# NIDCR Guidelines for Level of Clinical Site Monitoring

Clinical site monitoring is one element of the overall data and safety monitoring of clinical research. The purpose of clinical site monitoring is to ensure compliance with the protocol, Good Clinical Practice, Federal and local regulations, and institutional policies. This guideline pertains to NIDCR’s external monitoring of intramural and extramural clinical research studies and describes standards for implementing clinical site monitoring.

The Guidelines for Level of Clinical Site Monitoring provide a general understanding of the practices of monitoring for NIDCR clinical research studies. A Clinical Monitoring Plan (CMP) is created for each study that will be monitored. The information provided below serves as a guideline for developing the clinical site monitoring plan. The levels of complexity are based on human subject risk, size, nature, and complexity of the study. Note that while clinical studies have been assigned to a level of complexity in this guide, a final determination of the level of monitoring will be based on the specific design and study population of each individual protocol and will be detailed in the approved Clinical Monitoring Plan for each study.

Communications for each type of planned or scheduled monitoring visit include a site monitoring confirmation letter, on-site post monitoring visit debriefing, and a follow-up letter and/or visit report and Action Item Tracker.

Monitoring visits will be scheduled at a frequency to maintain review of the items described in the monitoring plan and as deemed appropriate and determined from assessment of study compliance and individual study team needs.

**Minimal Complexity Studies (Does not apply to Division of Extramural Research)**

Study examples: Screening protocols, natural history studies, epidemiological studies, training studies, sample repository studies

## Areas of Focus

* Site assessment review and staff training (reference the [Site Assessment Questionnaire](http://www.nidcr.nih.gov/nidcr2.nih.gov/Templates/Toolkit.aspx?NRMODE=Published&NRNODEGUID=%7b09426ABC-1182-4433-9A7D-A57674A5334F%7d&NRORIGINALURL=%2fResearch%2ftoolkit%2f&NRCACHEHINT=Guest#startup8)).
* Human subjects protection.
* Protocol compliance.
* Regulatory compliance (specifically Human Subjects Protections - 45 CFR 46).
* Laboratory SOPs and compliance.
* Laboratory sample disposition, storage, and handling.
* Integrity of research data and samples.

## Monitoring Plan

* Review of credentials, training records, and delegation of responsibility logs.
* Review of Consent Forms:
* 100% reviewed for studies with < 100 subjects.
* 100% reviewed for studies with 101-499 subjects, unless otherwise instructed by OCTOM and the NIDCR.
* Random selection (up to 90%) reviewed for studies with > 500 subjects. Results of findings may lead to 100% review of consent forms. Additional details of consent review, if any, will be specified in the CMP.
* Review reports on missed events, missing data, and protocol deviations for a determined sample of subjects.
* Compare source documentation and CRFs to ensure data are accurate and complete. Any information access limitations, or special circumstances with respect to involvement of a data management system, will be specified in the approved, study-specific CMP. The CMP will include the percentages and processes of data review by the monitor, including a discussion of electronic databases used to collect data and the scope of involvement if there is a separate Data Coordinating Center.
* Regulatory review of IRB approvals in the Investigator Site File.
* Laboratory Review of labeling, handling, maintenance of cold chain, shipping, storage, and documentation of specimens.

## Visit Schedule

* The first monitoring visit is generally within 3-6 months after first subject is enrolled and/or as outlined in the approved, study-specific CMP.
* Interim monitoring visits at least annually for active studies that have completed active enrollment and have subjects returning for follow-up visits.
* Ad hoc or for-cause monitoring as needed or requested.

**Medium Complexity Studies**

Study examples: Behavioral intervention, complex observational, complex or sample collection studies that are more than minimal risk

## Areas of Focus

* Site assessment review and staff training (reference the Site Assessment Questionnaire).
* Human subjects protection.
* Protocol compliance.
* Regulatory compliance.
* Laboratory SOPs and compliance.
* Quality assurance.
* Adverse event reporting.
* Integrity of research data and samples.

