MONITORING PLAN ACTIVITIES:

**Visit frequency**: Onsite visits should occur at a maximum interval of every 8 weeks, with an online or phone visit scheduled between each onsite visit. The following activities may be conducted at each :

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.
- 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 **¡Error! No se encuentra el origen de la referencia.**>

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 site coordinator and the principal investigator 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 **¡Error! No se encuentra el origen de la referencia.** for further information on action item follow up.