# DATA COLLECTION GUIDELINES

## Hyperbaric Oxygen Brain Injury Treatment (HOBIT) Trial

A Multicenter, Randomized, Prospective Phase II Adaptive Clinical Trial Evaluating the Most Effective Hyperbaric Oxygen Treatment Paradigm for Severe Traumatic Brain Injury

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# 1 General Guidelines

This trial uses electronic case report forms (eCRFs). The eCRFs in WebDCU are the only occurrence of these forms. PDF or paper representations of the CRF are considered worksheets only. These may be used as source documents or as data collection tools to prepare for completion of the eCRF, but are not original CRFs.

Paper worksheets are not required. Data may be directly entered into the eCRF from a source document (such as the electronic health record or worksheet), or directly data entered from a contemporaneous observation (in which case the eCRF would be the source document). If a paper worksheet is the first place the data are recorded, it is source documentation.

Every effort is required to avoid missing data, except as allowed by a skip pattern. However, if a data value is unknown and permanently unavailable, leave it blank and dismiss the warning.

If a data item is unknown or missing, leave it blank. Do not enter 0 (zero) for unknown or missing numerical data.

'Radio buttons' ⚪, indicate that you must choose only one answer.

'Check boxes' ⬜, indicate that you should 'check all that apply'.

Use the following format for all date fields: DD-MMM-YYYY (e.g., 31-JAN-2015)

Complete dates should be entered, whenever possible, for all date fields. If the complete date is not known, partial dates are allowed for select data points.

When multiple valid sources for a data item are available, such as heart rate, blood pressure, and ICP monitoring, then either: (1) All available data values must be used; (2) A decision must be documented regarding which values will be used consistently and why; or (3) A decision must be documented regarding why one value or a set of values was chosen for a particular subject. Ultimately, the site PI must determine the most valid source for data items to be used for subjects enrolled at his/her site when multiple valid values exist.

If another source is used, please enter a general comment indicating the source of the information.

## 2 **Source Documentation** (3 A's and 3 C's)

The **source document** for all data recorded in the CRF is the first location where those data are recorded. Source documents may be the electronic health record, paper medical records, paper worksheet representations of the study CRF or other worksheets or notes, or the eCRF itself (if data are observed and directly data entered). Source documents should be:

Accurate
Accurate, consistent and real representation of facts directly observed or otherwise reliably obtained and corroborated by observation.

Attributable
It should be clear who has documented the data on the source document. Attribution is typically evident in the electronic health record. When the source is a paper worksheet, the name of the person collecting the data and the date it was collected must be recorded on the worksheet. When directly data entered into the eCRF, attribution is to the WebDCU user completing the form unless documented otherwise in the eCRF.

Available
Original source documents or exact copies must be readily accessible to investigators, study monitors, and any auditors or inspectors. Originals must be maintained.

Complete
Source documents should not have gaps, omissions, or redactions. Missing components of sources documents should be identified and explained. A source document must be legible.

Consistent
When the same event is recorded in more than one source, all sources should report the same data. Discrepancies should be identified, explained, and the preferred source justified.

Contemporaneous
Data are recorded on source documents at the time that the observation occurs. Any delay or latency between the occurrence of the data and time the data are recorded on the source document must be identified and justified in the source document.

Modified from Chitra Bargaje, Good documentation practice in clinical research, Perspect Clin Res. 2011;2: 59–63

## 3 CRF Collection Schedule

| Form | Form Name | Baseline | Randomization | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Hospital Discharge | Day 30 | Day 90 | Day 180 | End of Study |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| N/A | Subject Enrollment | XM | | | | | | | | | | | | |
| F101 | Inclusion and Exclusion Criteria | XM | | | | | | | | | | | | |
| F102 | Randomization | | XM | | | | | | | | | | | |
| F104 | Adverse Event | | | ORM | ORM | ORM | ORM | ORM | ORM | ORM | ORM | ORM | ORM | ORM |
| F105 | Laboratory Tests | XM | | XM | XM | XM | XM | XM | XM | | | | | |
| F106 | Medical History | XM | | | | | | | | | | | | |
| F112 | Concomitant Medications | | | XM | XM | XM | XM | XM | XM | | | | | |
| F117 | Vital Signs | XM | | | | | | | | | | | | |
| F123 | Hospital Discharge | | | | | | | | | XM | | | | |
| F126 | End of Study | | | | | | | | | | | | | XM |
| F138 | Glasgow Coma Scale | XM | | XM | XM | XM | XM | XM | XM | | | | | |
| F156 | Glasgow Outcome Scale - Extended | | | | | | | | | | XM | XM | XM | |
| F172 | Surgical and Procedural Interventions | | | | | | | | | XM | | | | |
| F181 | Biosample Collection | | X[C3] | X[C3] | X[C3] | X[C3] And X[C4] | | X[C3] | | | | | X[C3] | |
| F212 | Informed Consent Log | X | | | | | | | | | | | | |
| F254 | NeuroImaging File Collection | XM | | XM | | | | | | | | | | |
| F269 | Abbreviated Injury Scale | | | | | | | | | | | | | XM |
| F274 | Pre-Hospital Events | XM | | | | | | | | | | | | |
| F275 | Study Therapy | | | XRM[C1] | XRM[C1] | XRM[C1] | XRM[C1] | XRM[C1] | ORM[C1] | | | | | |
| F286 | Pupil Reactivity | XM | | XM | XM | XM | XM | XM | XM | | | | | |
| F287 | Therapy Intensity Level Scale | | | XM | XM | XM | XM | XM | XM | | | | | |
| F296 | Demographics | X | | | | | | | | | | | | |
| F312 | Vital Status Search | | | | | | | | | | | | | X[c5] |
| F501 | Hourly Monitoring | | | XM | XM | XM | XM | XM | XM | | | | | |
| F502 | Ventilatory Parameters | | | XM | XM | XM | XM | XM | XM | | | | | |

