Non-Significant Risk (NSR) Device-only Study

Clinical Monitoring Plan (CMP)

Protocol CMP version <#.#>, date <dd-Mmm-yyyy>

Study Overview

Protocol Title:	<full protocol title>		
Protocol Number:	<number>	Version Date:	<dd-Mmm-yyyy>
Lead Principal Investigator:	Dr. <first and last name>	NCI CCR Branch:	<branch name>
Sponsor:	CCR OSRO		
Protocol Summary:	<This should be a brief summary of the study design/description.> <Include primary and secondary objectives.> <Bulleted information, add bullets as needed.> <If available, add study schematic or diagram> Monitors will review the detailed criteria in the protocol. Do not include: • Any 'Precis' truncated/abbreviated inclusion/exclusion criteria. • exploratory objectives.		
Protocol N:	<Total number of participants to be enrolled> <If applicable, provide the number of participants per cohort, per arm, or for the 'lead-in' period, as applicable> The section is for metrics/# of participants to be included. Planned numbers are often available in the treatment assignment or protocol statistical sections. Exclude a narrative summary of how this works.		
Protocol Accrual Rate	<The expected time frame, e.g., months/years to reach the study accrual ceiling> This section is for metrics. A planned accrual rate (e.g., participants per month) is often available in the statistical section of the protocol itself. Do not include the narrative summary of how this works.		
NSR Device(s)	<Include the name of each device used>		
Single Site or a Multi-Center Study	☐ Single Site or ☐ Multi-Center If a Multi-Center study, is the Coordinating Center Communication Plan on file? ☐ Yes ☐ No		
Clinical Site(s):	NIH, NCI, <Branch Acronym, include the title of 'Coordinating Center' if the protocol is a multicenter trial>		

	NIH Clinical Center 10 Center Drive, <PI office room number per-protocol cover page> Bethesda, MD 20892 <Other non-NIH locations include institutional name and street address> <Other non-NIH locations include pharmacy name and street address> <For each external non-NIH site, note whether a monitoring Site Assessment Visit (SAV) is or is not required>

1. Purpose

The purpose of clinical trial monitoring is to verify:

1. The rights and well-being of human participants are protected.
2. The reported trial data are accurate, complete, and verifiable from source documentation.
3. The conduct of the trial follows the currently approved protocol/amendment(s), with Good Clinical Practices (GCP), and with applicable regulatory requirements.

This document identifies key monitoring activities and specifies the data to be reviewed. Study monitoring is a Sponsor responsibility as outlined in E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R2) Good Clinical Practice, FDA Guidance, 5.18 Monitoring and FDA regulations, specifically 21 CFR Parts 50, 54, 56, and 812. The Plan has been developed prior to study initiation and will be amended throughout the study as appropriate to reflect study and monitoring updates that may be triggered by protocol amendments, non-adherence to the protocol, GCP or Sponsor requirements, or the identification of new risks to study integrity.

Refer to FDA's Information Sheet Guidance regarding the Sponsor's responsibilities as it relates to Non-Significant Risk (NSR) Medical Device Studies: https://www.fda.gov/media/75459/download

2. Site Monitor

Site Monitors are appropriately trained and qualified to monitor clinical trials under an NIH IRB-approved protocol using a Non-Significant Risk (NSR) Device.

Monitors are responsible for ensuring the appropriate conduct and documentation of a study. Monitors will thoroughly understand the research study background, design, procedures, objectives, and related requirements. Monitors will be independent of the study team and will not be involved in collecting data or the modification of study-related documentation.

2.1. Monitor Responsibilities

To verify:

1. Enrolled Participants meet eligibility criteria, including a documented informed consent process that includes a properly signed informed consent document.
2. Site essential regulatory documentation is present, current, and complete.
3. NSR device is stored and handled in accordance with the protocol, device manual, and Sponsor requirements.
4. NSR device receipt, use, return, and disposition are controlled and accurately documented.

5. The clinical trial is conducted in compliance with the protocol, GCP, and regulations.
6. Unanticipated Adverse Device Effects (UADE) are recorded and reported in accordance with the protocol.
7. Protocol non-adherence is documented in participant source records and reported as required.
8. Participant withdrawal of consent is documented in the study records.
9. Non-adherence to the protocol, GCP, and regulations are reported, and action taken to prevent recurrence, as appropriate.

