National Institute of Dental and Craniofacial Research

Tool Summary Sheet:
Clinical Monitoring Plan Template

Purpose: MS Word template to be used as a starting point for preparing a Clinical Monitoring Plan.

Audience/User

Clinical Research Associates responsible for preparing a Clinical Monitoring Plan

Details

This template includes a proposed structure for a Clinical Monitoring Plan as well as draft language and other guidance.

Best Practice Recommendations

- Review this draft template and customize to the specific needs and requirements of the monitoring group. Sample text may be updated as needed.
- If the study is utilizing a Data Coordinating Center (DCC), ensure that communication and interaction between the monitoring group and the DCC is clearly outlined in pertinent sections.
- "CROMS" is used as the monitoring group throughout this template. Replace with monitoring entity as applicable.

Technical/Formatting Notes

- Instructions and explanatory text are indicated by *{blue italics}* ("CROMS_Instruction" style). Instructional text will also be enclosed in braces to signify this text for screen-readers used by the visually impaired.
- Text enclosed with <> is a placeholder for a specific detail (e.g., <protocol title>); replace as appropriate.
- Delete template-specific *{instructional text}* as well as this Tool Summary Sheet during the monitoring plan development process.
- Leave the template version information in the lower left hand corner of the document. Add "Based on" in front of "Template Version" of desired.
- It is easiest and cleanest to use the styles that are embedded in the document. (In MS Word 2007: From the Home menu, select the bottom right arrow key to bring up the styles box, select "Options", under "Select Styles to Show" select "in current document".)
- Ensure that a placeholder and example text is replaced with the study-specific information.

Tool Revision History:

Version Number	Version Date	Summary of Revisions Made:
1.0	21Feb2011	Approved version
2.0	22Dec2011	Updated the Communication Plan section; included List of Abbreviations in the TOC; included language and reference to the CMP template tool for use by Program for determining visit frequency; editorial updates to selected sections to reflect current practice; revised ICF references to consent document.
3.0	15Dec2017	Reformatted Tool Summary Sheet; made administrative edits and revisions for broader external use; revised signatory lines; revised 'subject' to 'participant' and updated references to Sponsor; revised monitoring visit follow-up timeline; added Quality Management to SIV and IMV sections; and revised document retention bullets in COV section.

Clinical Research Operations and Management Support
Clinical Monitoring Plan
Protocol Number <protocol number>

<protocol title>

By signing below, I acknowledge my agreement to this plan.

OCTOM Representative

Name: _____

Signature: _____ Date: _____

Study Representative

Name: _____

Signature: _____ Date: _____

Table of Contents

{This table uses the Table of Contents function in Microsoft Word that will automatically update headings and page numbers used in the body of the report. In the body of the report, add, delete, or modify headings as needed in order to best reflect your study.}

1.0 LIST OF ABBREVIATIONS 5
2.0 INTRODUCTION 6
3.0 MONITORING COMMUNICATION PLAN 6
3.1 Email Distribution 6
3.2 Website Distribution 8
3.2.1 Final Visit Reports 8
3.2.2 Other Monitoring Communications 8
4.0 VISIT SCHEDULING 8
5.0 ESSENTIAL DOCUMENTS/TRIAL MASTER FILE 9
5.1 Required Essential Documents 9
5.2 Trial Master File (TMF) 10
5.3 Monitor's Role in Essential Document Maintenance 11
6.0 MONITORING REPORTS / ACTION ITEMS 11
7.0 TYPES OF VISITS AND MONITORING ACTIVITIES 12
7.1 Site Initiation Visit Activities 13
7.2 Interim Monitoring Visit Activities 16
7.3 For-cause Visit Activities 22
7.4 Close-out Visit Activities 23

1.0 LIST OF ABBREVIATIONS

{Add, delete or modify abbreviations as necessary per study protocol. It is recommended that abbreviations be listed alphabetically.}

AE	Adverse Event
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
COV	Close-Out Visit
CRA	Clinical Research Associate
CRF	Case Report Form
CROMS	Clinical Research Operations Management and Support
CSOC	Clinical Study Oversight Committee
DCF	Data Correction Form
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ED	Essential Documents
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IMV	Interim Monitoring Visit
IRB	Institutional Review Board
ISF	Investigator Site File
MOP	Manual of Procedures
NIDCR	National Institute of Dental and Craniofacial Research
NIH	National Institutes of Health
OBA	Office of Biological Agents
OCTOM	Office of Clinical Trials Operations and Management
OHRP	Office for Human Research Protections
PI	Principal Investigator
SAE	Serious Adverse Event
SC	Study Coordinator
SIV	Site Initiation Visit
SOP	Standard Operating Procedures
TMF	Trial Master File
UP	Unanticipated Problem

