

## METRC Monitoring Procedures

The following information is an excerpt from the METRC-wide Standard Operating Procedures (SOP) for monitoring. The overall monitoring plan is designed to verify site compliance with each study protocol, study-specific and METRC-wide SOPs, and applicable regulations for a given study or studies. This plan facilitates compliance with good clinical practice (GCP) guidelines (5.18.1), and with FDA guidelines and regulations (21 CFR 312 and 812) which require sponsor verification of the following:

- The rights and well-being of human subjects are protected.
- Reported trial data are accurate, complete, and verifiable from source documents.
- The conduct of the trial is in compliance with the currently approved protocol, with GCP, and with applicable regulatory requirements.

Consistent with FDA Guidance document, *Oversight of Clinical Investigations* (August, 2013), the METRC Coordinating Center's (MCC) monitoring plan incorporates a risk-based approach to monitoring that includes a combination of on-site and centralized activities.

### *Ongoing Monitoring Activities*

Once a METRC site begins enrolling study patients, the MCC assures GCP compliance and data quality through a combination of onsite and remote monitoring activities. Onsite and centralized monitoring activities are used by the MCC to fulfill the following primary responsibilities as designated by the study sponsor:

- Verify that the investigator or designee has completed signed and dated current versions of case report forms (CRFs);
- Verify that data recorded on CRFs is consistent with data that are entered into the REDCap database;
- Verify that source documents exist (either in the medical record, study notes, or, if specified in the protocol, as the CRF itself) and are consistent with data recorded on the CRF (*FDA Compliance Program Guidelines, Part III*) and in REDCap;
- Review the site's data and source documents in terms of organization, secure data collection material storage, completeness of data collection forms, accuracy of data on CRFs and in REDCap, and legibility;
- Verify that any corrected errors are signed and dated, in accordance with GCP;
- Verify that any dose or therapy modifications are well documented;
- Verify that adverse events, concomitant medications, and underlying illnesses are reported accurately on the CRFs, in REDCap, and in accordance with the protocol;
- Verify that clinical laboratory testing (including EKGs, X-rays, etc.), is documented by the presence of completed medical records in the patient chart (*FDA Compliance Program Guidelines, Part III*);
- Verify that Administrative CRFs are completed and entered to reflect all missed follow-up visits and any tests, examinations, or surveys that were not completed or that were completed out of window;

- Verify that patient deaths, withdrawals, dropouts, and subjects lost-to-follow-up are reported and explained on CRFs and in REDCap and that all forms are complete with verification of source documentation;
- Inform the investigator of any CRF or data entry errors and ensure that appropriate corrections are made, dated, explained (if necessary), and initialed by the investigator or designee authorized to make such changes.

### ***Verification of Investigator and Study Team Qualifications***

With regard to assuring qualifications of the principal investigator and study team, the MCC verifies, through a combination of on-site and remote monitoring activities:

- A complete delegation of authority log, matching the list of personnel on the site's IRB application for the study and the list of personnel certified by the MCC;
- A curriculum vitae for the PI and any other investigators certified by the MCC to participate in the study;
- Current Human Subjects Training certification for all personnel certified by the MCC to participate in the study;
- Current licenses for all study personnel performing study procedures, appropriate to the scope of practice of the individual (e.g. medical licenses);
- Current Good Clinical Practices Training certification for the PI and primary research coordinator for the study;
- Current METRC-wide Standard Operating Procedures (SOPs) and study-specific SOPs available for review (with past SOPs archived) as well as documentation of review (Training Completion Form) by all MCC-certified personnel;
- Copies of any Policy and Procedure or Clarification Memoranda issued by the MCC.