3. Procedures

The intensity and modality of clinical site monitoring are determined by a risk assessment based on the risk exposure to study Participants. The FDA guidance on the risk-based approach to monitoring is a document that outlines the principles of risk-based monitoring and will be utilized. A link to the guidance is provided: FDA Guidance on Risk-Based Approach to Monitoring, August 2013.

3.1. Site Assessment

General description:

The goal of the Site Assessment Visit (SAV) is to confirm that the Principal Investigator (PI), any Sub-investigators, and associated staff have adequate qualifications and that the site has the capacity to support the safe and proper conduct of the study and access to the study target population. In advance of the visit, the Monitor will confirm the visit location (on site) and date and include a description of the intention of the visit, expected activities (e.g., facility tour), any records required for review, and any personnel who should be available for the evaluation of the Site and Staff to conduct the clinical trial requirements. It is expected that the site PI will attend the SAV.

The Monitor will meet with the PI and site Staff to discuss the clinical trial protocol, procedures, and reporting requirements. The Monitor will tour the facility to confirm the adequacy of administrative and clinical areas, facilities, and equipment. Access to the study target population will be evaluated. In advance of the visit, the Monitor will review the FDA disqualification list and public notification of 483s for PIs and proposed Sub-investigators. The Monitor will discuss any significant findings with OSRO Operations. After the visit, the Monitor will complete an SAV report of all site assessment data, including an impression of the PI/site's ability to conduct a well-controlled clinical trial based on visit findings and any identified issues requiring follow-up. The SAV report will be submitted to the OSRO Operations Coordinator. A Follow-Up Letter summarizing the SAV activities will be sent to the site PI.

OSRO will not require SAVs for NIH NCI Clinical Center campus facilities and CCR Research Staff. The SROS Clinical Site Monitoring Team will maintain a master description of the facility and processes supporting studies conducted at the NIH Clinical Center and ancillary departments.

OSRO SROS clinical site monitoring SAVs will be required for multicenter protocol sites outside the NIH Clinical Center. Note: SAV requirement will be deferred if the site has had an Assessment Visit within the last 12 months or if the site is participating in another OSRO SROS monitored trial at the same site (same PI and facility).

All SAV findings and identified issues requiring follow-up will be reported to OSRO. Before an SAV, the Sponsor, in collaboration with the NCI Coordinating Center of the multicenter protocol, may require non-NIH site(s) to complete a pre-SAV customized questionnaire to gather preliminary information regarding site experience and

capabilities. Based on the SAV findings, the Sponsor, in collaboration with the respective NCI Coordinating Center team, will determine if the non-NIH site will participate in the study.

At the Sponsor's discretion, a combined SAV/SIV approach may be utilized.

3.2. Site Initiation

Prior to site activation, the site will request a clinical site monitoring Site Initiation Visit (SIV) via the SROS Request for Services (RFS) online system. The site will provide up to three preferred SIV dates.

3.2.1. SIV Prerequisites

- Required site essential regulatory documents per OSRO's 203 Clinical Trials Records policy have been uploaded to the SROS eTMF; any review findings, issues, or discrepancies have been resolved; and SROS Essential Regulatory Documents Group (ERDG) has determined that the documentation is appropriate and complete.
    - The OSRO electronic Clinical Site Delegation of Authority Log and applicable Signature Sheet(s) is complete and provided along with relevant training records.
- The SROS Clinical Site Monitoring Team has finalized the Clinical Monitoring Plan (CMP).
- The Source Location Record (SLR) form will be provided to the site for review and completion. The completed SLR should be provided to the Monitor prior to the SIV.