{Add, delete, or modify headings as needed in order to best reflect your study. Abbreviations may need to be revised throughout the document as text is added or deleted.}

2.0 INTRODUCTION

{Briefly describe the purpose of the CMP. Include additional information as it relates to the CMP (e.g., changes in PI, changes in clinical research management, protocol amendments).}

{The sentence listing "monitoring tasks performed in accordance with" should be modified to reflect a regulated or non-regulated study. Currently language reflects a regulated study.}

The Clinical Monitoring Plan (CMP) establishes the guidelines for conducting monitoring visits and related tasks for monitoring National Institute of Dental and Craniofacial Research (NIDCR) Protocol <protocol number, protocol title>. The CMP was developed by Rho's Clinical Operations Management and Support (CROMS) group, in collaboration with the NIDCR Office of Clinical Trials Operations and Management (OCTOM) and the Principal Investigator (PI). CROMS Clinical Research Associate(s) (CRA(s)) will perform monitoring tasks in accordance with the protocol specific requirements, Title 45, Part 46 of the Code of Federal Regulations (CFR), the International Conference on Harmonisation (ICH) Good Clinical Practice Guidelines (GCP), The Code of Federal Regulations Part 312, and other applicable requirements.

3.0 MONITORING COMMUNICATION PLAN

{Describe the process for distributing monitoring communication. Ensure that all stakeholders are reflected in the plan (DCC, NIDCR, PI, etc.) modify as appropriate}

3.1 Email Distribution

The CROMS designee will send monitoring communication to include: site visit confirmation letters, agendas, follow-up letters, action item trackers and, <insert other relevant documents to be included such as: consent review trackers, pathology report review trackers, etc.> to the following:

Program Contacts

Representative	Role
Study Program	
	Principal Investigator
	Study Contact

Representative	Role
Study Sites *{for multi-center studies, include as appropriate}*	
Site PIs listed in the table below	Site PI
Primary Site Contacts in the table below	Primary Site Contact
NIDCR-PROGRAM	
	Program Official
	Medical Monitor
	Health Specialist
NIDCR-OCTOM	
CROMS	

*Primary study contact at organization *{indicate above the primary study contact}*

Site Contacts:

Representative	Role
<Insert Site Name>	
	Site PI
	Primary Site Contact
<Insert Site Name>	
	Site PI
	Primary Site Contact
<Insert Site Name>	
	Site PI
	Primary Site Contact
<Insert Site Name>	
	Site PI
	Primary Site Contact
<Insert Site Name>	
	Site PI
	Primary Site Contact

Current contact information for individuals listed above is maintained on the CROMS website.

3.2 Website Distribution

3.2.1 Final Visit Reports

The following groups or individuals will have access to final site monitoring visit reports via the CROMS website:

- <insert name of Study Program PI>
- NIDCR-Program
- NIDCR-OCTOM
- CROMS

3.2.2 Other Monitoring Communications

Final versions of agendas, confirmation and follow-up letters, action item trackers, and <insert other study specific items associated with monitoring visits> will be posted to the study webpage on the CROMS website.

Access to the study webpage is password protected and restricted to individuals listed above, other approved study team members, CROMS, and its designees.

4.0 VISIT SCHEDULING

{Describe the process for scheduling monitoring visits and expectations for the site study staff during the visits. Include language detailing the frequency of monitoring and the expectation of the site and monitor with respect to timeline for visit scheduling requests.}

The CROMS designee will work with the Site Principal Investigator (PI) and Site Primary Contact to schedule monitoring visits. The Study (Grant) PI, NIDCR-Program, and NIDCR-OCTOM will be apprised of visit scheduling.

