NIDCR

CLINICAL

MONITORING

GUIDELINES

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Glossary and Definitions

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| **AE** | Adverse Event: Any untoward medical occurrence in a patient or clinical subject administered a pharmaceutical product or other intervention and which does not necessarily have a causal relationship with the product/intervention. |
| **CAPA** | Corrective and Preventative Action |
| **CFR** | Code of Federal Regulations |
| **CMP** | Clinical Monitoring Plan |
| **COV** | Site Close-Out Visit: The visit that is conducted when a study is officially completed, usually defined as, all subjects are off study, no further data will be collected, and the IRB is notified that all subjects have completed the study. |
| **CRA** | Clinical Research Associate: Monitor; person who monitors the progress of the investigation as well as sites participating in a clinical study and who is responsible for assessing study conduct in adherence with protocol requirements. |
| **CRF** | Case Report Form: A printed, optical, or electronic document designed to record all protocol required data to be reported to the sponsor on each study subject. |
| **CRIS** | Clinical Research Information Systems: A database program which maintains clinical laboratory data at NIH Clinical Center. |
| **CROMS** | Clinical Research Operations and Management Support |
| **Data Queries** | Questions regarding the legibility, correctness, or logic of data that are identified by a set of data standards. |
| **DCF** | Data Clarification Form: Form used to identify, record, and correct data errors or discrepancies detected during the monitoring visit. It requires signature of the PI and return to the CRA after indicated corrections are made by the study team. |
| **DSMB** | Data and Safety Monitoring Board (may also be a Committee: DSMC) |
| **eCRF** | Electronic Case Report Form |
| **FDA** | Food and Drug Administration |
| **Form 1195** | NIH Clinical Research Protocol Initial Review Application; this form captures and summarizes information about the proposed clinical study. The form is placed on the top of a protocol and is designed to carry the protocol though the entire review process. |
| **Form 1195-1** | NIH Clinical Research Protocol Continuing Review Application; this form captures, summarizes, and updates information about an active study. The form is placed on the top of the protocol and is designed to carry the protocol though the entire continuing review process. |
| **Form 1572** | FDA Statement of Investigator Form; signing of this form indicates a commitment by the Principal Investigator that they will comply with 21 CFR. |
| **FWA** | Federalwide Assurance: A document that designates the Institutional Review Board that will review and oversee the research, specifies the ethical principles under which the research will be conducted, and names the individuals who will be responsible for the proper conduct of the research. |
| **GCP** | Good Clinical Practices: A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical research studies designed to provide assurance that the data and reported study results are credible and accurate, and that the rights of subjects are protected. |
| **ICH** | International Conference on Harmonisation |
| **IDE** | Investigational Device Exemption |
| **IMV** | Interim Monitoring Visit: A visit conducted by a CRA to review source documents and study related materials and to ensure protocol and regulatory compliance. This visit takes place during the conduct of the study. |
| **IND** | Investigational New Drug: The clinical investigation of a previously untested drug or biologic that is generally divided into three phases of study. Each phase is designed to ensure the safety and rights of subjects and to help assure that the quality of the scientific evaluation of drugs/biologics is adequate to permit a scientific evaluation of the drug’s effectiveness and safety. |
| **IoR** | Investigator of Record |
| **IRB** | Institutional Review Board: An independent body constituted of medical, scientific, and nonscientific members, whose responsibility is to ensure the protection of the rights, safety, and well-being of human subjects involved in a study by, among other things, reviewing, approving, and providing continuing review of protocols and amendments, and of the methods and material to be used in obtaining and documenting informed consent of the study subjects. |
| **ISF** | Investigator Site File: The collection of essential documents maintained at each clinical site which represents the regulatory history of the study. These documents include, but are not limited to: the protocol and amendments, IRB-approved consent document templates, IRB approvals and communication, study personnel CVs and licenses, AE/SAE/UP reporting documentation, and records of Investigational Product use. |
| **NIDCR** | National Institute of Dental and Craniofacial Research |
| **NIH** | National Institutes of Health |
| **OCTOM** | Office of Clinical Trials Operations and Management |
| **PI** | Principal Investigator: The person responsible for the conduct of the clinical research study and who makes important study-related decisions at a study site. |
| **Protocol Exception** | An exception to an inclusion or exclusion criteria of a clinical protocol that is granted by the sponsor of IND protocols prior to enrollment of a subject in the clinical study. |
| **Protocol Violation** | A protocol violation is a variance or deviation between the IRB approved protocol and the actual activities or procedures performed. |
| **RAC** | Recombinant-DNA Advisory Committee |
| **SAE** | Serious Adverse Event: Any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or results in a congenital anomaly/birth defect. |
| **SIV** | Site Initiation Visit: A meeting with the PI, all clinical site personnel, and sponsor personnel that takes place prior to the start of the clinical research study. The purpose of this meeting is to review the protocol, Investigator’s brochure, all procedures, forms, and documents related to the conduct of the study. |
| **Source Documents** | Original documents, data and records, such as hospital records, clinical and office charts, laboratory results, notes, memoranda, pharmacy dispensation records, evaluation checklists, or as defined in the protocol. |
| **TMF** | Trial Master File: The collection of essential documents maintained by the Sponsor which represents the regulatory history of the study. These documents include documents for each site and the study overall. Examples include: the protocol and all protocol amendments, IRB-approved consent document templates, IRB approvals and communication, study personnel CVs and licenses, AE/SAE/UP reporting documentation, and records of Investigational Product use. |
| **UP** | Unanticipated Problem: The Office for Human Research Protections considers unanticipated problems to be any incident, experience, or outcome that meets *all* of the following criteria: 1) Is unexpected in terms of nature, severity, or frequency given a) the research procedures that are described in the IRB-approved research protocol and informed consent, and b) the characteristics of the subject population being studied; 2) Is related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and 3) Places subjects or others at a greater risk for physical, psychological, economic, or social harm than was previously known or recognized. |