3.2.2. SIV Attendance

- In addition to the PI, a quorum of Staff with delegated responsibility for protocol tasks/duties must attend the SIV. A quorum includes at least one Staff member responsible for each of the following roles:
    - Sub-Investigator that is a licensed physician
    - Study Coordinator
    - NCI Laboratory of Pathology (LP) Staff representative (if the NSR Device is an assay)
    - Non-LP Staff representative (if the NSR Device is handled in an area outside of the NCI Laboratory of Pathology).
- If the SIV format is in-person, all SIV attendees should sign the SIV Attendance Sheet. A copy of the SIV Attendance Sheet should be maintained in the site's regulatory files.
- The SIV web-based meeting log-in record, supplemented by a list of those who phoned in, will constitute the SIV participant list for the SIV Report and record of training on the Protocol version presented during the SIV.
- The monitor will notify OSRO if a quorum of Staff is not in attendance at the SIV and site activation may be delayed.

3.2.3. SIV Meeting Modality

Remote **web-based** SIV will be utilized for NSR device-only studies (unless otherwise specified).

The Monitor will send an SIV confirmation letter after the OSRO Clinical Trial Records Policy 203 pre-SIV requirements have been met.

If applicable, the Monitor will request an onsite facility visit to confirm the readiness of:

- Laboratories supporting the study's primary and/or secondary endpoints and
- NSR device storage facility / room.

- If an SIV-related onsite facility visit is necessary, the onsite visit activity may be deferred until the first onsite interim monitoring visit. This will be determined on a case-by-case basis and upon discussion with OSRO.

Notes:

- An onsite facility visit during the time of SIV is only required if not previously conducted for another SROS-monitored protocol within the required time frame (see section 3.3.2 for details).
- For multicenter studies (when non-NIH external sites are participating), the SIV for multiple sites can be combined if all sites meet the SIV prerequisite and with the Sponsor's approval.

3.2.4. SIV Presentation

The Monitor will prepare the PowerPoint protocol presentation for the PI to present during the SIV. The CCR Lead PI for multicenter studies will be responsible for the presentation of the protocol. The Monitor will present administrative and procedural topics (clinical site monitoring expectations) related to:

- Site Essential Regulatory Documents
- Participant Record Review
- Sponsor Protocol Non-Adherence Reporting
- NSR Device Storage and Handling
- Monitoring Visit Activities
- GCP, Regulations and Guidelines, HSP, Federal-Wide Assurance (FWA) for the Protection of Human Participants
- Source Documentation
- Informed Consent Process
- Unanticipated Problems, Sponsor Safety Recording, and Reporting Requirements
- Sponsor Responsibilities
- Investigator Responsibilities
- Site Activation
- If applicable, any specific NSR Device Study requirements

3.2.5. After the SIV

- The Monitor or the CSM will provide OSRO Operations with the list of SIV attendees.
- The Monitor will generate a draft SIV report on the information reviewed and any findings and/or action items. The draft report will be submitted to OSRO Operations for review and acceptance. OSRO Operations staff will review and provide feedback on the draft report. Review comments will be addressed by the Monitor before the SIV report is finalized.
- Once finalized, the SIV report will be sent to the PI, the NCI Protocol Support Office, and the Center for Cancer Research Quality Assurance (CCR QA).
- If the IRB has approved a protocol amendment after the SIV and before site activation, the following are required before the site will be activated:

- OSRO may notify the Monitor and SROS ERDG in writing that the IRB has approved a protocol amendment. A formal notification will be sent by SROS SIO to SROS Monitoring when IRB approvals are received.
- All protocol amendment-related essential documents will be uploaded to the eTMF (per the OSRO 203 Clinical Trial Records Policy).
- A record of Protocol training on the amendment for all Staff delegated duties/tasks on the Clinical Site Delegation of Authority, and Staff Signature Log (DOA) must be submitted to the Sponsor eTMF.
- The updated essential regulatory documents have been submitted to SROS for review; any review findings, issues, or discrepancies have been resolved, and SROS ERDG has determined that the documentation is appropriate and complete.

- Refer to OSRO Clinical Site Activation Policy (document number 206) for site activation requirements.

3.3. Interim Monitoring Process

IMVs may be conducted onsite or remotely unless there are persistent and/or significant issues or concerns that would preclude remote monitoring activities, as determined by OSRO Operations.

