Section 8

Continuing Review of Ongoing IRB-Approved Research (Revised 7/1/10)

The IRB shall conduct continuing review of all research activity in compliance with 45 CFR 46 and 21 CFR 56. Continuing review is required for all research protocols approved by the IRB at TMH (unless the protocol was categorized as “exempt” by the IRB at the time of submission) for the term of the research, as long as individually identifiable follow-up data are being collected or analyzed.

It is the responsibility of the principal investigator (PI) to comply with continuing review requirements.

Continuing review includes, but is not limited to, the following:

8.1 Progress Reports
8.2 Re-Activation of Terminated Protocols
8.3 For-Cause Compliance Audits
8.4 Routine Audits
8.5 Modifications (Amendments)
8.6 Protocol Exceptions
8.7 Protocol Violations
8.8 Adverse Events / Unanticipated Problems
8.12 Termination of a Protocol
8.13 Withdrawal of a Protocol
8.14 Other Activity as Determined by the IRB

8.1 Progress Reports (Previously Continuation Review) – (Revised 7/1/10)

According to federal regulations, a research protocol can only be approved for a maximum of 365 days. Within that time period, continuing review is conducted at intervals specified at the time of initial approval. Those intervals are based on the degree of risk to study subjects. If the risk/benefit ratio changes at any time during the study, the PI is obligated to notify the IRB; the IRB has the authority to modify the continuing review interval and/or request changes to the protocol. The IRB also has the authority to require additional information at any time or to request an audit of the research to assure the safety of subjects and compliance by the research team.

To renew the approval period, the PI must submit a progress report and any requested relevant documents to the IRB before the project’s expiration (the date at which the current approval ends). Since the IRB does not have the authority to extend the approval period beyond the expiration date, it is essential that the PI submit a complete progress report by the due date set by the IRB.

It is the PI’s responsibility to comply with institutional policy and provide the IRB with the required progress report. As a courtesy, the IRB may provide a reminder to the PI to submit the progress report in advance of the project’s expiration date. If the PI successfully complies with the progress report request by the due date set by the IRB, the study will be presented at the next convened IRB meeting prior to renewal.
When continuing review of a research protocol does not occur prior to the end of the approval period specified by the IRB, IRB approval expires automatically. All research activities must cease and desist. Federal guidance indicates that short-term continuation of the research procedures beyond the IRB approval date may be permissible for the safety of enrolled research subjects that involve therapeutic intervention or interaction, if the investigator is actively pursuing renewal with the IRB, and the IRB believes that over-riding safety concerns or ethical issues are involved. There must be notification, in writing, to the Office of Research/IRB of all such situations, including a justification for interaction while the study is in the process of being re-activated. It is critically important that the investigator re-activate the protocol rapidly (see Re-activation of Terminated Protocol).

If a progress report is submitted and received prior to the expiration date but is deficient, the Office of Research/IRB will contact the PI/Research Coordinator with details regarding the deficiencies. If a complete and correct progress report is not received within the required time frame, the project is subject to the same termination procedures outlined above. The IRB is not authorized to extend the approval period for any research project.

8.2 Re-activation of Terminated Protocols (Revised 7/1/10)

A protocol that has been terminated, for any reason, cannot be re-activated unless it is re-reviewed and approved by the IRB. If a PI wants to re-activate a terminated protocol, he/she must submit a progress report within 90 days of the study expiration date. If a progress report – continuation review is not submitted within 90 days of the expiration date, the PI must re-submit it to the IRB in accordance with the requirements for new protocols (see How to Submit a Protocol to the IRB).

In addition to the protocol application, the PI may be required to submit a Report of Major Protocol Violation (Form 8c) to the IRB, detailing the circumstances which led to the protocol closure, along with his/her reasons for re-activating the protocol. If termination was due to administrative problems (e.g., a delinquent progress report), he/she must include a description of the corrective action he/she has taken in order to avoid such closures in the future.

8.3 For-Cause Compliance Audits (Revised 7/1/10)

When necessary, the IRB may request information beyond regular progress reports in order to ensure the rights and welfare of research subjects are protected. Upon discovery of a potential problem, the IRB or IRB Chair/designee will consider the issues and has the authority to suspend a protocol if a deficiency or situation poses a risk to subjects.