# BACKGROUND AND PURPOSE

## Introduction

Investigators who receive funding from the National Institute of Dental and Craniofacial Research (NIDCR), National Institutes of Health (NIH) are obligated to protect the human subjects who participate in clinical research studies and the integrity of the research data gathered from those subjects. These guidelines will assist Investigators to meet these obligations. The guidelines specify the responsibilities of the Investigator, the designated site study team, the Office of Clinical Trials Operations and Management (OCTOM), and the Clinical Research Operations and Management Support (CROMS) team.

This document will provide the guidance necessary to develop a Clinical Monitoring Plan for the clinical research study. These guidelines describe the procedures before, during, and following a monitoring visit. These procedures may vary depending on the type of study and the type of visit being conducted: site assessment visit, site initiation visit, site interim monitoring visit, for cause visit, or site close-out visit. Discussions with the Principal Investigator (PI) may take place to further clarify issues around certain types of studies.

It is important that each member of the study team involved in clinical research understands and applies these guidelines, where applicable.

## Background

The NIH research community recognizes the importance of defining the needs and infrastructure for clinical research in order to ensure patient safety and protocol integrity. It is the policy of the NIH that “each Institute and Center (IC) should have a system for the appropriate oversight and monitoring of the conduct of clinical trials to ensure the safety of participants and the validity and integrity of the data for all NIH-supported clinical trials” (NIH Policy for Data and Safety Monitoring). The NIDCR supports clinical research, interventional clinical trials, and observational studies that vary in size and complexity. It is NIDCR's responsibility to ensure the appropriate oversight and monitoring of the conduct of all research studies being conducted within the Institute for both Intramural and Extramural investigators. The NIDCR endorses the International Conference on Harmonisation guidelines and Good Clinical Practices (ICH/GCP) regarding the responsibilities of the research sponsors.

## Purpose

These guidelines are designed:

* To help ensure that the rights, safety, and well-being of human subjects enrolled in NIDCR clinical research studies are protected.
* To have an objective assessment of the Investigator’s adherence to the protocol, to all applicable government regulations, and to ICH/GCP guidelines.
* To validate the integrity of the data collection and recording process.