The frequency of monitoring visits can occur more or less frequently and visit length can vary (typically 1-3 days), as warranted by enrollment rates and/or status of monitoring, study timelines, or as needed, based on data quality and adherence to the protocol and GCP. The Monitor will determine the length of the visit, but it is generally advised to seek OSRO Operations feedback if the Monitor needs more than two days.

Monitoring activities will be conducted over the study duration, but not all or necessarily the same activities will be conducted at each visit.

3.3.1. Interim Monitoring Visits

Study Milestones Met	Corresponding Visit Intervals
First monitoring visit is conducted after the *first* Participant is enrolled	Within 6-8 weeks
Participants have entered the active treatment phase	Every 6 months +/- 4 weeks
Participants have entered the post-treatment phase	Annually

Note: The frequency of monitoring visits will be based on enrollment status, safety concerns, data quality, and protocol adherence.

- Source Document Review (SDR) is a review of documentation to check the quality of the source, review professional compliance, and ensure critical processes and source documentation are adequate.

Risk-Based Monitoring Requirements include the Participants and Participant Records **selected for monitoring** as follows:

• 100% SDR of the informed consent and re-consent documents, as applicable (**including screen failures**).
• 100% SDR of **eligibility criteria** met and unmet (**excludes screen failures**)
• 100% SDR of all UADE
• 100% of NSR-device records, as applicable

- SDR of the first 5 Participants enrolled. Thereafter, 25-50% of those enrolled (calculated as % after enrollment is complete).

Notes:

- Participants(s) selected for monitoring will be selected at random. A random number generator will be used to document which participants will be monitored. Before each monitoring visit, the monitor will randomly select which participants will be monitored. These participants will be documented in an excel spreadsheet to ensure the percentage of monitored participants does not exceed the above requirements.
- It is expected that the percentage of monitored participant(s) may exceed the above requirements due to the number of Participants that have experienced an UADE.
- The Participants selected for SDR will follow the above criteria, however, the number of participants selected and the extent of record review at each visit will be based on the progress of study enrollment, as well as any concerns that may appear regarding increased risk to the safety of Participants or protocol adherence.

3.3.2. Facility Monitoring Visits

	Visit Intervals and Modality		
Facility	**SAV/SIV**	**IMVs**	**COV**
***Research Laboratory** **<NSR Device and diagnostic laboratories generating data for primary and secondary endpoints. Include laboratory name, Laboratory POC and address, including room number>** **<Add more rows as needed>**	Onsite monitoring visit will be conducted **prior to the SIV** if not previously visited **within the past 2 years**	Onsite monitoring visit will be conducted **biennially**	Onsite monitoring visit may be conducted prior to site closure.

*Refer to SROS Monitoring Visits to the NIH Clinical Center Research Laboratory Guidance

3.3.3. Site Essential Regulatory Documents (ERD) File Review

- The Monitor will ensure that the site essential documents are complete and current.
- The scope of ERD review will vary with the visit type and timing. The site pre-visit confirmation notice will include visit instructions for ERD review.
- If the Regulatory file is limited to or primarily paper-based:
  - Ask what their standard process is for storing electronic correspondence and accessing the electronic files in the future.
  - Ask how they determine whether a hard copy printout is necessary.
  - Ask in the event of an audit, how they would provide access or the documents.
  - This should be documented in the monitoring visit report at the first IMV.
  - If there have been any changes in subsequent monitoring visits from what was previously stated, this should be documented in the monitoring visit report.
- ERD review activities:

- A **full** site essential regulatory document file review will be conducted before the SIV, during the first IMV, at least annually during a routine IMV, and during the site Close-Out visit (COV).
  - Refer to the SROS Essential Regulatory Document Review Form for list of documents and the respective review criteria and information that should be verified.
  - Monitors will address requests from SROS ERDG to follow up with site Staff regarding discrepancies.
  - Monitors should contact SROS ERDG during site visits as necessary to inquire about the status of documents that may be in process.
  - Remind site Staff to submit any new or outstanding documents to SROS ERDG or directly into the Sponsor eTMF in a timely fashion.