Prior to the visit, the PI will receive a visit confirmation letter, agenda and a list of participants to be monitored. Please see Section 7.2 for details on the selection of participant files for review. The CRA will ensure that this information is communicated to the site personnel within a mutually agreed upon timeframe to allow sufficient time for record requests. The PI and research staff will be expected to secure workspace for the CRA(s) and to be available during

the visits to facilitate monitoring activities. The CRA will be available at the end of each monitoring visit day to discuss findings and answer questions from the study staff. The Site PI and Primary Site Contact are also expected to be available for a wrap-up meeting at the conclusion of the visit, as schedules allow. These expectations will be explained in the visit confirmation letter.

5.0 ESSENTIAL DOCUMENTS/TRIAL MASTER FILE

{Describe required essential documents (ED), process for review, collection and submission of ED as it relates to monitoring. Identify owner of the study's Trial Master File (TMF).}

5.1 Required Essential Documents

A binder(s), which for purposes of this clinical monitoring plan will be defined as the investigator site file (ISF), will be maintained at the trial site and serves as the central source for essential document (ED) maintenance at the site.

{If the site is maintaining a combination of paper and/or electronic files, consider the following additional information.}

EDs for this trial will be maintained by each study site as a combination of paper and electronic documents. The contents of the ISF will include:

- Essential documents maintained in paper form
- Essential documents maintained electronically at the site will have a page referencing the electronically maintained location of the ED. Note: The site may elect to file a paper copy of the electronically maintained document in the ISF

The following documents represent a complete site essential document packet and are to be maintained in the ISF: *{customize as appropriate}*

- Form <insert appropriate form for study: 1572, 1571, etc.> *{if applicable; if not, remove}*
- Principal Investigator's (PI) Curriculum Vitae (CV)
- Copy of PI's current <insert dental, medical, etc.> license
- PI Human Subject Protection Training documentation
- PI Financial Disclosure Form (FDF) *{if applicable; if not, remove}*
- Sub-Investigator(s) (Sub-I) CV

- Copy of Sub-I Dental/Medical License(s)
- Sub-I Human Subject Protection Training documentation
- Sub-I(s) FDF *{if applicable; if not, remove}*
- Protocol/Protocol Amendment(s) Signature Pages
- Site Specific Consent Document; Assent Form *{if applicable; if not, remove}*
- Institutional Review Board (IRB)-Approved Protocol, Consent Document, Protocol Amendments and approval documentation
- IRB approved Advertisements, Participant Handouts, <insert specific items pertinent to the protocol; dosing diaries, dosing instructions, etc.>
- IRB Compliance Documentations
    - FederalWide Assurance number (FWA#)
- Letter from site to justify use of a central IRB in lieu of a local IRB *{if applicable; if not, remove}*
- Laboratory Certifications *{if applicable; if not, remove}*
- Laboratory Reference Ranges *{if applicable; if not, remove}*

5.2 Trial Master File (TMF)

{Identify the owner of the TMF and also the entity designated to maintain the TMF during the course of the study, as applicable. There are four primary scenarios for TMF maintenance. The first four reflect possibilities for a regulated study and the last for a non-regulated study:

1. *If the PI maintains the TMF during the study, and the study is single site, originals of above referenced documents and any other necessary study documentation will be maintained at the site, i.e., the TMF will be held by the site.*
2. *If the PI maintains the TMF during the study, and it is a multi-center trial, CROMS can be delegated to maintain the TMF, or the PI can elect (in agreement with NIDCR) to maintain the TMF.*
3. *If a DCC is holding the TMF for the study, the level of interaction between the CROMS monitor and the DCC will dictate the level of ED oversight and review. When a DCC holds the TMF, the CROMS monitor will not be responsible for collection of ED.*

4. *If the study is non-FDA regulated (non-IND or IDE) essential documents can be maintained on the study website, if one is used.}*

5.3 Monitor's Role in Essential Document Maintenance

During the course of routine monitoring visits, the CROMS CRA will review for accuracy and completeness, the ISF and all associated documents as noted in section 5.1.

As noted in section 5.2, <insert owner of TMF> is tasked with maintenance of the TMF. The CROMS CRA or designee will support this endeavor by:

- <insert language reflective of support of TMF owner. See examples below>

{When the site is maintaining the TMF, the monitor will review ED for completeness and accuracy. No original documents will be collected. The monitor will alert the study staff to discrepancies and upcoming expiration dates.

If CROMS is maintaining the TMF, the CROMS monitor will collect original documents and ensure that a copy of all pertinent ED are contained in the ISF.