# ROLES AND RESPONSIBILITIES

The Office of Clinical Trials Operations and Management (OCTOM) within NIDCR has direct oversight of the CROMS team to ensure that NIDCR Intramural and Extramural protocols are monitored according to the NIH standards for clinical research. OCTOM makes recommendations to the NIDCR Clinical Director and Program Officials on the basis of those monitoring findings.

Clinical Research Associates (CRAs) from CROMS will perform all on-site monitoring responsibilities for NIDCR Intramural studies. Monitoring for Extramural studies may be done by CROMS CRAs or a designee.

## Role of OCTOM

OCTOM is responsible for reviewing the monitoring reports, action items, and follow-up letters sent to Investigators, and for assessing the adequacy and acceptability of any suggested corrective actions. OCTOM will also follow-up where significant deficiencies have been identified and recommend to the NIDCR Clinical Director and Program Officials that corrective actions be followed. To ensure consistency in the conduct of monitoring visits, an OCTOM representative may attend site initiation visits, routine monitoring, for cause visits, and site close-out visits, when appropriate.

In addition, the OCTOM staff will serve as an educational resource for NIDCR Office of the Clinical Director, NIDCR Program Officials, and investigators on clinical study implementation, monitoring, and applicable regulatory requirements.

## Role of CROMS

The primary role of the CROMS team, with regard to clinical monitoring, is to validate the integrity of the data collected and to assess site compliance with the IRB approved protocol and applicable regulatory requirements. The CROMS CRAs/monitors or designees will operate according to their organization’s Standard Operating Procedures (SOPs).

Responsibilities include, but are not limited to:

* Verifying site adherence to applicable ICH/GCP guidelines for clinical research
* Monitoring adherence to the IRB approved protocol and reporting non-compliance issue(s) to OCTOM
* Performing site initiation visits
* Assisting sites with logistical issues as needed
* Assisting with the operational review of clinical research protocols and consent forms
* Performing routine monitoring visits for Intramural and Extramural NIDCR protocols as defined in Section 3, which would include:

1. Evaluating the progress of the study, including such factors as:
   1. Periodic assessments of data collection, recording, and submission timelines
   2. Performing investigational product accountability
   3. Ensuring that subject rights are protected by verifying informed consent
   4. Other factors that may affect a subject’s study continuation or study completion
   5. Verifying subjects’ demographic distribution
2. Making recommendations to the Investigators and OCTOM regarding data discrepancies, improvements in compliance, subject accrual progress, and retention methods
3. Ensuring that Adverse Events (AEs), Serious Adverse Events (SAEs), and Unanticipated Problems (UPs) are being reported to all required groups in accordance with the protocol plan [e.g., IRBs, the Rho Product Safety Group, and the Data and Safety Monitoring Boards (DSMBs)]

* Assisting the PI and study team in the preparation for any potential audit(s)

## Role of Principal Investigator and Study Team

The PI is responsible for conducting all clinical studies within NIDCR in compliance with applicable regulatory requirements and applicable ICH/GCP guidelines. During a monitoring visit, the PI or designee’s responsibilities include:

* Providing direct access to all relevant study-related records:

1. Study data in hard copy tables, listings and/or CRFs (electronic or paper)
2. Source documents, such as:
   1. Patient medical records
   2. Laboratory results and diagnostic reports
   3. Other applicable source documentation (e.g., patient diaries, vital signs)
   4. Consent documents
   5. Screening documents
   6. Other study-specific documents as necessary
3. Regulatory file/Investigator Site File
4. Drug accountability records, which may necessitate a pre-arranged appointment with Pharmaceutical Development Section (PDS) pharmacy or other Institutional Pharmacies
5. Laboratory specimen collection, processing, storage, and shipment records

The PI and/or designee should be available at the start of the monitoring visit for set-up questions and at the conclusion for a summary of site visit findings. The site Study Coordinator (SC) or designee will be available, as needed, to meet with the CRA during the visit.

# MONITORING

All clinical research teams conducting clinical research studies within NIDCR, whether domestic or international, will be considered for monitoring of protocol adherence and human subjects protection monitoring (according to ICH/GCP and other applicable regulations). These include both IND and non-IND clinical trials and natural history/pathogenesis studies.