3.3.4. Informed Consent Form (ICF) Review

- Verify the following for all who signed an informed consent form:
  - Original signed consent (not copy version) present on site, all pages are present. (**Note**: a scanned version of the signed ICF per NIH Clinical Center SOP is deemed equivalent to original paper version.)
  - The correct and most current version of the IRB-approved ICF (e.g., language, assent, or consent) was signed and dated by the Participant, parent/guardian, or legally authorized representative.
    - As applicable, the site complies with the IRB-required re-consenting process (noted on the amendment IRB Approval Letter), and source documentation is available confirming that the IRB-required re-consent process was followed (e.g., Participant was re-consented at the next study visit.
  - Consent was obtained prior to initiating any screening or, for enrolled participants, any study procedures.
  - A copy of the signed consent form was provided to Participant.
  - Source documentation includes a description of the consent process including a description of the format, e.g., consented via the electronic NIH iMed application platform, a hybrid telephone process – verbal followed by use of electronic or paper-based signed informed consent form.
  - Participant consent for future use of samples/specimens is documented and in agreement with laboratory records.

3.3.5 Source Documentation Review

- Verify the following:
  - The site has completed the site SLR Form.
  - Accurate, complete, and current source documentation (e.g., research records, medical records, pathology reports, laboratory reports, radiology/imaging reports, outside medical records) pertaining to the NSR device is maintained.
  - Participants' eligibility reviewed and in compliance with protocol.
  - All NSR-device procedures/usage outlined in the protocol were completed.
  - Missed study visits, clinical procedures, assessments, and/or tests are recorded appropriately, and deviation reports are submitted to the Sponsor and to the IRB per IRB guidelines.
  - UADE and protocol deviations are documented and reported according to the protocol.

- Queries will be discussed with the site PI and study Staff during the end-of-visit meeting/debrief.
- Periodically during the visit and if time is allocated, work with site staff to resolve queries while onsite (i.e., review any issues, discrepancies, or concerns identified over the course of the visit). These meetings will allow Staff to provide clarification of findings, ask questions, and work with the Monitor to address certain issues at the time of the monitoring visit.

3.3.6. Research 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.

3.3.7. NSR Device Accountability / Documentation /Labeling

(NSR Device may be stored in a research laboratory (e.g. assay) or other designated location as described in the protocol)

- Confirm that the NSR device is stored and maintained according to the device manual.
- Confirm that NSR Device is being dispensed according to protocol.
- Confirm that the NSR Device accountability records are accurate, current, and reconciled.
- Ensure NSR Device accountability log documentation is completed in chronological order and is current.
- Ensure all transactions are documented on NSR Device accountability log.
- Ensure NSR Device shipment receipts are retained.
- Ensure Certificate of Analysis (or other acceptable documentation) is on file for each device received (as applicable).
- Ensure NSR Device is returned/destroyed as mandated by protocol.
- Ensure no NSR Device is returned/destroyed prior to Sponsor authorization to proceed (unless otherwise specified).
- Ensure NSR Device return/destruction documents are retained per applicable local requirements.
- Ensure that the NSR Device labeling requirement is implemented.
    - In accordance with Federal Regulation 21-CFR-812.5: An investigational device or its immediate package shall bear a label with the following information:
        - The name and place of business of the manufacturer, packer, or distributor (in accordance with § 801.1),
        - The quantity of contents, if appropriate, and the following statement:
            - ***CAUTION - Investigational device. Limited by Federal (or United States) law to investigational use***

- The label or other labeling shall describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.

3.3.8. Protocol Non-Adherence

- Confirm that all protocol non-adherence/deviations are documented appropriately in each Participant's source record and on the appropriate protocol non-adherence/deviation form.
- Ensure that the site has reported all protocol deviations to the IRB, as defined by IRB policy and/or SOPs.
- Address any protocol non-adherence with site Staff during the monitoring visit and during the end-of-visit meeting with the PI and Staff.
- Note: Deviations will be reported to the Sponsor via the Protocol Deviation Tracking System (NIH sites) (starting December 2022) or protocol deviation/non-adherence log (non-NIH/external sites). Protocol deviation predating PDTS will not be captured in the system.