If a DCC is maintaining the TMF, the CROMS monitor may be tasked with alerting the site or DCC as to upcoming expiration dates for ED. The DCC and CROMS monitor will need to establish and document in the CMP a method for communication.

If the study is non-regulated, the CROMS monitor can, in conjunction with the site, ensure that all indicated ED are contained in the ISF and uploaded to the study website, as applicable.}

6.0 MONITORING REPORTS / ACTION ITEMS

{Describe the process and timeframe for providing monitoring reports.}

Monitoring visit findings and resulting action items will be documented in trip reports. CROMS will send drafts of the reports to NIDCR-OCTOM within 14 calendar days of the last day of the monitoring visit, and NIDCR-OCTOM will send final comments back to CROMS within 14 calendar days. Once the visit documents are finalized, documents will be made available to identified study team members as noted in section 3.0.These documents should be printed and stored in the ISF. <insert where originals will be maintained based on information contained in TMF section> Ideally, documents will be provided to the site in approximately 4 weeks of visit conclusion.

A CROMS designee will work with designated site staff to resolve any outstanding action items as communicated in the Action Item Tracker presented as an attachment to the <insert

appropriate document, for example the detailed follow-up letter or 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.

7.0 TYPES OF VISITS AND MONITORING ACTIVITIES

{Describe the types of monitoring visits to be conducted during the study and the purpose of each visit.}

CROMS is responsible for conducting <insert number> types of monitoring visits for this study.

- A Site Initiation Visit (SIV) will be conducted prior to site activation to confirm preparedness for protocol execution, satisfactory site facilities, clarify the applicable regulations and requirements of the protocol, carefully review the process of implementing the protocol at the site and conduct any necessary training prior to the assigned Program Official activating the site for enrollment.
- Interim Monitoring Visits (IMVs) will be conducted to confirm participants' rights are being protected; the study is being conducted according to the protocol and applicable regulations, including GCP; confirm accurate reporting of participant safety data and study endpoints.
- For-cause visits (FCVs) are conducted to address any unanticipated issues that arise which require training, remediation or other situations in which the site requires assistance. For-cause visits can be mandated by the NIDCR, its designees, or can be requested by the site.
- A Close-Out Visit (COV) will be conducted to ensure that all study data and other study documentation is complete and accurate and that all study records have been reconciled. The types of activities that may be conducted at each onsite visit are described in detail below.

{Describe monitoring activities in detail for each visit. Modify text to accommodate specific visits, EDC, eCRFs, SAE/UP reporting, etc., as appropriate.}

7.1 Site Initiation Visit Activities

{Provide language detailing responsibility for the SIV agenda. When monitoring is the primary service by CROMS, sites are responsible for creating the agenda and running the SIV with input from NIDCR and CROMS. If CROMS is providing service in multiple areas of the study, the CROMS designee will hold responsibility for the agenda and leadership of the SIV.}

The SIV will be conducted prior to participant enrollment. The following activities may be conducted during the SIV:

a) Investigator and Site Responsibilities

- Verify that the PI understands and accepts the responsibility to obtain IRB approval of any amended protocols, consent documents, or advertisements, and to ensure continuing review of this study by the IRB.
- Verify that the PI understands and accepts responsibility for overseeing the conduct of the study in accordance with the protocol, applicable regulations and GCP, as well as ensuring the conduct of all staff performing study procedures.

b) Review of Facilities

- Tour of site facilities where study activities will be conducted, including but not limited to: consent discussions, participant visits, laboratory specimen collection, processing, and storage, records and ISF management, and monitoring workspace.
- Verify presence of study-required equipment, including but not limited to: <insert protocol specific study-required equipment>

c) Protocol Review

- Review study objectives, study design, and study population.
- Review study inclusion/exclusion criteria.
- Review participant randomization. *{remove if not applicable}*
- Review the study schedule of events and sample collection.
- Review protocol required clinical and laboratory assessments.
- Review responsibility to review, sign, and follow-up on laboratory reports.
- Review guidelines for premature discontinuation of study participants.

d) Informed Consent Process

- Discuss the site's informed consent procedures.
- Verify that the PI understands and accepts the responsibility to obtain informed consent in accordance with all applicable regulations and to document the informed consent process for each participant.

e) Manual of Procedures (MOP) / Standard Operating Procedures (SOP)