At present time, the following types of protocols may be monitored by CROMS:

* All IND studies
* International protocols and domestic protocols conducted by Extramural investigators, funded by NIDCR or with an NIDCR PI listed as the Principal Investigator
* Protocols enrolling pediatric subjects or other vulnerable populations, independent of protocol type
* Special requests from NIDCR (example: non-IND studies with significant risk)
* Special requests from the Principal Investigator

## Monitoring of Sponsor-held INDs

It is the responsibility of the sponsor holding the IND to monitor the clinical trial(s) under the auspices of that IND. If a PI holds the IND and is therefore considered to be the sponsor, OCTOM and NIDCR may provide approval for CROMS to fulfill monitoring obligations on behalf of the PI.

## Clinical Site Monitoring Plans

A study-specific Clinical Monitoring Plan (CMP) will be developed by CROMS in consultation with OCTOM and finalized prior to the first site visit. The plan will outline the types of site visits to be conducted, the timing and frequency of the visits, and the study documentation/materials that may be reviewed at each visit. Factors such as risk level, number of subjects to be enrolled, frequency of visits, and study endpoints will be taken into consideration when developing the CMP.

## Principles of Monitoring a Clinical Protocol

### Commensurate with the Size and Complexity of the Research Study

The frequency and percentage of clinical protocols monitored by CROMS or a designee in support of NIDCR depends on the size and scope of the research effort. The degree of monitoring for each clinical protocol is based on 4 factors:

1. The type of clinical protocol
2. The level of risk to the subject as defined in Title 45 CRF Part 46
3. The complexity of the study as determined by assigned Program Officials and OCTOM with input and collaboration from CROMS
4. The anticipated frequency of visits with respect to enrollment considerations

#### Clinical Protocol Types

* Screening Protocol: designed to determine if subjects may be suitable candidates for NIH protocols
* Training Protocol: designed to allow staff physicians and other health care workers to maintain or improve their professional skills by following particular types of subjects
* Natural History/Disease Pathogenesis Protocol: designed to study normal human biology and disease pathogenesis
* Interventional Clinical Trial Protocol: Phase I through Phase IV clinical trials
  + *IND Clinical Trial*: an investigational new drug application is required for use of a drug or intervention in disease treatment or for diagnostic purposes
  + *Non-IND Clinical Trial*: an investigational new drug application is not required for use of the drug or intervention in disease treatment or research purposes , including behavioral studies

#### Level of Risk (See Appendix 1: Title 45 CRF Part 46 Protection of Human Subjects)

* Minimal Risk: [45 CFR 46.102(i)] the probability and magnitude of harm or discomfort anticipated in the research is not greater than what is ordinarily encountered in daily life or during the performance of routine physical or psychological examinations and tests. Examples of minimal risk studies would include screening protocols, natural history/disease pathogenesis studies, or epidemiological studies.
* Greater than Minimal Risk:
  + *Medium Risk*: Behavioral intervention, sample collection greater than minimal risk
  + *High Risk*: Phase I-III interventional study (novel product) and all studies under an IND or Investigational Device Exemption (IDE)

Refer to Appendix 1 regarding research involving children, CFR 45 part 46.405 and 46.406: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.405>

In general, the focus of monitoring minimal risk, non-IND studies will be on informed consent with the goal of monitoring Informed Consent Processes for all subjects, depending on the number of subjects enrolled. A smaller subset of subjects will be selected for more extensive chart review. This subset can be expanded or contracted as needed and indicated by CRA-identified trends and observations.

Studies involving a great level of risk, including IND and non-IND studies, will be monitored more rigorously and may include complete chart reviews for all subjects.