3.3.9. Visit Conclusion

- At the end of the visit, the Monitor will meet with the PI and site Staff to review visit activities, findings, and answer questions. The Monitor will discuss the following topics, at a minimum:
- Enrollment status
- Consent process and documentation
- Study conduct and documentation of study activities
- UADE
- Protocol Non-adherence/deviations
- Scheduling of the next Monitoring Visit

3.3.10. Communications

If, during a visit, the Monitor identifies any of the following significant or critical issues or trends, including but not limited to:

- Unresolved or protracted non-compliance
- Evidence of non-compliance with
  - Participant eligibility criteria
  - Informed consent process or consent documentation
  - Study product chain of custody, cold chain, dose administration, record-keeping
  - Safety event reporting
- Evidence of inadvertent unblinding/disclosure or lost treatment key/allocation codes
- Breach in Participant confidentiality
- Inability to perform the visit, e.g., due to delays, transportation issues, IT issues, illness or other emergency, etc.

The Monitor will promptly notify the SROS CSM and, or the OSRO Operations Coordinator within the same business day. The OSRO Operations Coordinator will work closely with the SROS Monitoring team and other OSRO functional groups to assess risk, need for an immediate ad hoc monitoring activity, research team notification and/or CMP modification.

3.4. Close-Out Monitoring

The site may request a closeout visit (COV) via the RFS system. Upon receipt, the SROS Monitor and CSM conduct a site COV Readiness Assessment to confirm if the requirement of the CMP has been met. Upon completion of the

assessment, the CSM contacts OSRO Operations with their assessment of the site readiness for a COV. The Sponsor may also directly determine that a COV Readiness Assessment may need to be conducted.

The Monitor may conduct COV procedures in conjunction with the final monitoring visit or later, depending on site/study timelines. During the close-out visit, the Monitor will perform the following:

- Confirm the resolution of all outstanding prior visit action items.
- Ensure all previous monitoring corrections have been addressed.
- Ensure the return or destruction of the NSR Devices (if applicable).
- Conduct a full laboratory review, which includes verification of biological specimens' status (e.g., all specimens have been placed in long-term storage or arrangements have been made to ship remaining specimens) and corresponding retention records, including appropriate participant informed consent for future use/long-term storage, if not previously completed (if applicable).
- Collect outstanding logs and study forms (ex., Screening/enrollment and monitoring logs).
- Perform a final review of the essential regulatory study file documents. Copies of the following items should be obtained:
    - Participant Screening/Enrollment Log
    - Monitor Log
    - Site Delegation of Authority and Staff Signature Log
    - Retained specimen records (Note: All biological samples, including those in repositories or central labs, must be destroyed unless the Participant agrees to their specimens being retained for future use)
    - Final Close-out Monitoring Visit Report or Notification to IRB of Site Close-out.
    - Study product accountability records (including Accountability forms, shipping receipts, and documentation of destruction and/or return)
- Review the plans and location for study record retention. Obtain the following information regarding the archiving of the study documents:
    - Address where the study documents will be archived.
    - Timepoint at which the study documents will be archived.
    - If the study used both paper and electronic files, discuss how and where the paper and electronic files are maintained, and if the documents will be stored together or separately.
    - How much notice is needed to request/obtain archived documents for future inspections.
    - Confirm that the documents will be contained in a secure environment, fireproof, waterproof, temperate-controlled location.
- Ensure all UADE have been reported appropriately.
- Advise the PI to notify the local IRB of the site closure.

The monitor will discuss the following with the site during the COV:

- Inform PI of ongoing responsibilities
- Disposition of any remaining study product as per written guidance from OSRO.
- <if sites are retaining lab specimens, add the following> site staff should contact OSRO prior to destroying or de-identifying any laboratory specimens for Participants who chose to have their samples destroyed or de-identified at the end of the study.
- Follow-up on any unresolved non-serious and serious adverse events
- Study record retention requirements
- Audit possibility

- Possibility of additional data queries
- Follow-up on any unresolved action items
- Keep financial disclosure current (1 year)
- Keep protocol approval current until IRB is notified of study closure
  The monitor will prepare the final close-out monitoring visit (COV) report and submit the draft COV report to OSRO Operations for review and acceptance.