O: Optional
R: Repeatable
X: Required
C1: Non-Control Subjects
C3: BioHOBIT subject
C4: BioHOBIT subject not randomized to control
C5: F126 End of Study, has a reason for termination that is not 'Study completed' or 'Death'

## 4 Subject Enrollment Form

The subject enrollment form is entered into WebDCU prior to entering any case report forms and includes the identifiers “Gender”, “Ethnicity”, “Race”, “Age”, “Date of informed consent”, “Informed consent was obtained prior to participation in the study, and Enrolled with exception from Informed Consent.”

**Gender:** Self-reported gender of the participant/subject. Gender is the socially constructed identity of sex. Gender is equated with phenotypic sex. Gender may differ from the sex of an individual determined genetically. For more information, see the NIH Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research and The Office of Management and Budget Directive No. 15.

**Ethnicity:** Category of ethnicity the participant/subject most closely identifies with. This is self-reported or self-identified data field that is required by the NIH. Choose one answer. Response is obtained by report of the participant/subject or caretaker. This field should be marked “Unknown” only if the subject/family members/medical records cannot provide the ethnicity. Please follow the NIH guidelines for reporting ethnicity:

> **Hispanic or Latino:** A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race.

**Race:** The patient's self-declared racial origination, independent of ethnic origination, using OMB approved categories. Choose all that apply. Response is obtained by report of the participant/subject or caretaker. This field should be marked “Unknown” only if the subject/family members/medical records cannot provide race. Please follow the NIH guidelines for reporting race:

> **American Indian or Alaska Native:** A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
> **Asian:** A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.
> **Black or African American:** A person having origins in any of the black racial groups of Africa.
> **Native Hawaiian or Other Pacific Islander:** A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
> **White:** A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

**Age:** Age should be obtained from objective documentation, such as a driver's license, other formal identification, or official record. Subject, family, or acquaintance can provide age in circumstances where objective documentation is not available.

**Informed consent was obtained prior to participation in the study**: Indicate if informed consent was obtained prior to participation in the study.

**Date of informed consent:** Defined as the date the LAR signed the informed consent.

**Subject enrolled with Exception from informed consent:** A situation that arises when a participant whose critical condition makes it impossible for the patient to give meaningful prospective consent, and it is also not feasible to obtain meaningful prospective consent from the patient's Legally Authorized Representative (LAR). Events that may lead to a prospective informed consent from LAR should be documented within F212, Informed Consent Log.

## 5 Screen Failure Report

The most current version of the Screen Failure Report is located in WebDCU™ under Toolbox > Project Documents. Paper versions of the Screen Failure Report will be reviewed during the monitoring visit, if applicable.

Enter screen failure reporting information for all patients 16-65 years of age who presented to the enrolling institution within 18 hours of blunt head trauma, had a GCS of 3-8 and were hospitalized but not randomized. Source document verification of the screening logs may be monitored by the HOBIT monitor. Sites should provide a comprehensive administrative report (trauma registry, EHR or other) of GCS 3-8 / intubated TBI patients in the time period requested by the monitor.

Sites that are required to track screen failures should enter the data monthly into WebDCU™. Screen failures for the previous month must be reported by the 10th of the following month.Sites that are required to track screen failures should enter this data into WebDCU™ within 5 days of screening.

Answer the 'Yes' and 'No' questions for each known reason for screen failure.

## 6 Site Case Report Forms (CRFs)

**Baseline**: From injury until randomization.

**Day 1:** From randomization until the end of the day (23:59pm)

**Day 2:** From the end of day 1 (midnight, 00:00) through 23:59 pm.

### HOBIT CRF Submission Timeline

| Form | Form Name | Timeline of Submittal |
|---|---|---|
| N/A | Subject Enrollment Form | Prior to Randomization |
| 101 | Inclusion and Exclusion Criteria | Prior to Randomization |
| 102 | Randomization | Prior to Randomization |
| 104 | Adverse Event | Serious Adverse events must be reported within 24 hours of discovery. All other adverse events within 5 days of discovery. |
| 105 | Laboratory Tests | Within 5 Days of Visit Date |
| 106 | Medical History | Within 5 Days of Visit Date |
| 112 | Concomitant Medications | Within 5 Days of Visit Date |
| 117 | Vital Signs | Within 5 Days of Visit Date |
| 123 | Hospital Discharge | Within 60 Days of Visit Date |
| 126 | End of Study | Within 5 Days of Visit Date |
| 138 | Glasgow Coma Scale | Prior to Randomization at Baseline visit. Other visits within 5 days of collection. |
| 156 | Glasgow Outcome Scale - Extended | Within 5 Days of Visit Date |
| 172 | Surgical and Procedural Interventions | Within 5 Days of Hospital Discharge |
| 181 | Biosample Collection | Within 5 Days of Visit Date |
| 212 | Informed Consent Log | Prior to Randomization and Within 5 Days of Visit Date |
| 254 | Neuroimaging File Collection | Within 5 Days of Visit Date |
| 269 | Abbreviated Injury Scale | Within 5 Days of Visit Date |
| 274 | Pre-hospital Events | Within 5 Days of Visit Date |
| 275 | Study Therapy | Within 10 Days of Visit Date |
| 286 | Pupil Reactivity | Within 5 Days of Visit Date |
| 287 | Therapy Intensity Level Scale | Within 5 Days of Visit Date |
| 312 | Vital Status Search | Within 5 Days of Visit Date |
| 501 | Hourly Monitoring | Within 5 Days of Visit Date |
| 502 | Ventilatory Parameters | Within 5 Days of Visit Date |

| | | |
|---|---|---|
| N/A | Screen Failure Report | Within 5 Days of Screening |
| N/A | Monthly Monitoring Log | Submitted monthly by the 10th day of the following month |