### Purpose of Site Monitoring Visits

The purpose of Site Monitoring Visits is to verify:

* The rights and well-being of human subjects are protected
  + Subjects’ agreement with study participation by reviewing consent documents
* The reported study data are complete and verifiable from source documents
* The study is conducted in compliance with the current, approved protocol/amendment(s), applicable ICH/GCP guidelines, and all applicable regulatory requirements
  + SAEs are being reported as required by the protocol to all appropriate groups: IRBs, other PIs, Rho Product Safety Group, and Data and Safety Monitoring Boards, as applicable
  + Proper storage, handling, accountability, and disposition of investigational product

### Visit Types

* Pre-Study Site Assessment Visit (PSSAV)
* Site Initiation Visit (SIV)
* Interim Monitoring Visit (IMV)
* For Cause Monitoring Visit
* Site Close-Out Visit (COV)

# PREPARATION FOR MONITORING

## Existing Protocols

### Notification of Monitoring for Existing Protocols under an IND

The CROMS team will monitor protocols where the IND has been transferred to NIDCR for a study that has already been activated and where CROMS was not involved in start-up. Examples of such studies could include internationally run studies, pediatric patient studies or special requests made by the Investigator and/or the Clinical Director. In these instances, OCTOM, the NIDCR Clinical Director, or the identified Program Official will send a formal letter to the Investigator informing him/her that CROMS will conduct future monitoring visits.

### Monitoring Plans for Existing Protocols under an IND

For the above mentioned protocols, CROMS, in collaboration with OCTOM, will develop a monitoring plan for the protocol based on criteria in Section 3.3.1. Every site will be monitored at least annually, although more frequent monitoring may be needed for some sites and dependent on the type of protocol. This will be discussed with the Principal Investigator during the site initiation visit.

### Monitoring Plans for Existing Protocols not under an IND

CROMS, in collaboration with OCTOM, will develop a monitoring plan for the protocol based on criteria in Section 3.3.1. Every site will be monitored at least annually although more frequent monitoring may be needed for some sites and dependent on the type of protocol. This will be discussed with the Principal Investigator during the site initiation visit.

## New Protocols

### Monitoring Plan for New Protocols

A Clinical Monitoring Plan will be developed for those protocols determined to require Clinical Monitoring.

### Pre-Study Site Assessment

A Pre-study site introductory teleconference or site visit may be scheduled to provide CROMS/OCTOM an opportunity to speak to the investigator and team to assess the current suitability for conducting the study at the site. After introduction by the Program Official or NIDCR Clinical Director, a representative from CROMS will contact the study team in advance of the initiation visit to schedule this introductory call.

### Site Initiation Visit/Meeting

Under the direction of NIDCR, a CROMS team member will conduct a Site Initiation Visit (SIV), or participate in a Site Initiation Meeting, depending on the level of CROMS support requested, for all new protocols. This visit is to ensure that the study personnel are trained on the regulatory requirements for study conduct and approved protocol procedures, to discuss study staff’s roles and responsibilities, to review the monitoring plan included in the protocol, and to review data collection (database system and/or CRFs/eCRFs). The CROMS representative will also review all study-related documents/materials such as sample handling procedures and control of the investigational product when applicable. This visit will serve to outline the frequency of monitoring visits expected for this study. If CRFs are used, a review of how they are completed and the process the CRA will follow when verifying the data and collecting the completed forms will be discussed. This visit should ensure that all study team members, including the CROMS team, are aware of each person’s responsibility and role in conducting the study. The visit must occur prior to site activation and/or enrollment of any subject into a protocol.

## Responsibility of CROMS Team

It is the responsibility of the assigned CRA to schedule the date for a routine monitoring visit with the Investigator and/or Study Coordinator. The date for the site visit will be confirmed approximately one month, or a mutually agreed upon time, prior to the visit. A reminder of the scheduled visit will be mailed/emailed to the Investigator and/or site Study Coordinator. At least two weeks prior to the visit, the CRA will send a confirmation letter to the Investigator stating what study-related documents and materials the CRA will require.

## Responsibility of Investigator

The PI is responsible for ensuring that all relevant and available study materials requested by the CRA are present for review during the site visit. The Investigator should also ensure that the appropriate study staff members are available throughout the course of the visit should the CRA have questions, or should a finding require immediate resolution. The PI or designee will coordinate any visits by the CRA to ancillary departments at the site, as requested in the visit confirmation letter. The PI or his/her designee must make certain that he/she is available for the wrap-up meeting usually conducted on the last day of the visit.