### ***Regulatory File Management and Compliance***

With regard to assuring regulatory compliance, the MCC verifies the following through a combination of on-site and remote monitoring activities:

- Complete compendium of correspondence to and from the IRB, from initial submission, including any clarifications or amendments;
- IRB-approved versions of protocol, consent form and any other regulated materials (e.g. patient interviews, patient recruitment materials, etc.);
- IRB approval letters or memoranda for initial approval and each subsequent amendment, if applicable;
- Complete compendium of correspondence to and from the DoD, from initial submission, including any clarifications or amendments;
- DoD approval letters or memoranda for initial approval and each subsequent amendment, if applicable;
- Documentation of receipt of annual continuing review (if over 1 year has passed since study initiation) from the IRB and DoD;
- Copies of monthly electronic reports generated by the MCC;

- Results of remote CRF audits conducted by the MCC;
- Previous monitoring reports or other communication with the MCC (i.e. study memos).

### ***Compliance with Study Protocol***

With regard to compliance with the study's IRB approved protocol, MCC monitors utilize a combination of on-site and centralized monitoring activities to do the following:

- Verify that the (current) IRB approved protocol and the (current) protocol in the regulatory file are the same;
- Verify that all versions of the protocol are maintained in the regulatory file;
- Check for documentation of distribution of the currently approved protocol and Investigator Brochure (where applicable) to the study team;
- Verify that the number of subjects screened and enrolled at the site was confined to the number approved by the local IRB (*FDA Compliance Program Guidelines, Part III*);
- Verify that no deviations from or changes to the protocol have been implemented without prior review and documented approval of the IRB and, when applicable, the DoD;
- For cases selected for CRF review, verify that written consent was obtained before subjects' participation. To accomplish this, the MCC representative:
  - Verifies correct version of IRB-approved consent form was used
  - Verifies the date and time the consent form was signed and dated
  - Verifies documentation of capacity to consent
  - Verifies Legally Authorized Representative documentation (if applicable)
  - Verifies, against the subject's medical record, source documentation that the consent was signed before any research test or procedure was performed.
- For cases selected for CRF review, verify the patient signed and dated a HIPAA form prior to enrollment, as applicable;
- Verify that only eligible subjects are enrolled. To accomplish this, the MCC representative:
  - Verifies documentation of patients meeting all applicable inclusion criteria and no exclusion criteria on CRF 00 (the screening CRF) and the presence of documented informed consent for all cases selected for CRF review
  - For cases selected for CRF review, compares the protocol inclusion/exclusion criteria against the subject's medical record, or other source documentation, to verify the enrolled patient is eligible for inclusion in the study
  - Verifies that enrolled patients who do not meet all eligibility criteria were given an exemption in order to participate by the PI or MCC lead investigator and that documentation of this exists in both the CRF and source document.

### ***Reporting Findings to the Investigator***

During a monitoring visit, the monitor meets with the PI or co-investigator to review any findings of the visit. Following the visit, the monitor prepares a monitoring report which is circulated to the MCC Director. In this report, the site's activities relative to each study is classified as "Acceptable," provided no further action is needed, or any findings were corrected while the monitor was at the site, "Acceptable, Follow-up" if deficiencies were found which

require the site Principal Investigator to address, or “Unacceptable,” if significant findings observed by the site monitor could have a potential effect on patient safety or undermine the quality of data collected. If the finding is “Unacceptable,” the monitor alerts the Director of the MCC and Chair of the Consortium, who convenes the METRC Executive Committee either by teleconference or through email, to discuss next actions.

The monitoring report describes the findings of the visits, unresolved issues, and follow-up required. The monitor retains an electronic copy of the fully executed report and a copy is distributed to the site. The site also retains the copy in their Regulatory file. A copy of every monitoring report is shared with the DoD or the JHSPH IRB, as requested.

Items identified for follow-up are responded to by the Investigator within 10-15 business days (as stipulated by the monitors) with plans for addressing them. The resolution of these items is verified and documented. The report includes, but is not be limited to, the following:

- A list of documents reviewed, i.e. regulatory materials, subject charts, hospital records, lab slips, etc.;
- Number of case report forms reviewed by research subject number and visit date;
- Statement regarding whether there was any evidence of under-reporting of adverse events;
- Statement regarding protocol adherence.