*Payment is contingent upon the subject's data being submitted.

### Form 101: Inclusion and Exclusion Criteria

Before this form can be submitted, Form 138 Glasgow Coma Scale (baseline) must be submitted in WebDCU™.

The purpose of the form is to capture eligibility violations. The form must be completed and submitted with all eligibility criteria questions answered. Eligibility violations may sometimes need to be reported even if they were not known or could not have been known at the time of enrollment. For a detailed description of the use of the word "known" on the eligibility form please refer to the a FAQ document that can be found in the ***HOBIT online toolbox.*** In a situation where an eligibility violation is discovered after randomization and submission of the form, this form should be updated to document the eligibility violation.

If a site is an approved EFIC site, they should answer 'Version 6' to question 25, and non-approved EFIC sites should answer 'Version 5' to question 25.

- Question 10 needs to be answered when 'Version 5' is chosen for question 25
- Question 24 needs to be answered when 'Version 6' is chosen for question 25.

Question 7 should remain unanswered unless one or more of the following criteria are met:

- Question 3 of Form 101 is answered 'Yes'
- Question 7 of Form 138 is answered '5'
- Question 8 of Form 138 is answered '7' or '8'

Question 17, contradiction to ICP monitor placement, is an inclusion/exclusion criteria that should be discussed with the HOBIT PI Hotline if there are any questions about eligibility. You may also refer to the ***Manual of Procedures*** for more guidance.

If the HOBIT participant is approved and enrolled without ICP monitoring, sites should document the following statement in the general comments on F101 - [Subject enrolled without ICP, approved by PI hotline on MM/DD/YYYY]. Additionally, sites should add an issues record to the Issues table in WebDCU with a similar statement.

***If you have questions pertaining to a participant's eligibility, please call the WebDCU™ HOBIT 24/7 Clinical Emergency Hotline at 1-833-HOBIT-PI (833-462-4874) to speak with someone.***

**Form 102: Randomization Form**

Before this form can be submitted and a randomization number assigned to the subject, the Subject Enrollment form, Form 138 Glasgow Coma Scale (baseline) and Form 101 Inclusion and Exclusion Criteria must be submitted in WebDCU™ with all eligibility criteria met.

Select the appropriate responses for this form. Submit the form to obtain a randomization assignment. Randomization cannot be undone. Once the randomized treatment is assigned, this subject is enrolled in the trial and must be followed until the end of study or withdrawal of consent.

***If you are unable to access the study database due to connectivity issues, please call the WebDCU™ Emergency Randomization Hotline at 1-866-450-2016 to request a randomization assignment.***

**Form 104: Adverse Event**

The adverse events (AEs) reporting form is used from enrollment through subject's End of Study. Serious adverse events (SAEs) occurring at any time between enrollment and subject's end of study are to be reported. All non-serious AEs must be reported from randomization through Day 6 or Discharge, whichever comes first.

Adverse Event Name

When reporting an AE, you should report the diagnosis and not each individual symptom if possible. It would be incorrect to report pneumonia as 4 separate events (fever, cough, chest pain, crackles). Pneumonia should be reported as one AE with the AE name (Question 01) being 'pneumonia'. The site PI is expected to use clinical judgment in describing the likely syndrome or complication. Diagnostic certainty is not required or expected. Report isolated symptoms as the AE name only when no coherent etiology or pathology is suspected.

Death, surgery, intubation, etc. are not adverse events. They are outcomes of adverse events. When a subject dies, has surgery, is intubated, etc. please enter the reason for the death, surgery, intubation, etc. in the response to Q01. If the subject dies after being withdrawn from life support and placed on comfort care secondary to their neurological injury, that should be reported in one of 2 ways. 1) If they were deteriorating neurologically, the AE should be reported as "neurological deterioration." In the vast majority of cases, the death should be reported this way. 2) In the unusual circumstance that the subject remained neurologically stable or improved, the SAE may be reported as "withdrawn from life support." The GCS at the time of enrollment

and the one closest to withdrawal from life support should be included in the SAE narrative. In addition, refrain from using abbreviations or sentences in AE names.

When entering the first 2-3 letters of the Adverse Event Name into the name field, the name will auto populate with a list of possible Adverse Event Names from the MedDRA code list. Choose the most appropriate name for the event you are entering. If the list does not appear, the name you are entering is not found in the MedDRA code list and you must choose a different name for your event, otherwise you will not be able to save the adverse event form.

Severity

Severity is often used to describe the intensity (severity) of a specific event (as in mild, moderate, severe myocardial infarction). However, the event itself may be of relatively minor medical significance (such as severe headache). Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Choose the one severity that best describes the investigator's assessment of the intensity of the AE. Severe events interrupt the participant's/subject's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating. Consequently, a change in severity may constitute a new reportable AE. Severity is not synonymous with seriousness. A severe rash is not likely to be an SAE. Likewise, a severe headache is not necessarily an SAE. However, mild chest pain may result in a day's hospitalization and thus could be an SAE.