# CONDUCTING THE SITE MONITORING VISIT

During a monitoring visit, the CRA will review specific data and regulatory documents related to the clinical protocol, as described in this section, and verify signed consent forms for each study subject. Prior to enrolling in a study, patients at the NIH Clinical Center may have been enrolled in a “Screening” protocol. If this is the case, the screening protocol consent forms will also be monitored. Source documents should be used to independently verify study data. Source documents may include but are not limited to the following:

* Medical records
* Progress notes
* CRIS laboratory result pulls
* Radiology reports and other procedural reports
* Lab reports including safety labs and specific labs related to the protocol
* Other source documents such as diary cards and record of vital signs

## Assessing Monitoring Findings

A monitoring visit consists of:

* Assessing protocol adherence, compliance with ICH/GCP and/or Federal Regulations when applicable
* Evaluating subject enrollment
* Verifying signed consent documents, CRFs, or data queries
* Performing source document verification
* Ensuring all AEs, SAEs, and UPs are reported in accordance with applicable regulatory requirements
* Reviewing regulatory documents/Investigator Site File
* Assuring proper investigational product storage, handling, disposition, and accountability documentation, if applicable.
* Assuring proper collection, processing, storage, and shipment of laboratory specimens, if applicable

The monitoring visit documents are usually sent to the Investigator within 3 weeks of the last day of the site visit. It is recommended that the PI respond and/or develop a corrective action plan (CAPA) to pertinent items referenced in the Action Items Tracker in a timely manner.

### Protocol Adherence

The approved study protocol and the records from enrolled subjects will be monitored for protocol adherence and adherence to all applicable regulations and GCP guidelines during the study.

Protocol non-adherence issues identified by study staff prior to the monitoring visit will be assessed by the CRA during the monitoring visit and then reported on appropriate forms. If the site identifies a protocol deviation prior to a monitoring visit, the site should inform their IRB per internal policies. Following is the definition the CRA will use for these types of occurrences:

Protocol Deviation Definition: A protocol deviation is a variance in a research study between the protocol that has been reviewed and approved by the IRB and the actual activities or procedures being done for that particular subject. Protocol deviations may be minor, when it does not significantly affect the subject’s rights or safety, or more significant, when the subject’s rights, safety or welfare are adversely affected. Willful or known misconduct would also be considered significant deviations.

All deviations are recorded on the protocol deviation CRF/eCRF. These are reviewed by the CRA at each monitoring visit. The PI must also ensure that deviations are reported to the IRB per their reporting requirements. The NIDCR may request that the PI develop a CAPA that outlines actions that will be taken to prevent further noncompliance. The CRA can assist the site in formulating this plan.

### Subject Enrollment

The inclusion/exclusion criteria and subjects’ eligibility will be reviewed to confirm that subjects meet enrollment criteria.

### Addressing Data Discrepancies

#### Case Report Forms

The following description outlines an example of how to address data discrepancies when using paper Case Report Forms:

A vital signs field on the CRF has an incorrect value. The recorded BP is 80/120, the error being that the systolic and diastolic values are reversed. This is considered a transcription error on the actual CRF. If the error is noted during the course of the monitoring visit, the correction can be made directly onto the case report form. If this error was recognized after the CRFs were monitored and collected, a Data Clarification Form (DCF) would be filled out and forwarded to the site for resolution on the CRF. A copy of the DCF will override the field on the CRF page. The DCF should be filed with the actual CRF that has the error in order to note the correction. The original completed DCF will be returned to the assigned CRA at the CROMS office.

#### Electronic Case Report Forms

An example of how to address data discrepancies when using an electronic data capture system will vary on the electronic system used and the applicable protocol. The process and forms needed to do this will be presented to site personnel once established.

#### Data Query Review

The CRA will review the site’s responses to data queries to verify that the data correction made in response to the query is accurate and complete.

### Subject Medical Records Review

Subject medical records are source documents that may be used to verify data captured in the CRFs or data tables. These documents include but are not limited to progress notes, interdisciplinary notes, admission/discharge summaries, and laboratory results. The CRA will work with the study coordinator prior to the visit to ensure that appropriate access to medical records will be available during the visit.