- Review to ensure understanding of the necessity of standardization of protocol execution across all relevant study team members.
- In the absence of a MOP, review the applicable site SOPs.

f) Study Documentation

- Review the document retention requirement for all study-related records. Inform the PI that all study records must be retained <insert timeframe (e.g., until disposal is authorized by the Sponsor; See detailed text regarding retention requirements in COV Section 7.4)>
- Verify that the PI understands that he/she is responsible for retaining all study records and making them available for monitoring and audits during the conduct of the study and throughout the retention period.

g) Investigator Site File

- Sign and date the site visit log each day of the visit.
- Verify that all study documents are present in the ISF and make the PI and site personnel aware of their responsibility to keep the file complete and current.
- <Insert appropriate task for review and/or collection of ED based on section 5.0>
- Verify that the Delegation of Responsibilities Log is current and signed by the PI.

h) Electronic Case Report Form (eCRF) Review and Laboratory Tracking Training *{remove if not applicable}*

- Review and provide training on the use of the electronic data capture system and the specimen management and tracking system for the study.

i) Safety Reporting

- Review adverse event (AE), serious adverse event (SAE), and unanticipated problems (UP) definitions, grading, attribution, reporting, and review.

- Review requirements for IRB and Office for Human Research Protections (OHRP) notification of UPs, AEs, and SAEs.

j) Review Source Documentation Requirements and eCRF Completion. *{remove the "e" if paper CRFs}*

- Review requirements for maintaining adequate source documentation that supports the data recorded in the eCRFs.
- Review and provide instruction for eCRF completion, as well as completion instructions listed in the MOP.
- Ensure that the PI and site personnel are aware of eCRF correction and data clarification requirements.

k) Review Laboratory Supplies and Procedures

- Verify that the site has adequate supplies available as detailed in <insert where the complete list of study supplies can be found>.
- Review collection, handling, storage, and transport procedures for laboratory samples. Samples collected for this study include: <insert list of samples to be collected, i.e., clinical samples, DNA, future use, etc>.

l) Discuss Site-Level Quality Management Activities

- Discuss CRA review of site-completed QM reports during IMVs, if applicable

m) Discussion of General Items

- Obtain documentation of all site personnel present for the SIV on the SIV Training Log.
- Ensure that all required supplies/clinical trial materials (e.g., CRFs, MOP, ISF) have been received by the clinical study site prior to screening or enrolling the first study participant.
- Discuss the expected schedule of monitoring visits with site personnel, including the timing of the first monitoring visit, personnel availability, and monitoring space availability.
- Initiate discussion of site close-out procedures. Study close-out procedures will be discussed in further detail during IMVs.

- Review the findings and action items of the visit with the PI and appropriate site personnel.

7.2 Interim Monitoring Visit Activities

{Modify text as appropriate for each study keeping in mind the purpose of an IMV as noted in description of monitoring visits at the top of section 7.0. Multiple factors should be taken into consideration when determining the amount of source document verification per patient, frequency of monitoring, and timing of first monitoring visit. Considerations include but are not limited to: the complexity of the protocol, target enrollment, number of participant visits, data collected at each visit. Also available for use is the Clinical Monitoring Plan Development Tool. This tool assists in determining a baseline frequency and level of monitoring based on the aforementioned considerations.}

{Below, find sample text for instances in which the first visit to a site occurs after the site has begun enrollment. In this situation, the first IMV will contain elements of assessment as well as interim monitoring.}

The following activities may take place at the first site visit:

During the first visit at each study site, in addition to performing IMV associated tasks, the CRA will confirm operational and facility related items as discussed in site assessment calls and previous communication with the study staff.

Items for confirmation may include:

a) Roles and Responsibilities for site personnel

- Communication between team members
- Appropriate delegation of study tasks to qualified team members

b) Site record keeping

- ISF
- Participant source documentation

c) Protocol submissions, deviations and associated regulatory reporting

d) Safety Reporting

- Process
- Safety Reports to date

e) Data collection methods

- Case Report Forms
- Entry
- Query resolution
- Interaction with the DCC

f) Facilities appropriate to study execution

- Office set up appropriate to GCP and patient privacy
- Adequate facilities for study supply storage, sample processing, availability to necessary technology for data entry

g) Enrollment: target, current, recruitment strategies

At the conclusion of the visit, or after review of the above, (to include site files) the CROMS CRA will meet with the Site PI and Site Study Coordinator (SC) to determine a monitoring strategy for future visits. This strategy will include the type of data to be monitored, an anticipated standard percentage of data to be monitored, as well as any other administrative or study support items for which the site may be delinquent. The first IMV report will include in the overall comment section a bullet point outline of the strategy to be implemented. This strategy may be modified or updated as needed or requested by the NIDCR, CROMS, or the site.