The IRB will notify the Office of Research/IRB in writing with a summary of the issues and ask that a “for-cause” audit be conducted. The Office of Research/IRB will notify the
PI in writing that an audit has been requested. The letter will outline the reason for the request and detail any information that is needed. The PI will be given adequate opportunity to respond. The Office of Research/IRB staff or designee will arrange a time to review the investigator’s study files and any other information necessary for the conduct of the audit. The IRB shall be kept apprised of any such action at their bi-monthly meeting. If the Office of Research/IRB audit indicates monitoring is necessary to investigate an immediate concern regarding the safety of study subjects, the IRB Chair/designee may act accordingly without convening an IRB meeting, however, no protocol may be permanently terminated without the concurrence of the full Board at a convened meeting.

Under Department of Health and Human Services regulations, a for-cause suspension of IRB approval must be reported to Office of Human Research Protections (OHRP). Any suspension resulting from a for-cause audit will be immediately reported to the Institutional Official, department chair, funding agency (if applicable), OHRP, and, if a drug or device is involved, the FDA. Other IRBs that are relied upon by the IRB at TMH may also be notified regarding findings regarding investigator compliance as appropriate.

For-cause audits may also be prompted by information obtained from sources outside the IRB, such as internal/external whistleblowers, regulatory agencies, industry sponsors, or research subjects. Information from any of these sources that raise concerns about a protocol will be directed to the Office of Research/IRB.

### 8.4 Routine Audits (Revised 7/1/10)

The Office of Research/IRB will conduct routine audits of IRB approved studies. The IRB, in conjunction with the Office of Research/IRB, will select the studies to be audited. The goals of the routine audits are to:

- assure protection of human subjects and data integrity,
- provide education and training to research staff,
- ensure that federal, state, and institutional regulatory standards are met.

The Regulatory Readiness Coordinator or designee will notify the PI of the audit in writing and the Office of Research/IRB staff will arrange a time to review the investigator’s study files. The audit process will usually include an inspection of the IRB files for the study and an on-site review of the investigator's files and records including:

- study personnel CVs and licenses,
- source documents and case report forms,
- regulatory binder documents,
- review of information about recruitment and the consent process,
- informed consent forms (blank and signed versions),
- subject files and data,
- subject inpatient or outpatient medical records as appropriate,
- drug or device accountability records,
• study samples and shipping receipts,
• laboratory licenses and certifications,
• any other documents deemed appropriate.

The Office of Research/IRB will generate a report summarizing the audit findings and recommendations. The Office of Research/IRB will send a draft version of the audit report to the PI for review and will provide the PI with adequate opportunity to respond. A final version will be disseminated to the PI, the IRB, the Office of Research/IRB and appropriate health system leadership. Any routine audit found to have significant issues will be presented to the IRB, which will determine if any action is required (i.e., enrollment hold, etc.). The PI will be required to develop a corrective and preventive action plan, which may require follow-up by the IRB or Office of Research/IRB.

**Note:** Significant findings may also be reported to external authorities as required (e.g., OHRP, FDA, etc.).

### 8.5 Modifications (Reviewed 7/1/10)

Changes (amendments/modifications) to a protocol **may not** be initiated without prior IRB approval, except when necessary to eliminate **immediate** hazards to the subjects. When changes are implemented to eliminate an immediate hazard, the IRB must be notified of the change promptly (within 3-5 business days).

**8.5.1 Major modifications** are changes to the protocol that alter the risk/benefit ratio for study subjects, that significantly change or affect the conduct of the study, and include any new information that may affect safety and/or willingness of subjects to participate.

**8.5.2 Minor modifications** are changes that do not alter the overall risk-benefit profile of the study, would not potentially affect the willingness of enrolled subjects to remain in the study, or the willingness of potential subjects to enroll in the study, and do not alter the scientific validity of the study design.

It is the responsibility of the PI to submit, in a timely manner, all protocol modifications, revised consent forms, changes in investigators, changes to FDA Form 1572 (for clinical trials), and any other information which may affect the conduct of the research study.

Minor changes in the protocol and/or consent form, may be reviewed through the expedited review procedure (see *Expedited Review*). However, all other changes will be reviewed by the IRB at a convened meeting, in which case deadline dates for submission apply.