### Adverse Events/Serious Adverse Events/Unanticipated Problems Review

AEs, SAEs, and UPs occurring during the study will be reviewed to ensure that they have been reported within the defined protocol requirements and required regulatory guidelines to the IRB(s), Rho’s Product Safety Department, and other required bodies (e.g., DSMB, RAC/OBA) as applicable. Appropriate information will also be filed in the Investigator’s study documentation.

### Investigator Protocol/Regulatory File Review

#### IRB Documentation

The following are the minimum set of items to be reviewed:

* Documentation of full IRB approval of initial protocol/consent form
* Completed signed 1195 Form (if applicable)
* Documentation of full IRB approval of continuing reviews for the protocol/consent form/completed signed 1195 Form (if applicable)
* FDA form 1572 (if applicable)
* Investigator of Record (IoR) (if applicable)
* Documentation of IRB approval for all protocol and consent form amendments
* IRB approved advertisements, brochures, questionnaires, and diary cards
* IRB membership roster and/or Federalwide Assurance (FWA)

#### Curriculum Vitae (CV)/Medical Licenses

The CRA will review the CVs and medical licenses that are on file to ensure that they are updated, and properly filed in the Investigator Site File and with the Sponsor Master Files. CVs should be signed and dated within two years of the study start date. Updated CVs should be filed if there is a substantial change (e.g., change of address), however, the original CV should remain in the file. CVs should be filed for the PI and any Associate Investigators as well as all key study staff. Medical licenses should be filed for all applicable study staff members. Licenses should be maintained for the duration of the study; expired licenses should remain in the file to document valid licensure at the start of the study.

#### FDA Form 1572

For IND held studies, the CRA will ensure that the FDA Form 1572 filed is current and up-to-date. All updated FDA Form 1572s should be completed, signed by the PI and verified by the CRA. As scoped, the CRA will provide a copy of the revised form to the CROMS Regulatory Department for submission to the FDA. The CRA will file the original in the Trial Master File.

A listing of applicable study related documents considered to constitute a complete Essential Document Package can be found in the CROMS CMP template and should be customized to reflect protocol specific needs. These documents may be reviewed by the CRA during IMVs.

### Drug Accountability

All studies under an IND will require some method of investigational product (IP) accountability. The method of accountability will be reviewed with the site pharmacy during each interim monitoring visit, when possible. IP accountability is generally necessary for non-IND studies. This will be discussed with the site at the SIV.

## Conclusion of Monitoring Visit

At the conclusion of the visit, the CRA will conduct a summary meeting with the PI, Study Coordinator and/or designee to review the findings and discuss any recommendations. This meeting provides an opportunity for immediate dialogue, feedback, clarification, and education. During this meeting, the CRA will review visit findings with the site so that they are made aware of the key issues found during the visit and that require site follow-up. These items will also be summarized as an Action Items Tracker attached to the monitoring visit documentation.

Monitoring visit findings and resulting action items will be documented in monitoring visit reports as well as an Action Items Tracker. For Intramural studies, once finalized, the monitoring visit report, with Action Items Tracker and the follow-up cover letter will be sent to the PI for review and filing in the ISF. For Extramural studies, the finalized detailed follow-up letter and Action Items Tracker will be sent to the PI for review and filing in the ISF. A CROMS designee will work with designated site staff to resolve any outstanding action items as communicated in the Action Item Tracker. At a mutually agreed upon time, or approximately 4 to 6 weeks post visit, whichever is earlier, the CROMS designee and site research staff designee will meet via telephone conference to discuss resolved, in process, and pending action items. At this time the need for and frequency of subsequent meetings will be discussed. In general, the follow-up letter, final monitoring visit report and Action Items Tracker will be sent within 3 weeks of the last day of the site visit.