The severity of adverse events will be documented using the grading system outlined in the NCI Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE). The CTCAE provides a grading (severity) scale for each AE term and AEs are listed alphabetically within categories based on anatomy or pathophysiology. The CTCAE (v 4.03) displays Grades 1-5 with unique clinical descriptions of severity for each AE based on this general guidance:

| CTCAE Severity Grading Summary | |
|---|---|
| Grade 1: | Mild AE |
| Grade 2: | Moderate AE |
| Grade 3: | Severe or Disabling AE |
| Grade 4: | Life-threatening AE |
| Grade 5: | Death related to AE |

The complete definitions of these grades are:

- Grade 1 - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated AE.

- Grade 2 - Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
- Grade 3 - Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4 - Life-threatening consequences; urgent intervention indicated.
- Grade 5 - Death related to AE.

For every AE, one should go to the CTCAE document and look up the AE being reported by name or category and review the diagnosis specific severity criteria. While it is tempting to choose a severity by gestalt, this should be avoided to ensure accurate and consistent reporting. It is also important to reference CTCAE before determining severity because not all grades are allowable for all AEs.

Seriousness

The seriousness of an AE is based on patient/event outcome or action.

Choose either Yes or No. This question should only be answered Yes if the outcome of the AE results in at least one of the following:

- Death
- Life-threatening situation
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect

An elective surgery or procedure planned prior to randomization is not an SAE, provided the condition has not been exacerbated since randomization.

All serious AEs must be data entered and submitted in HOBIT WebDCU™ within 24 hours of first knowledge of the event. Each clinical site PI is responsible for reporting SAEs to its own IRB/REB per their local IRB policy.

If an AE is serious, this provides a trigger that additional information must be provided by the site investigator. The site investigator then completes the Adverse Event (AE) form. Additionally, the site institution and/or IRB may also have an SAE form and procedures for reporting SAEs.

Relatedness to study intervention

One of the most important components of reporting is determining the cause of the SAE. It is imperative that the investigator assess SAE causality in terms of overall study participation and make an independent determination as to whether the SAE was thought to be related to any study-related activity (i.e., study intervention, test article administration, study-related tests or procedures). For each adverse event, the relationship to the study treatment must be recorded as one of the choices on the following scale:

| Algorithm to Determine Relatedness of Adverse Event to Study Agent | |
|---|---|
| **Unrelated** | The temporal relationship between treatment exposure and the adverse event is unreasonable or incompatible and/or adverse event is clearly due to extraneous causes (e.g., underlying disease, environment) |
| **Unlikely** | **Must have both of the following** 2 conditions, but may have reasonable or only tenuous temporal relationship to intervention. |
| | 1. Could readily have been produced by the subject's clinical state, or environmental or other interventions.<br>2. Does not follow a known pattern of response to intervention. |
| **Reasonable Possibility** | **Must have at least 2** of the following 3 conditions |
| | 1. Has a reasonable temporal relationship to intervention.<br>2. Could not readily have been produced by the subject's clinical state or environmental or other interventions.<br>3. Follows a known pattern of response to intervention. |
| **Definitely** | **Must have all 3** of the following conditions |
| | 1. Has a reasonable temporal relationship to intervention.<br>2. Could not possibly have been produced by the subject's clinical state or have been due to environmental or other interventions.<br>3. Follows a known pattern of response to intervention. |
| Modified for HOBIT [in which dose reductions and re-introduction of intervention do not occur, and in which the CDE required removal of the 'probably' designation] from: Adverse Events Reporting Requirements SOP. NIH-NIAID. http://www.niaid.nih.gov/ncn/sop/adverseevents.htm, accessed 11-30-04. | |

Date/Time of Onset

Record the date (and time) the adverse event started. There should be no AE start date prior to the date/time of randomization. Any AE that started prior to the randomization date/time belongs instead in the medical history. If an item recorded on the medical history worsens during the study, the date of the worsening is entered as an AE with the start date as the date the condition worsened.

Date of Resolution

Record the date the adverse event was resolved.

Outcome

The site should actively follow up with unresolved AEs at each subject contact until resolution or end of study, whichever comes first. Choose one outcome. The outcome of an AE may not be captured at the visit during which it was first reported, but must eventually be captured to provide a complete picture of the event. Entering the outcome of an AE may be deferred until the AE is resolved, or the participant/subject completes the study. For AEs that have not resolved at the time of a study visit, the outcome should be marked as "Continuing at end of study" or "Continuing at time of death" on the AE case report form.

Action taken

Indicate the type of action taken for adverse event in relation to study intervention. Choose all that apply.

Type of Event

The purpose of this question is to track certain types of events using specific case definitions created for safety monitoring in this trial. Careful attention to these definitions is essential when completing this question. Select the most appropriate term for the type of event for the AE term See study definitions of each event type in the ***Manual of Procedures***. If an event does not meet the specific study definition, then one should mark this question as "other adverse event". It is possible, for example, for an event to be named 'pneumonia' on Q01 because that diagnosis is made and treated by the clinical team, but for Q12 to be answered as "other adverse event" if the study definition is not met.