Frequency of future IMVs will be based on the developed monitoring strategy taking into consideration: enrollment status, data quality, protocol compliance, and the prescribed amount of data to be monitored according to the monitoring plan. Irrespective of other factors, the site will be monitored twice per year.

At a minimum the following participant data will be included in the monitoring strategy to be monitored at each visit:

{Below, find sample text monitoring oversight began with a site initiation visit.}

The first IMV will be conducted at each site after approximately <insert number of participants> have been <insert qualifier, i.e., screened, enrolled, randomized>, subsequent visits will be conducted after approximately every <insert number of participants and qualifier>. Frequency of future IMVs will be based on enrollment status, data quality, protocol compliance, and the prescribed amount of data to be monitored according to the monitoring plan.

{Below is sample text where 100% source document verification will be conducted for a percentage of participants.}

At a minimum the following participant data will be monitored at each visit:

- 100% review of consent documents for all participants consented or re-consented since the last onsite visit
- 100% of SAEs
- 100% of study files for <insert percentage> of participants enrolled at the site overall. The CROMS statistical programmer will randomly select <insert the agreed upon number> participant files for CRA review at each interim visit. Once selected, these participants will be monitored through the entirety of their participation in the study.

{Below is sample text where source document verification will be 100% of key variables for 100% of participants}

At a minimum the following participant data will be monitored at each visit:

- 100% review of consent documents for all participants consented or re-consented since the last onsite visit
- 100% of AEs, SAEs and UPs
- 100% of key variable CRF pages noted below for unmonitored participants:
    - <insert bullet points to reflect CRF pages to be source document verified>

{Below is sample text for 100% source document verification for all participants}

All data for all participants will be monitored over the course of the trial, but not necessarily at each visit. The participants selected for monitoring and the extent of record review at each visit will be based on the progress of enrollment, as well as any concerns that may emerge about the safety of human participants or the integrity of study data.

At a minimum the following participant data will be monitored at each visit:

- 100% review of consent documents for all participants consented or re-consented since the last onsite visit
- 100% of SAEs
- 100% of participants dosed since last onsite visit

While follow-up data will be monitored for all participants, the amount and frequency of follow-up data monitored at each visit will vary based on time and resources.

{Below is sample text for all studies. Text includes references for paper as well as EDC studies. Modify as appropriate per protocol and circumstance.}

Findings of the CRA that might indicate lack of understanding of protocol requirements, deviation from GCP (for example: inadequate attention to protection of human participants), unreported or underreported safety information or other non-compliance may result in an increase in the percentage of participant data monitored or monitoring visit frequency. Changes will be implemented after consultation with NIDCR.

The following activities may be conducted at each IMV:

{Below is sample text to be customized based on study specific need.}

a) Consent Document Review For All Participants

- Verify consent was obtained prior to initiating study procedures.
- Verify appropriate signatures and dates were obtained.
- Verify that the correct version of the consent document was signed and dated.
- Verify that ongoing participants were re-consented with updated consent documents as directed by the IRB.
- Verify that source documentation includes a description of the consent process.

b) Source Documentation and CRF Review

- Verify that accurate, complete, and current source documentation is maintained.
- Verify participant eligibility.
- Verify that all procedures outlined in the protocol were completed.
- Verify that missed visits, clinical procedures, and tests are recorded appropriately and reported to the IRB as protocol deviations, as defined by IRB policy.
- Verify that the PI assessed all abnormal lab values for clinical significance.
- Verify that all withdrawals and dropouts of enrolled participants are recorded in the source documentation and on the CRF.
- Verify that AEs, SAEs, UPs, and concomitant medications are documented and reported according to the protocol.