### 8.5.3 How to Submit Modifications to the IRB (Revised 7/1/10)

A request for a change in key personnel or other study modifications are summarized...
and reported to the IRB using *IRB Form 8a*. This form should accompany the **complete revised version of the modified document** (e.g., revised protocol, revised consent form, etc.) with an explanation of the modification and its impact on the risk/benefit assessment written by the PI.

**8.6 Protocol Exceptions** (Revised 7/1/10)

A protocol exception is any **temporary** protocol deviation that is approved by the IRB **prior to its initiation**, e.g., enrollment of a subject who does not meet the eligibility criteria. An exception request form (*IRB Form 8b - Request for Protocol Exception*) gives investigators the opportunity to request a change in procedure and/or protocol activity for a single, isolated event. The PI should only request approval for exceptions that could affect a subject’s safety, welfare, comfort or rights.

**8.6.1 How to Request a Protocol Exception** (Reviewed 7/1/10)

In order to obtain approval for a protocol exception, the PI must submit a request to the IRB using *IRB Form 8b*. The form should include a description of the requested exception and a justification for deviating from the protocol. All approved protocol exceptions should be listed on the progress report.

**8.6.2 IRB Response/Action** (Revised 7/1/10)

The Office of Research/IRB will process protocol exception requests. Each request will be evaluated on a case-by-case basis by the IRB Chair or designee, and when appropriate, by the convened IRB committee. Investigators will be informed in writing regarding the IRB’s decision. No exception may be implemented without IRB approval.

**8.7 Protocol Violations** (Revised 7/1/10)

A protocol violation is a **deviation that is not approved by the IRB** prior to its initiation or implementation. Protocol violations may be major or minor:

**A major protocol violation:**

- Affects subject safety
- Damages the scientific integrity of the data collected
- Affects a subject’s willingness to participate in the study

**A minor protocol violation:**
• Does not affect subject safety
• Has no effect on value of the data collected
• Does not affect a subject’s willingness to be in a study

Examples of **major protocol violations** include (but are not limited to):

• Failure to obtain informed consent (i.e., no documentation of informed consent, consent obtained after study procedures were initiated)
• Informed consent for IND/IDE studies obtained by unauthorized individuals (i.e., someone other than a licensed physician investigator)
• Enrolling a subject who does not meet inclusion/exclusion criteria
• Use of study procedures not approved by the IRB
• Failure to report a serious adverse event to the IRB and/or sponsor
• Failure to perform a required lab test that could affect subject safety or integrity of data
• Error in dispensing or dosing of drug/study medication
• Error involving use of a device
• Study visit conducted outside of required timeframe, only if it affects subject safety
• Failures to follow safety monitoring plan
• Failure to submit a continuing review application to the IRB before study expiration
• Missing subject signature on consent form
• Missing investigator/person consenting signature on consent form
• Use of invalid consent form (i.e., use of outdated or unapproved consent form)
• Enrollment of subjects after IRB-approval of study expired

Examples of **minor protocol violations** include (but are not limited to):

• Missing original signed and dated consent form (only photocopy available)
• Inappropriate documentation of informed consent, including:
  o Copy not given to the person signing the consent form
  o Someone other than the subject dated the consent form
• Deviations from the approved study procedure that do not affect subject safety or data integrity
  o Study procedure conducted out of sequence
  o Omitting an approved portion of the protocol
  o Failure to perform a required lab test
  o Missing lab results
  o Study visit conducted outside of required timeframe
• Failure of subject to return study medication

It is the responsibility of the PI to determine if a violation is major or minor. **Major protocol violations must be reported to the IRB within ten (10) working days of discovery.** Minor protocol violations may be reported at continuing review. Reports of protocol violations should be submitted to the sponsor according to the sponsor’s protocol.
8.7.1 How to Report a Protocol Violation to the IRB (Revised 7/1/10)

Major protocol violations should be submitted to the Office of Research/IRB using IRB Form 8c - Report of Major Protocol Violation. Minor protocol violations may be reported and detailed on the Minor Protocol Deviation Table (IRB Form 8e) and submitted with the Progress Report form at the time of continuing review.

8.7.1.1 Correcting Protocol Violations (Revised 7/19/10)

The PI is responsible to ensure that a systematic review of protocol violations is conducted. The review should determine the root cause of the problem and address the underlying issue to prevent a recurrence. The root cause analysis includes the following steps:

- Define the problem/gather the facts
- Assemble an interdisciplinary team
- Determine the sequence of events
- Identify contributing factors
- Select root causes
- Develop corrective action & follow-up plan

Any Report of Protocol Violation which does address the underlying systems issues will be returned for correction.

Responding to Violation/Deviation - Whether the seriousness of a protocol violation/deviation is described as minor or major, it should succinctly and completely state how the outcome differed from the expectation. The investigator should identify the underlying systems issue responsible for the violation/deviation. A plan developed with the appropriate stakeholders to modify the system and an implementation plan based on a root cause analysis to prevent future occurrences.

A root cause analysis (RCA) is a problem solving method used to uncover the basis for problems or incidents. Addressing only a sign or a symptom of the problem does not eliminate it. Directing focused attention to eliminating the root cause of a problem using a systems approach offers an improved opportunity to minimize or eliminate recurrence of the issue. Looking at the systems that cause the event removes distractions of personalities and personal agendas promoting an atmosphere of transparency and safety.

An RCA is done after an incident occurs. When implementing a new process or procedure, conducting a failure mode and effects analysis (FMEA) can help develop systems that engineer processes and procedures which prevent problems from occurring. There are several methodologies and tools that may be used to define a root cause analysis. The primary principals needed are:

1. Identify the root cause of a problem in order to create effective corrective actions that will prevent that problem from ever recurring.
2. Perform a systematic investigation, with conclusions and the root cause backed up by documented evidence.
3. Stick with the analysis, there is always one true root cause for any given problem.
4. Establish a sequence of events or timeline to understand the relationships between contributory factors, the root cause and the defined problem.
5. Reduce the instances of problems occurring over time within the environment where the RCA process is operated.

Tools to help with an RCA:

- Cause & Effect Diagrams, Ishikawa Diagrams or Fish Bone Diagrams
- Causal Factor Tree Analysis
- Current Tree Reality (Theory of Constraints)
- Five Whys
- Flow Charts

These are common quality assurance/improvement tools. Please ask for assistance if you are not sure how to proceed.

An example of an unacceptable protocol violation/deviation corrective action plan:

**Event:** The pre-study potassium was not obtained.
**Reason for event:** The sample was hemolyzed.
**Corrective action plan:** The study coordinator will be more diligent.

An example of an acceptable protocol violation corrective action plan:

Asking “Five Whys” was the key to determining the cause of the issue for this event.

**Event:** The study was not renewed prior to expiration date.
**Reason for event:**
- The root cause analysis determined that there was not a tracking system in place to alert principal investigator/study coordinator in advance of expiration date to renew the study.
**Corrective action plan:**
- When the approval letter is received for each study, the study expiration date will be noted. A date six weeks prior to expiration date will be entered into electronic calendars to automatically alert research team that study renewal is due.
- Tracking log (spread sheet of studies) – including study name and expiration date, date needed to submit renewal packet to IRB, responsible parties identified.

Any Report of Protocol Violation which does address the underlying systems issues will be returned for correction.

**8.7.2 IRB Response/Action (Revised 4/1/10)**

Reports of major protocol violations are reviewed by the IRB chair or designee, Administrative Liaison/IRB and/or Regulatory Readiness Coordinator. Further inquiry or review may be initiated depending on the violation. If the violation proves to be serious,
the IRB chair or designee may choose to suspend or terminate the protocol. The report and any action taken by the IRB chair or designee, Administrative Liaison/IRB and/or Regulatory Readiness Coordinator on behalf of the IRB will be reported at the next convened meeting.

If review indicates that the violation is a result of non-compliance, the matter may be referred to the full IRB for further consideration. Actions taken to suspend or terminate a study due to a major protocol violation will be reported to the Institutional Official, the department head (as appropriate), the FDA (as appropriate), any funding agency (as appropriate), and the OHRP (as appropriate). Any subsequent action, such as changing or lifting a suspension will also be reported to the appropriate agencies and/or department heads. Reports may also be shared with other IRBs having responsibility for the study. Investigators will be informed in writing of all IRB inquiries and determinations.