SAE Narratives

These sections are used to provide additional relevant details about Serious Adverse Events. This section should be as complete as possible but only include information pertinent to the SAE. These narratives should not include any identifying patient or site information.

To assist the medical monitors reviewing all SAEs, certain information is required for each SAE entered.

Describe the event concisely, but with enough detail to allow clinical evaluation of the event. Emphasize relevant facts. Do not report tangential or non-germane details. Do not identify any study participant, physician, or institution by name.

The following are specific items to include in the SAE narrative:

- Provide age, gender, most pertinent history and time/date of randomization.
- Include dates and times for the enrolling event and relevant procedures/clinical assessments.
- Include a description of what happened. Include only relevant clinical information (medical status prior to the event, signs and or symptoms).
- Summarize only relevant portions of the subsequent clinical course (including outcomes of treatment and relevant test/laboratory results: both positive and negative).
- Investigators may elaborate on their assessment of event relatedness to study intervention if desired to further explain their determination. Include a clear statement from the investigator stating whether the event was related to the study intervention.

Narrative templates for common events will be provided as a separate document. When available these will be found in the study toolbox and linked here.

Relevant Tests/Laboratory Data

Record relevant tests or laboratory data, including dates.

Other Relevant History, Including Pre-existing Medical Conditions

Record medical history including pre-existing medical conditions.

Investigator Review

Each SAE must be reviewed by a Site Investigator prior to data submission. The clinical judgment of the investigator is key to properly distinguishing and reporting AE in a meaningful way. Investigators' clinical judgment is key to making sure that related symptoms are reported as a likely syndrome or unified diagnosis rather than as separate events. Investigators' judgment is also needed to ensure that only clinically significant abnormal laboratory values are reported as AEs or SAEs rather than every value that is outside the normal range.

## Form 105: Laboratory Tests

If labs are collected more than once daily, the first labs of the day should be recorded on the CRF. If any values are abnormal and clinically significant, complete the AE form.

1. At the baseline visit
    a. All labs should be collected prior to randomization.
    b. If any values were collected after randomization they should be left blank.

    c. If one or more are collected prior to randomization but collected at a different time then those values should be entered into the corresponding fields. The time the value was collected should be entered in the general comments for the monitors review.
2. At the Day 1 visit
    a. These labs should be collected after randomization but on the same calendar day as randomization.
    b. If no other labs were collected on the same day as randomization then this Qa "Data Collected" should be No with a general comment explaining that the labs weren't collected after randomization.
    c. If any values were only collected prior to randomization they should be left blank.
    d. If one or more are collected after to randomization but collected at a different time then those values should be entered into the corresponding fields. The time the value was collected should be entered in the general comments for the monitors review.

### Form 106: Medical History

This form is intended to document both the data obtained from the patient, his/her family and the medical record while screening the patient, and pre-existing conditions that are discovered after randomization into the trial.

For pre-existing conditions discovered after a patient is randomized and after the Medical History CRF has been submitted, the Study Coordinator or data entry staff should edit the CRF accordingly AND enter a notation in the General Comments section at the bottom of the CRF. The General Comments notation should indicate the date the information became available and a brief description of the circumstances (e.g., On dd-mmm-yyyy pre-existing condition X revealed by patient when admitted for Y on dd-mmm-yyyy at Hospital Z.)

### Form 112: Concomitant Medications

At the Day 1 visit, indicate if the subject was receiving pressors/anticonvulsants at the time of randomization. At subsequent visits, indicate if the subject was on pressors/anticonvulsants at any point within the 24-hour period.

### Form 117: Vital Signs

Vitals recorded from an arterial line on the vital signs flow sheet(s) in the subject's medical record should be used whenever available. Record the date and time that vital signs were taken

closest and prior to randomization. The oxygen saturation recorded should be the lowest reliable pre-intubation oxygen saturation.

### Form 123: Hospital Discharge

This form should be completed after the subject is discharged from the hospital, or at the end of study if the subject is not discharged from the hospital. This form must be completed for every subject that is randomized.

Discharge is inclusive of release from the hospital, death while hospitalized or transfer from hospital.

If a subject or LAR declines/withdraws consents then Q02 "Discharge location" should be 'Other' and Q01 'Date of discharge' should be left blank.

Number of years of education: For years of education completed, after the age of 5, code the number of years attained normed to someone moving full time at the usual pace, i.e. a year that was repeated counts as only 1 year and the usual single-year full-time load completed over several years counts as 1 year. Certificate and technical programs do NOT count no matter how specialized. The number of years of typical completion of the relevant program is counted. If the subject obtained their education outside the United States, ask about their educational system to estimate the correct coding.

If years of education are unknown, the field can be left blank by dismissing the warning in WebDCU. Do not indicate an unknown answer with the value of 0.

### Form 126: End of Study

This form is required for all subjects enrolled in the trial. The end of study visit occurs at different time points depending upon the subject's disposition: If the participant completes the trial in its entirety, the End of Study form is to be completed following hospital discharge or after day 180 post-enrollment (whichever comes first). If the participant expires prior to the discharge or day 180 post-enrollment, the form should be completed when the investigator is made aware of the death. If the participant declines/withdraws consent for full participation prior to discharge day 180 post-enrollment, this form should be completed at the time that consent is declined/withdrawn. Study data collected prior to the subject's withdrawal, and any data collected from public records, may be retained.

If consent was withdrawn or declined due to an adverse event, an adverse event form should be completed for the subject. If the subject has died, a corresponding adverse event form should generally be completed for the subject that describes the event that resulted in the death (remember, death itself is not an AE).

Within the Subject CRF Binder tab pick the subject whose End of Study (EOS) is being completed. Click 'Add New Visit' and choose 'End of Study' from the pull down menu. Enter the date of EOS visit and click 'Add Visit' to populate the EOS form.

The **site PI** must review and affirm that the information reflected on all case report forms for the subject has been personally reviewed and is deemed to be accurate. This review is documented in items Q10 - Q12.

### Form 138: Glasgow Coma Scale

The GCS should be the most reliable documented GCS obtain by a qualified clinician. At Baseline this must be collected post resuscitation and prior to randomization. GCS should be obtained off sedation and paralytics. Subjects who are intubated and have a GCS motor score of 6 cannot be randomized.

For patients requiring craniotomy at baseline, the GCS can be pre- or post-craniotomy, provided it is the last reliable GCS before randomization.

Upon obtaining a reliable GCS, ensure that it is documented in the medical record for source document verification.

If a patient is intubated at the time of the assessment, the verbal score should be indicated as (1) None. If there are any concerns within the clinical assessment, these can be addressed with the CCC PIs.

More information on the Glasgow Coma Scale can be found in the ***Manual of Procedures***

### Form 156: Glasgow Outcome Scale - Extended

This form should be completed by a trained, certified and blinded assessor at 30, 90 and 180 days after randomization. See the ***Manual of Procedures*** on recording of GOS-E data.

Methods of Assessment

The GOS-E can be assessed either in person, by phone or using real time video. Those methods of assessment are defined as follows:

In person - Assessor is physically in the room with the subject at the time of assessment.

Telephone - Assessor has audio contact with the subject but no means of visual assessment.

Real-time Video - Assessor is not physically in the room with the subject but has real-time audio and video contact in order to perform the assessment. This type of assessment includes video conferencing, skype calls, and facetime.

The GOS-E format used in HOBIT incorporates logical skip patterns. This programmed pattern allows unnecessary questions to be skipped in WebDCU and is also reflected on the paper CRF. Source documents should match data entered in WebDCU. If there is any discrepancy between the paper and electronic CRFs, contact the Data Manager at the DCC for guidance.

**EXAMPLE 1:** Q02a is answered 'Yes'. The assessor should have asked and received responses for Q02b and Q02c. Enter data as it appears on the paper CRF.

**EXAMPLE 2:** Q02 is answered 'No'. The assessor should have skipped asking Q02b and Q02c. However, these questions were asked and responses given, as indicated on the paper CRF. Contact the Data Manager at the DCC for assistance.

### Form 172: Surgical and Procedural Interventions

Enter all surgical and procedural interventions from injury through Day 6 or Hospital Discharge, whichever comes first. Select the appropriate code(s) that correspond with surgical/procedural intervention(s).

Codes should be included ONLY when a surgical or procedural intervention is present.

**EXAMPLE 1:** A brain tissue oxygen monitor is initially placed and recorded on F172. There are mechanical issues with the monitor or the twist drill hole into which it was placed, requiring removal, assessment and reinsertion. The monitor is replaced into the same twist drill hole. This would not be considered a surgical/procedural intervention and would not be recorded.

**EXAMPLE 2:** A brain tissue oxygen monitor is initially placed and recorded on F172. There are mechanical issues with the monitor or the twist drill hole into which it was placed, requiring removal, assessment and reinsertion. The monitor is unable to be replaced into the same twist drill hole and a new hole must be drilled. Even if the same monitor is reused, this would be considered a surgical/procedural intervention and would be recorded.

### Form 181: Biosample Collection

This form is designed to record the blood and CNS sample data for Bio-HOBIT subjects. All instructions pertaining to collection and submission are outlined within the ***Bio-HOBIT Manual of Procedures***.

### Form 212: Informed Consent Log

The ICL-CRF is a living CRF that should be updated on a rolling basis in chronological order as soon as new information is available until a final outcome has been reached. The tracking process should continue until written consent (or revocation) is obtained. It is expected that a concerted effort will be made to identify and locate an LAR/guardian and obtain a consent decision in the first 24 hours of enrollment, except in rare circumstances (no LAR identified,

LAR not available, patient identification is unknown, patient expires prior to consent being obtained, etc.).

Subjects enrolled under EFIC with no known LAR will be consented if deemed competent (ability to verbalize understanding of the Informed Consent Form), before reaching the end of study [or discharge, whichever comes first].

In the rare case where no LAR/guardian consent is obtained and the subject remains incapable of consent at end of study, documentation of the attempt process and condition of the subject will be recorded on the Informed Consent Log CRF.

In help completing the ICL CRF fields, the following clarifications have been provided.

The first attempt on the ICL-CRF should always capture whether or not an LAR or another family member was at the patient's bedside prior to randomization; e.g., no LAR or family member present, LAR or family member at bedside but seeking no objection was not feasible, or it was, etc.

Column C: Contact Person

Three options are available: Subject, LAR, and Other. Subject and LAR are strictly reserved for attempts made directly between the study team and the subject or the LAR/guardian. In cases where someone else is looking for the LAR or reporting back on subject status, the code: Other should be used.

Column D: Description

Include details such as who made the attempt and related information, e.g.,

- Patient's nurse contacted; no family has been present to see patient
- Per ED social work, pt identity unknown at this time
- According to SW and bedside RN, patient's husband will be in later in the day
- Patient remains unidentified. Family or friends are not present per clinical team
- Family located and notified of hospitalization-family lives out of town-will be here ASAP
- Notified patient's sister. Sister stated that she did not want to make any decisions
- The study was explained to the patient's sibling via telephone. The right to refuse continued participation on their behalf was discussed. At this time, sibling has no objection to subject staying in the study

Column E: Outcomes

Consent obtained: to be used when the contact person (Column B) = LAR or Subject and they have signed the consent form.

Consent declined: to be used when the contact person (Column B) = LAR or Subject and they have refused to sign the consent form or they have signed the Informed Withdrawal Addendum.

Notification only: This code can be applied to anyone who has had direct communication with the study team about HOBIT.

Notification only – Subject deceased: should be selected when a subject has expired prior to the LAR having any contact with the study team about the trial.

No determination of consent or notification: Commonly used when: (1) subject ID is unknown, (2) LAR is unknown or unavailable, (3) subject continues to have altered mental status, etc.

NOTE: As attempts made to obtain consent reflect an outcome code above the previously one used, that new outcome code should be carried through for ongoing attempts made until a code higher on the list, is obtained. Example: If Notification only is obtained, but future attempts do not result in consent declined or consent obtained, "Notification only" would continue to be carried forward.

LAR/Subject Post-enrollment Survey

While ongoing attempts are being made to collect the LAR/Subject Post-enrollment Opinion Survey, select "Other." After a final survey decision has been reached, this question should be completed with one of the three final codes: Completed, Not given or Refused.

### Form 254: Neuroimaging File Collection

This form is only collected at the baseline and Day 1 visit. The Head CT files will be uploaded into WebDCU™ utilizing the secure IBM Aspera® web-based platform. Instructions for Aspera can be found in the ***HOBIT Imaging Core Lab Manual*** within the [Project Documents] under [Toolbox] in WebDCU.

The baseline images should be the first non contrast head CT closest to injury time, and before any surgery. If this scan is not available, reach out to the CCC.

### Form 269: Abbreviated Injury Scale

The information on this form should be collected from the trauma registry. This form is not due until the subject has completed the study. The Abbreviated Injury Scale is an anatomical scoring system first introduced in 1969. Since this time is has been revised and updated against survival

so that it now provide a reasonably accurate way of ranking the severity of injury. The latest version of the AIS score is

the 1990 revision. Injuries are ranked on a scale of 1 to 6 with 1 being minor, 5 severe and 6 an unsurvivable injury. This represents the "threat to life" associated with an injury and is not meant to represent a comprehensive measure of severity. Typically, the AIS is scored by experienced professional at each site under the auspice of the Trauma Registry - American College of Surgeons. The scoring should be completed using the AIS Manual for coding. The study team should not be calculating these scales. Please obtain the information from the trauma registry after the subject is discharged from the facility. It may take 1-2 months for this information to be available.

### Form 274: Pre-hospital Events

This form documents injury-related events occurring prior to hospital arrival.

### Form 275: Study Therapy

This form should be completed for each treatment dive or treatment dive attempt. This form will not be posted for subjects randomized to the control group. Q02 "Study treatment initiated" should be 'Yes' if the patient leaves the ICU to go to the hyperbaric chamber. If this happens and the HBO treatment does not occur please document that reason in Q24 "Reason for abort". For subjects where dives are permanently discontinued, there should still be a total of 10 forms posted. When treatments are discontinued permanently please provide an explanation in the general comments. Q11 "Peak ICP greater than 22 mmHG was sustained for over 20 minutes during study treatment" is inclusive of both NBH and the dive.

**EXAMPLE 1:** The subject is at the Day 2 visit with one successful dive on Day 1 and two instances of PF ratio less than or equal to 200 on Day 2. HBO treatments are permanently discontinued as instructed in the ***Manual of Procedures***.

**ACTION:** Continue uploading study therapy forms as would have been scheduled prior to discontinuation. Indicate the reason for not initiating subsequent dives 4-10 as 'Permanently discontinued'. . Provide any pertinent information as general comments if clarification is necessary.

Dive Log Upload

The dive logs of **all** subjects randomized to HBO treatment at each site must be uploaded to WebDCU. A dive log should not be uploaded when study treatment is not initiated or if a subject receives NBH only.

**EXAMPLE 2:** The subject is at the Day 3 visit with four successful dives over Days 1 and 2. GCS has improved to following commands and HBO treatments are permanently discontinued.

**ACTION:** Continue uploading study therapy forms as would have been scheduled prior to discontinuation. Indicate the reason for not initiating subsequent dives 5-10 as 'Permanently discontinued'. Provide explanation in general comments that patient GCS improved to the extent applicable.

### Form 286: Pupil Reactivity

This form documents the reactivity of the pupils at baseline and each day on days 1-6.

### Form 287: Therapy Intensity Level Scale

This form should be completed beginning on Day 1 and for each subsequent day. The scale is designed to quantify the intensity of therapeutic interventions used to control ICP. It assigns numerical values to each different treatment modality and aggregates the individual values into a summary score. See the ***Manual of Procedures*** for guidelines on recording therapeutic intensity levels.

If the subject has different intensity levels on the same day, the highest intensity should be recorded.

### Form 296: Demographics

This form is intended to capture basic demographic information. It is important that all demographic information be verified through either self-report by the subject, medical records, or by a reliable individual accompanying the subject.

Month and Year of Birth: This information should be obtained from objective documentation, such as a driver's license, other formal identification, or official record. Subject, family, or acquaintances can provide age in circumstances where objective documentation is not available. The only information needed for this question is the month and year of birth.