## Monitoring Plan

* Review of credentials, training records, and delegation of responsibility logs.
* Review 100% of Consent Forms.
* Review reports on missed events, missing data, and protocol deviations.
* Compare CRFs to source documentation to ensure data are accurate and complete. Any access limitations, or special circumstances with respect to involvement of a Data Coordinating Center or the site(s) where the monitoring will occur, will be specified in the approved, study-specific CMP. The CMP will include the percentages and processes of data review by the monitor, including a discussion of electronic databases used to collect data and the scope of involvement if there is a separate Data Coordinating Center.
* Review documentation for all adverse events (AEs), serious adverse events (SAEs) and unanticipated problems (UPs).
* Critical fields monitored such as eligibility and study endpoints for a specified number or 10-25% of subjects enrolled.
* Regulatory Files:
* 100% of the Investigator Site File, with comparison to the Trial Master File\* reviewed at first and close-out visits.
* Limited reviews at interim visits, e.g., IRB annual reviews, safety reporting, IRB submissions, and updated essential documents.
* Laboratory Review:
* Full laboratory review of storage and handling of specimens at first and close-out visits and at least biannually for active studies.
* Assessment of laboratory specimens stored at the clinical site.
* Test Article Accountability:
* Full accountability review at first and close-out visits and at least biannually of active studies.
* Biannual review of accountability logs, dispensing records, and subject records.

## Visit Schedule

* Site assessment review and staff training (reference the Site Assessment Questionnaire).
* Study initiation on site.
* First monitoring visit to be scheduled early in the enrollment phase; to be specified in the CMP.
* Interim monitoring visits every 6 months based on site activity or as specified in the approved, study-specific CMP.
* Other monitoring as needed or requested.

**High Complexity Studies**

Study examples: Phase I –III interventional study (novel product), and all studies under an Investigational New Drug (IND) or Investigational Device Exemption (IDE) with FDA

## Areas of Focus

* Site assessment review and staff training (reference the site assessment questionnaire).
* Human subjects protection.
* Protocol compliance.
* Regulatory compliance, including verification of submission of annual reports to FDA and IRB.
* Laboratory SOPs and compliance.
* Quality assurance.
* Safety.
* Adverse event reporting.
* Integrity of research data and samples.

## Monitoring Plan

* Review of credentials, training records, and delegation of responsibility logs.
* Review 100% of Consent Forms.
* Review reports on missed events, missing data, and protocol deviations.
* Compare CRFs to source documentation to ensure data are accurate and complete.
* Review documentation for all AEs, SAEs, and UPs.
* Review 100% of all critical fields monitored such as eligibility, study endpoints, and SAEs.
* Regulatory Files:
* 100% of the Investigator Site File, with comparison to the Trial Master File\* reviewed at first and close-out visits.
* Limited reviews at interim visits, e.g., IRB annual reviews, safety reporting, IRB submissions of protocol deviations, and updated essential documents.
* Laboratory Review:
* Full laboratory review of processing and storage of specimens at first and close-out visits and at least biannually.
* Assessment of laboratory specimens stored at the clinical site.
* Test Article Accountability
* Full accountability review at first and close-out visits and at least biannually of active studies.
* Biannual review of accountability logs, dispensing records, and subject records.

## Visit Schedule

* Site assessment review and staff training (reference the Site Assessment Questionnaire).
* Study initiation on site.
* The first monitoring visit should be scheduled no more than 8 weeks after the first subject is enrolled or after a determined number of subjects have met a specific milestone. The intent is to schedule a first monitoring visit early in the recruitment phase.
* Interim monitoring visits at least at once every 12-24 weeks based on site activity and as specified in the approved, study-specific Clinical Monitoring Plan.
* Additional monitoring as needed, including the possibility of remote monitoring activities. Remote monitoring may include reviewing electronic case report forms or electronic regulatory documents from a location other than the clinical site.

\*Trial Master File may be held by the IND holder, Lead investigator, Grant Principal Investigator, or delegated to a contract research organization.