviation report. Blood collected “for the baseline sample” outside of 24 hour window.

General guidance for revising consent form to include additional baseline and 3-6 hour blood draws (optional site protocol).

Additional blood draw for Abbott:

As part of this study we are collecting an additional tube of blood at baseline and 2 tubes of blood 3 to 6 hours later. Part of this sample will be sent to Abbott Laboratories to conduct research assays on potential blood tests for diagnosis of traumatic brain injury. Your de-identified information that is stored in the study database will be shared with Abbott Laboratories.

Refusal to participate in having 2 additional blood draws for Abbott will not affect participation in the other portion of this study. Indicate below whether you consent for your participation in this portion of the study.

Blood draws for Abbott testing:

Agree to participate

Choose not to participate

Change Log V3 to V4 (July 16, 2014)

Section 6.1 (P. 34)

EXCLUSION CRITERIA

Added exclusion criteria: "11. Penetrating TBI"

Added exclusion criteria: "12. Spinal cord injury with ASIA score C or worse"

Section 7.1 (P. 35)

PROCEDURES – CLINICAL

Added "For ICU patients: continuous physiologic data from high resolution ICU monitors (e.g. Moberg monitors)."

Section 7.2 (P. 35)

PROCEDURES - BIOSPECIMENS

Added optional language for CSF acquisition, and modified original language for whole brain collection.

- *This is a site-specific protocol item.* At some sites (subject to local IRB approval), cerebrospinal fluid (CSF) will be drawn for patients with ventricular catheters. The amount and frequency will be determined by the Site PI and approved by the Executive Committee.
- *This is a site-specific protocol item.* At some sites (subject to local IRB approval), in the case of death, the subject's next of kin will be contacted to request donation of the brain for banking, validation studies of imaging and biomarker findings, and further research.

Section 8.4 (P. 40)

SUBJECT COMPENSATION

Original language:

"In addition to incurred travel costs to arrive at the testing center, subjects in the CA and CA+MRI cohorts will receive financial compensation in recognition of the extensive in-person time required by the study. This compensation schedule will be given as follows:

[...]

For BA patients, all outcomes will be phone based. Outcomes at 2 weeks, 3 months, 6 months, and 12 months will each have a reimbursement rate of \$75.00. 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."

New language:

"In addition to incurred travel costs to arrive at the testing center, subjects in the CA and CA+MRI cohorts will receive financial compensation in recognition of the extensive in-person and/or phone time

required by the study. Individual sites have the ability to determine their own reimbursement rate per timepoint as approved by local IRB. The suggested compensation schedule to be given as follows:

[...]

For BA patients, all outcomes will be phone based. Outcomes at 2 weeks, 3 months, 6 months, and 12 months will each have a suggested reimbursement rate of \$75.00. 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.”

Section 9.7 (P.42)

Added new section regarding Waiver of Consent:

9.7 WAIVER OF CONSENT

This is a site-specific protocol item. Sites may elect to enroll qualifying patients initially incapable of informed consent who have no legally authorized representative available for surrogate consent. This can be done under a “waiver of consent” rule in the emergency setting in order to procure and process the baseline blood sample for biomarker analysis within 24 hours of injury. Application to use the “waiver of consent” can be submitted by each individual site to their local IRB for approval.

Sample language as follows:

“If the subject is not capable of self-consent and there are no legally authorized representatives to sign in person or via fax, every effort will be made to follow-through with the subject as soon as s/he is capable of informed consent. However, in these situations, and for those 18 years and older, the 'Waiver of Consent' will be used to complete the CRF, to draw the blood within 24 hours of injury and to process the blood for separation of plasma (within 30 minutes of draw) or serum (within 1 hour of draw) because of the critical acute time element involved.

These scenarios are very common in the context of TBI and in the past have prevented much needed data from being collected from patients who are incapacitated from their injury and hospitalization, and/or who are under the influence of drugs or alcohol. We would like to be able to include everyone falling under the inclusion criteria, hence the waiver.”