Ethnicity: Category of ethnicity the participant/subject most closely identifies with. This is self-reported or self-identified data field that is required by the NIH. Choose one answer. Response is obtained by report of the participant/subject or caretaker. This field should be marked "Unknown" only if the subject/family members/medical records cannot provide the ethnicity. Please follow the NIH guidelines for reporting ethnicity and race:

Hispanic or Latino: A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race.

Race: The patient's self-declared racial origination, independent of ethnic origination, using OMB approved categories. Choose all that apply. Response is obtained by report of the participant/subject or caretaker. This field should be marked "Unknown" only if the

subject/family members/medical records cannot provide the ethnicity. Please follow the NIH guidelines for reporting ethnicity and race:

- American Indian or Alaska Native: A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
- Asian: A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.
- Black or African American: A person having origins in any of the black racial groups of Africa.
- Native Hawaiian or Other Pacific Islander: A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
- White: A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

### Form 312 Vital Status Search

To minimize bias due to missing outcome data, at minimum, we will strive to obtain vital status/death data from all enrolled participants. This includes those who are deemed "lost to follow-up" and those who withdraw from the study. For these participants, we ask enrolling sites to review publicly available data sources such as obituaries, or other public records of vital status/death after the 6 month visit date. Per FDA guidance, "an investigator may consult public records, such as those establishing survival status".

Findings from this search should be documented on the F312 Vital Status Search form in WebDCU. This is a repeatable form so the site can complete multiple vital status searches on a subject.

### Form 501: Hourly Monitoring

When a HOBIT participant is approved to be enrolled without an ICP monitor; the rule violation dismissal should be an explanation such as [No ICP monitor placed, approval obtained on XX/XX/XXX]

Mean arterial pressure (MAP)

MAP will be monitored daily during the first 5 days of enrollment. The clinical team will be trained to record hourly MAP values on ICU flowcharts at the start of each clock hour (for example 9 am to 9:59 am, or from 10 am to 10:59 am). MAP measurements that appear erroneous will be repeated for verification, prior to recording them. During episodes of

hypotension (MAP<70 mmHg), MAP should be recorded every 15 minutes on the ICU flowsheets, until MAP improves. Using the ICU flowsheet as the source document, the study team will document whether the MAP during any given clock hour was <70 mmHg (episode of hypotension) in WebDCU. If the clock hour MAP was less than 70 mmHg, the lowest MAP recorded during that hour will also be documented. If the lowest MAP during any hour is >70 mmHg, the lowest MAP variable will be left blank for that hour. Whenever the MAP is <70 mmHg, please document a corresponding ICP obtained at the same time. This will allow accurate calculation of the CPP.

Cerebral perfusion pressure

CPP will be monitored daily during the first 6 days of enrollment. The clinical team will be trained to record hourly CPP values on ICU flowcharts at the start of each clock hour (for example 9 am to 9:59 am, or from 10 am to 10:59 am). During episodes of brain tissue hypoperfusion (CPP<60 mmHg), CPP should be recorded every 15 minutes on the ICU flowsheets. CPPs may be calculated from ICP and MAP measurements. Using the ICU flowsheet as the source document, the study team will document whether the CPP during any given clock hour was <60 mmHg (episode of brain tissue hypoperfusion) in WebDCU.

CPP should be calculated from ICP and MAP values taken close to the same time point whenever possible. For instances where ICP and MAP values are taken at separate times within the hour, CPP should still be calculated and recorded from these values.

See the ***Manual of Procedures*** for guidelines on recording intracranial pressure, therapeutic intensity levels, and brain tissue partial pressure of oxygen.

### Form 502: Ventilatory Parameters

The partial pressure of oxygen (PaO2) obtained from arterial blood gas (ABG) measurements should be documented at midnight, 8am and 4pm daily, during the first five days of enrollment. Do not use the the PaO2 value that has been corrected for temperature if entered in the flowsheet. At each of the stated time points, PaO2 values from the ABG obtained closest to that time point should be documented.

Similarly, the FiO2 and PEEP should be documented at midnight, 8am and 4pm daily, during the first five days of enrollment. These values can be obtained from ventilator/respiratory therapy flowsheets.

If there was an arterial blood gas measurement close to the hour time point, enter values at the time of arterial blood gas measurement. Values for another time point should not be duplicated because no other measurement was taken. For example, if no ABG was taken at midnight, do not enter values from the previous day or from 0400 of that day.

If there was not an arterial blood gas measurement close to the hour time point, enter values measured closest to the hour.  Add +/- here to better indicate that previous day or duplicate values should not be used.

## 7 Monthly Follow-up Interview

The site study coordinator will hold monthly follow-up phone calls with all enrolled subjects/LAR during their time of enrollment (first 6 months post-randomization) and maintain a log of these calls. These calls are essential to maintaining contact with subjects/LAR and decreasing the likelihood of "loss to follow-up" at the 6-month visit. During these calls, study coordinators should inquire about the occurrence of any adverse events and ensure that subject/LAR's contact information is accurate and not expected to change in the coming month. The Monthly Follow-up Log form should be completed after these calls.

If the subject or relative/caregiver/friend is unable to be contacted, there should be a note added to reflect the attempt(s).

If the subject has experienced any adverse events since last contact, the coordinator must complete Form 104 Adverse Event.  The AE should be reported in WebDCU under the most recent visit (Hospital Discharge, Day 30, etc.).