- Ensure that the PI has reviewed, signed, and dated all required CRF pages <specify for paper based studies, wet ink signature, or electronically signed all necessary electronic Case Report Forms (eCRF) pages (for Electronic Data Capture (EDC) systems)>.
- Verify data entries in the CRF pages with the source documentation, and note any errors, omissions, or discrepancies by issuing manual queries <insert form or system as appropriate (e.g., on Data Correction Forms (DCF); within the EDC system), and revise other bullets/text accordingly.>
- Work with site staff to resolve queries while on-site and request the resolution of any remaining queries that cannot be resolved during the visit.
- Provide the site staff with copies of DCFs *{if paper based study}*.
- Verify that previously outstanding data queries have been resolved, signed, <wet ink signature for paper studies, remove if EDC> and dated by the PI or designee.

c) Unanticipated Problems, Adverse Events, and Serious Adverse Events

- Follow-up on previously reported UPs, AEs, and SAEs.
- Verify all newly reported UPs, AEs, and SAEs against source documentation.
- Confirm that all UPs, AEs, and SAEs have been reported to the IRB, Office of Biological Agents (OBA), and Food Drug Administration (FDA) as required.
- Identify any unreported UPs, AEs, and SAEs in source documentation.
- Review UP, AE, and SAE reporting procedures, as necessary.

d) Investigational Product

- Confirm that investigational product is stored at the correct temperature in a secure storage area.
- Review temperature logs to confirm stability of storage conditions.
- Confirm that investigational product is being dispensed according to protocol.
- Confirm that product accountability records are accurate, current, and reconciled.

e) Laboratory and Specimen Management

- Assess maintenance of research specimen logs and associated documentation.
- Review handling of laboratory specimens.

- Review specimen storage conditions and maintenance of temperature logs.
- Ensure organization and storage of specimens in a secure location.
- Ensure appropriate specimen labeling.

f) Protocol Deviations

- Verify that all protocol deviations are documented appropriately in each participant's research record and on the appropriate protocol deviation form.
- Ensure that the site has reported all protocol deviations to the IRB, as defined by IRB policy.
- Address any protocol deviations with site personnel during the IMV and identify ways to prevent the recurrence of similar issues.
- Protocol deviations will also be reviewed throughout the study with the PI during routine conference calls, which include CROMS staff and the clinical site. Any trends or serious errors will be discussed, and the group will develop a plan of action to prevent further problems.

g) Quality Management (QM) Documentation

- Review site-generated quality management efforts and documentation.
- Review site-generated quality management reports, if utilized, to confirm the items identified by the study team have been addressed. The CRA may offer suggestions for additional quality control efforts or additional follow-up for the site to consider.

h) Investigator Site File

- Ensure that essential document files are complete and current.
- <Insert appropriate task for review and/or collection of ED based on section 5.0>

i) Investigator and Site Personnel Responsibilities

- Ensure that the Delegation of Responsibilities Log is complete and signed.
- Ensure that the Authorized Signature Log is complete and signed.
- Verify that the PI and site personnel are adhering to the protocol and conducting the study according to regulatory requirements and good clinical practice guidelines.

- Verify that study activities are being performed by the PI or have been delegated to personnel qualified by appropriate education or training.

  Provide and document any necessary training for the PI and site personnel, such as training on good clinical practice guidelines and use of the data management and lab tracking system software.

j) Visit Conclusion

At the conclusion of the visit, the CRA will meet with the PI and site research staff to review visit findings and answer questions. The CRA will discuss the following topics at a minimum:

- Enrollment progress.
- Consent process and documentation.
- Study conduct and documentation of study activities.
- UPs, AEs, and SAEs experienced by study participants.
- Scheduling of the next IMV.

k) Action Plan for Identified Issues

The CRA will meet with the site SC and PI periodically during the visit to explain findings, ask questions, and work with the SC and PI to address issues at the time of the IMV. Issues identified and resolved at the IMV will be documented in the IMV report and associated follow-up letter. Additional actions that need to be taken by the site staff following the visit will be documented in the Action Item Tracker presented as an attachment to visit documentation. If the CRA encounters a serious issue, negative performance trend, or general non-compliance, the CRA will contact the CROMS SC, CROMS LCRA, NIDCR-Program and NIDCR-OCTOM to determine the appropriate course of action.

Please refer to section 6.0 for further information on action item follow up.

7.3 For-cause Visit Activities

During for-cause visits, the CRA may complete any of the activities listed for the IMV, discuss clinical operations and study management methods with the research staff, and/or provide training to the research staff.