8.8 Adverse Events/Unanticipated Problems (Reviewed 7/1/10)

It is the responsibility of the PI to promptly report any serious problems involving risks to subjects or others to the IRB. This reporting is in addition to, and does not supplant, periodic progress reports (see Progress Reports).

8.8.1 Definitions (Revised 7/1/10)

8.8.1.1 Adverse event (Revised 7/1/10)

An adverse event is any undesirable sign, symptom, medical, psychological condition which may or may not be related to the investigational drug/device/intervention. An existing medical condition/disease state present prior to beginning an investigational drug/device/intervention is considered an adverse event only if the condition deteriorates after the study treatment/intervention begins.

Any undesirable or unintended effect in human research subjects as a result of the collection of protected health information. Adverse events also include any problems associated with the use of an investigational drug/device/intervention that adversely affects the rights, safety or welfare of subjects.

Please note that sponsored studies often include a section defining adverse events. The PI is cautioned to adhere to the most stringent definition when assessing the situations to determine what should be reported.

8.8.1.2 Serious Adverse Event (SAE) (Revised 7/1/10)

A serious adverse is any undesirable sign, symptom, medical condition which may:

- result in death,
- be life-threatening (i.e., the subject was at risk of death at the time of the event. It does not include events that hypothetically might have caused death if it were more severe),
• require hospitalization or prolongation of existing hospitalization,
• result in persistent or significant disability/incapacity,
• constitute a congenital anomaly/birth defect,
• require intervention to prevent permanent impairment/damage (devices),
• be medically significant and which the investigator regards as serious based on appropriate medical judgment or
• result in unanticipated serious risk/harm to subjects and others.

8.8.1.3 Unexpected adverse event (Revised 7/1/10)
Any adverse event not identified by nature, severity and frequency in the protocol or the investigator’s brochure.

8.8.1.4 Unanticipated problem (Revised 7/1/10)
Any harmful or unfavorable non-medical occurrence or any development that potentially increases the likelihood of harm occurring to a subject or others in the future, or affects the validity of the research.

8.9 Internal Adverse Events (Revised 7/1/10)
An internal adverse event is one that occurs to a subject enrolled in a study at a research site under the jurisdiction of the IRB at TMH. If TMH is functioning as the coordinating center for a multi-site study, the PI must treat any adverse events from the involved sites as an internal adverse event and report them according to TMH guideline.

8.9.1 Reporting Requirements for Internal Adverse Events (Revised 7/1/10)
All internal, serious adverse events that are unexpected which occur during a study, or in a post-study period of reasonable duration (i.e., during follow-up), MUST be reported to the IRB promptly and the study sponsor, as appropriate. Prudent judgment on the part of the PI should guide the reporting time frame. The Office of Human Research Protections recommends reporting unanticipated problems that are serious adverse events to the IRB within one week of the investigator becoming aware of the event. Report all other unanticipated problems to the IRB within two weeks of the investigator becoming aware of the problem.

Any internal events that are expected but not serious should NOT be submitted.

Reports should identify subjects by unique code numbers rather than by subjects’ names, personal identification numbers, and/or addresses.
The IRB may determine that modifications be made to the consent form and/or protocol to assure the safety and willingness of the subjects to remain in the study.

8.10 External Adverse Events (Reviewed 7/1/10)

An external adverse event is one that involves a subject enrolled at a facility that is outside the jurisdiction of the IRB at TMH (e.g., safety report from a sponsor, collaborating site, Data Safety Monitoring Board (DSMB) report, etc.).

8.10.1 Reporting Requirements for External Adverse Events (Reviewed 7/1/10)

The FDA requires sponsors to notify all participating investigators of any serious and unexpected adverse event associated with the use of a test article that occurs at one of the participating sites of a multi-center study. These reports must be submitted to the IRB by the investigator as they are received, i.e., one week of the investigator becoming aware of the event, if the events are deemed related to the study agent. An assessment must be made by the principal investigator to determine whether or not a change to the consent form or other study documents are necessary as a result of the information in the report. If reports are received by an investigator in the form of a series of safety reports, or a periodic Data Safety Monitoring Board (DSMB) Report (often a compilation of adverse events), and meets the reporting requirements outlined above (i.e., serious, unexpected and related events) the investigator shall provide a written summary to the IRB along with the report.