# SITE CLOSE OUT

## Purpose of the Site Close-Out

The main purpose of the site close-out visit is to verify that the study team has completed gathering all study related data and no more study related procedures will be performed. The following are characteristics of a site prepared for close-out:

* Enrollment has been completed
* All subjects are off study (study activities complete, all drop outs documented)
* Data is monitored and collected according to monitoring plan, and all discrepancies have been addressed
* All agencies notified of study closure (such as the IRB, FDA or other health authorities as applicable)
* All AEs/SAEs/UPs reported to IRBs and the Rho Product Safety Department as applicable
* All regulatory documents on file

## Process of Site Close-Out

### Responsibility of CROMS

* Follow the same procedure as an IMV and include a plan to resolve any outstanding items via the Action Items Tracker and follow-up phone calls with site study staff
* Verify that all necessary study documents are present in the ISF and TMF as applicable
* Ensure that the Investigational Product is returned or destroyed and that this is recorded on final accountability logs (IND Applicable)
* Review record retention requirements with the Investigator [CFR Title 45 Part 46.115(b)]
* Obtain address/contact person for storage
* Discuss the planned course of action in the event of notification of an FDA audit
* Identify a contact person for any issues arising after study closure
* Ensure all AEs/SAEs/UPs have been reported to appropriate entities

### Responsibility of the Investigator

* Ensure the completeness and accuracy of all study documents
* Work with pharmacy to return or destroy the investigational product and record on accountability logs (IND Applicable)
* Notify IRB of study status
* Adhere to the requirements of record retention (ICH/GCP 5.5.12)
* Prepare a study final report and submit to the IRB (IND Applicable, 21 CFR 312.64c) (ICH/GCP 4.13)

# REPORT OF MONITORING VISIT AND FOLLOW-UP

## Monitoring Follow-Up Letter

All efforts will be made to provide a detailed visit report (Intramural studies) and detailed follow-up letter (Extramural studies) to the PI within 3 weeks of the site visit. Typically, copies will be sent to the Study Coordinator, OCTOM Director, and NIDCR Clinical Director for Intramural studies, and/or the Program Official for Extramural studies. A copy will be maintained in the CROMS master file.

### Contents of Follow-Up Letter

A Follow-up Letter summarizes items reviewed during the monitoring visit. The summary would also include any data discrepancies/findings noted during the monitoring visit and the actions required by the study team to correct these discrepancies. Examples of such findings may include issues with informed consent, drug accountability, and essential documents. A CROMS designee will work with designated site staff to resolve any outstanding action items as communicated in the Action Item Tracker attached to the Monitoring Visit Report. At a mutually agreed upon time, or 4 to 6 weeks post visit, whichever is earlier, the CROMS designee and site research staff designee will meet via telephone conference to discuss resolved, in process, and pending action items. At this time the need for and frequency of subsequent meetings will be discussed.

## Response to Report

The PI may elect to provide a written response to the letter, including a corrective action plan if there are issues to address, within 30 days from receipt of this letter. If there are any questions regarding the data findings or discrepancies, the PI or designee should contact the CRA for clarification.

# CONTACT INFORMATION

**OCTOM Director**

Michelle Culp, BSN, MPH

NIDCR

Voice: 301-594-4830

Email: mculp@nidcr.nih.gov

**CROMS Senior Research Scientist**

Nancy Yovetich, PhD

RhoFED

Voice: 919-595-6255

Email: Nancy\_Yovetich@rhoworld.com

**CROMS Project Director**

Cathie Snyder

RhoFED

Voice: 919-595-6291

Email: Cathie\_Snyder@rhoworld.com

# RESOURCES/BIBLIOGRAPHY

1. NIH Guide: NIH Policy for Data and Safety Monitoring, June 10, 1998
2. ICH/Guideline for Good Clinical Practice, Section 4 - Investigator, Section 5.18 - Monitoring, and Section 8 - Essential Documents for the Conduct of a Clinical Trial
3. 45 CFR Part 46: Protection of Human Subjects
4. FDA: www.fda.gov

Appendix 1

TITLE 45--PUBLIC WELFARE AND HUMAN SERVICES, PART 46--PROTECTION OF HUMAN SUBJECTS

Subpart D--Additional Protections for Children Involved as Subjects in Research

Sec. 46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject’s well-being, only if the IRB finds that:

1. The risk is justified by the anticipated benefit to the subjects;
2. The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
3. Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in Sec. 46.408.

Sec. 46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

1. The risk represents a minor increase over minimal risk;
2. The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
3. The intervention or procedure is likely to yield general knowledge about the subjects’ disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
4. Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in Sec. 46.408.