7.4 Close-out Visit Activities

Study closure activities may require more than one visit to ensure the proper closure of the study. These activities may be conducted during a series of on-site visits or by telephone. Close-out visits may be conducted at study completion or earlier in the case of study termination by the IRB, <insert appropriate Safety Oversight Group or other Regulatory Body: Data Safety Monitoring Board (DSMB), OBA, FDA, or Clinical Study Oversight Committee (CSOC)>. The outcome of the visit and other close-out activities will be documented in a report and follow-up letter.

CRAs will perform the activities below during the study close-out process:

a) Consent Documents

- Confirm that consent was obtained for each participant prior to initiating study activities.
- Confirm that consents contain appropriate signatures and dates.
- Confirm that the correct version of the consent document was signed and dated.
- Confirm that additional consent was obtained for protocol amendments as required by the site's IRB.

b) Investigator Site File

- Ensure that essential document files are complete and current.
- Identify any missing study documents.
- Ensure that the Authorized Signature and Delegation Logs are complete and signed by the PI.

c) Source Documentation and CRF Review

- Reconcile the final status of all participants listed on the screening log.
- Confirm that all required data fields have been verified against source.
- Confirm that all data queries have been resolved.
- Confirm that the PI has reviewed, signed, and dated all required CRF pages *{revise bullet to reflect use of an EDC system as applicable}*.
- Verify that the site has legible copies of all CRFs *{remove if using EDC}*.
- Confirm that protocol deviations are noted in the source documents.

d) Unanticipated Problems, Adverse Events, and Serious Adverse Events

- Confirm that all UPs, AEs, and SAEs have been reported to the appropriate regulatory agencies as required.
- Confirm that the site has and will continue to meet safety reporting requirements.
- Ensure that copies of SAE reports are filed with the corresponding site files.

e) Investigational Product

- Confirm that all investigational product accountability records have been maintained appropriately and are consistent with the amount of remaining product.
- Ensure that remaining IP will be destroyed per institutional requirements. Document proper destruction of any remaining product.

f) Laboratory Samples

- Confirm that all lab samples have either been analyzed or stored for future analyses.
- Confirm future use specimen disposition and labeling/de-identification, as appropriate.
- Confirm site process for identification and disposition of future use samples connected to participants who withdraw consent.

g) Regulatory Obligations

- Confirm that the PI has met and will continue to meet regulatory obligations.
- Confirm that the PI has provided written notification of study closure to the IRB and verify acknowledgement by the IRB of study closure.
- If the study was terminated prematurely, the CRA will confirm that enrolled participants were informed and that appropriate therapy and follow-up was initiated by the PI.
- Inform the PI of the possibility of future audits by regulatory authorities.

h) Records Retention

- For IND/IDE studies, review the document retention requirement for all study-related records: 21 CFR 312.57 (c), 45 CFR 46.115 (b), 45 CFR Part 74, as well as institutional and local IRB requirements; emphasizing that the more stringent retention policy should be followed.

- For IND/IDE studies, inform the PI that all study records and reports must be retained for 2 years after a market application approval for the drug, or until 2 years after shipment and delivery of drug for investigational use is discontinued and Food and Drug Administration (FDA) has been notified (21 CFR 312.57).]
- HHS protection of human subjects' regulations (45 CFR 46.115) require institutions to retain records of IRB activities and certain other records for at least 3 years after completion of the research.
- 45 CFR Part 74 states that financial records, supporting documents, statistical records, and all other records pertinent to an award shall be retained for a period of 3 years from the date of submission of the final Federal Financial Report (FFR) to the HHS awarding agency (National Institutes of Health (NIH)). *{Extramural studies only}*
- In addition, all study records must be retained in accordance with National Institutes of Health (NIH) policies on document retention and local IRB requirements. *{Intramural studies only}*
- Discuss PI's responsibility for retaining all study records and making them available for monitoring and audits during the conduct of the study and throughout the retention period.
- Instruct the PI to notify the Sponsor if the study files are to be relocated or responsibility for site files is transferred to another individual.

i) Visit Conclusion

At the conclusion of the COV, the CRA will meet with the PI and site SC to discuss:

- Any findings noted during the visit.
- Retention timeframes for study-related documents.
- Safety reporting requirements.
- Notification of the IRB that the study has concluded.
- Outstanding issues at study closure and a plan for their resolution.