When sponsor submission requirements and IRB policy are discordant, the IRB guideline shall be followed.

The following types of external serious adverse event reports should NOT be sent to the Office of the IRB:

- Expected events
- Unrelated events

If the Office of Research/IRB receives any reports that fit these two criteria, they will be sent back to the PI without acknowledgement.

8.11 How to Report an Adverse Event to the IRB (Revised 71/10)

All reportable events (see also AE maps for guidance on assessing and reporting) should be submitted to the IRB as follows:

- IRB Form 7a should be used to report serious internal adverse events. The investigator’s report should include:
  - A detailed description of the event
  - Category of event - expected or unexpected
  - Any resultant changes to the consent form
  - Event relation to study intervention
  - Rationale for assessment
• Outcome
• Site of incident

For internal reportable events, the PI must attach supporting information and materials such as progress notes, lab findings, death certificates, etc.

*IRB Form 7b* should be used to report **serious external adverse events**. The investigator’s report should include:

• A detailed description of the event
• Any resultant changes to the consent form
• TMH investigator’s assessment of event
• Site of incident

For **external** reportable events, the PI must attach supporting information and materials such as letters from sponsor, Medwatch reports, site investigator reports, progress notes, etc.

*IRB Form 7c* should be used to report **unanticipated problems involving risks to subjects or others**. The investigator’s report should include:

• A detailed description of the event
• Effect on subjects
• Effect of study validity
• Corrective action

The PI is the sponsor of investigator-initiated studies. As such, he/she must follow mandatory FDA reporting requirements. (See [www.fda.gov/medwatch/how.htm](http://www.fda.gov/medwatch/how.htm)). Copies of any reports submitted to the FDA should be sent to the IRB.

**8.11.1 IRB Response/Action** (Revised 7/1/10)

All reported serious adverse events receive review by the IRB chair/designee, IRB/Administrative Liaison or Office of Research/IRB staff.

All such events will be acknowledged by the IRB according to their severity and relation to the study (see *Internal AE map*).

The IRB or IRB chair/designee has the authority to suspend, and the IRB has the authority to terminate, approval of research at its site that has been associated with unexpected serious harm to participants. When the IRB or IRB chair/designee takes such action, a statement of reasons for such action shall be included in a notification letter to the PI. The IRB or IRB chair/designee shall promptly report its findings to the investigator and, if warranted, to Institutional Officials, study sponsor, Office of Human Research Protection (OHRP), and the FDA.

**8.12 Termination of a Protocol** (Reviewed 7/1/10)
The following are two different mechanisms by which a protocol may be terminated:

- **Voluntary termination** by the investigator or sponsor (study ends, investigator leaves the institution, etc.).

- **Administrative termination** by the IRB due to safety concerns, investigator non-compliance, or delinquent progress reports (failure to renew a protocol prior to expiration of IRB approval).

If a study is voluntarily terminated, the PI must notify the IRB by completing and submitting a *Termination Report* IRB Form 9.

The IRB will accept the termination report, place it with the study file and close the study. No formal written acknowledgement of the termination of a study to the PI or sponsor will be provided unless requested.

If a protocol is **administratively terminated**, the IRB Chair/designee will notify the PI in writing that the protocol has been terminated by the IRB or IRB Chair stating the reason for the termination, i.e., due to delinquent progress reports, concern for safety of human subjects, non-compliance, etc. In a case of immediate hazard to subjects, initial notification may be in the form of a telephone call or e-mail from the IRB Chair or designee.

### 8.13 Withdrawal of a Protocol  (Revised 7/1/10)

If a PI decides not to implement an IRB approved study, the IRB must be notified, preferably in writing, requesting study withdrawal.

### 8.14 Other Activity as Determined by the IRB  (Reviewed 7/1/10)

The IRB has the authority to request additional information, as necessary, to assure patient safety and compliance with federal and state regulations and institutional policy ensuing research is conducted and evaluated in accordance with the basic principles governing human subject protections.