3.5. Monitoring Visit Reports

- After the last day of each monitoring visit (onsite or remote), a draft IMV report will be submitted to the SROS Clinical Study Manager (CSM) for review.
- After the CSM review and corrections, the draft IMV report will be submitted to OSRO Operations for review and acceptance. The SROS Clinical Operations Manager (COM) may review the draft IMV report prior to submission to OSRO, as applicable.
- OSRO review comments will be resolved by the Monitor, and the report finalized.
- The final IMV report will be sent to the PI, the NCI Protocol Support Office, and the NCI CCR QA and copied to the OSRO Operations team.
- The site is expected to address all outstanding action items (including action items from previous monitoring reports) noted in the monitoring visit report and any queries in the clinical data capture system prior to the next visit or in the case of a close-out visit prior to final site close-out.
- The monitored site will keep monitoring reports in the site files for their records and will use the report as a reference in any subsequent monitoring visits.
- After close-out visits specifically, the Monitor will follow-up on any outstanding action items to confirm resolution within a reasonable timeframe and document action item closure/resolution via email to the site and OSRO Operations.

3.5.1. Monitoring Report Distribution

- SIV, IMV, COV, and Ad Hoc/For Cause
  - Draft reports are submitted to OSRO within the appropriate timelines. The final reports are sent to the Investigator and copied to all individuals per email templates.
  - OSRO approval is required for all Ad Hoc monitoring visits and/or activities.
- Note: SROS Monitors should refer to the most current Monitoring Timelines document for the timelines and process for submission, review, and finalization of all monitoring visit reports.

3.5.2. Monitor Assignment

- SROS monitoring team members will be assigned to specific protocols.
- Protocol CRA reassignments are facilitated by the study CSM.
  - If the outgoing Monitor is not available to assist the incoming Monitor with the site transition, the CSM will be responsible for transitioning the site to the incoming Monitor.
  - If there is a team member site assignment transfer after site activation, the outgoing Monitor will work closely with the incoming Monitor to transition the site whenever possible.

3.6. Site Communication

- PI debriefing must be done after each monitoring visit, whether in person or via telephone. If the PI is not available during the visit, then the PI should be contacted via phone as soon as possible after the visit to conduct the end-of-visit meeting.

- The Monitor should contact the protocol specific CSM with any questions while onsite. Any significant site visit issues, findings, or serious compliance issues are escalated to the protocol specific CSM via phone/email as soon as possible but must be prior to the close of business on the day the serious issue(s) are noted by the Monitor. The CSM or Monitor (if designated by the CSM) will be responsible for contacting OSRO or other collaborators within one business day, as necessary.
- Serious non-compliance issues include, but are not limited to:
    - "Suspected" investigator misconduct, the Monitor will contact CSM from a phone not located on-site.
    - Study Eligibility Deviations e.g., study inclusion/exclusion eligibility criteria not met, enrollment or randomization of non-protocol eligible Participants.
    - Unreported or Late Reporting of UADE per study requirements.
- Informed Consent Deviations from the informed consent process e.g., failure to obtain IRB approved written ICF prior to performing study specific procedures, use of the wrong form, inadequate consent form – e.g., although not the Monitor's primary responsibility, it was learned that informed consent elements are missing.
- Study product accountability, storage, handling, dose preparation discrepancies.
- Pervasive GCP non-compliance e.g., in the judgment of the Monitor there is a noticeable number of GCP non-compliance observations documented as protocol deviations or inadequate/discrepant source documentation.
- Consistent lack of evidence of PI involvement.
- Significant GCP non-compliance e.g., GCP non-compliance and/or protocol non-adherence that could result in compromising Participant safety or the integrity of study data. Also, non-compliance with the OSRO Guidelines for writing Notes to File.

4. References:

4.1.1. E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R2) Good Clinical Practice, FDA Guidance

4.1.2. Guidance for Industry – Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf

4.1.3. 21 CFR Part 50, Protection of Human Participants

4.1.4. 21 CFR Part 54, Financial Disclosure by Clinical Investigators

4.1.5. 21 CFR Part 56, Institutional Review Boards

4.1.6. Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors Significant Risk and Nonsignificant Risk Medical Device Studies
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf