Clinical Monitoring Plan

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

1. Study Overview

Protocol Title:	<full protocol title>		
Protocol Number:	<number>	Version Date:	<dd-Mmm-yyyy>
Principal Investigator:	Dr. <first and last name>	NCI CCR Branch:	<branch name>
IND Sponsor:	CCR Office of Sponsor and Regulatory Oversight (OSRO)		
Protocol Summary:	<This should be a brief summary of the study design/description.> <Bulleted information, add bullets as needed> <If available, add study schematic or diagram> Exclude any 'Precis' truncated/abbreviated inclusion/exclusion criteria. Monitors will review the detailed criteria in the protocol.		
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., subjects per month) is often available in the statistical section of the protocol itself. Do not include the narrative summary of how this works.		
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> <For each external non-NIH site, note whether a monitoring Site Assessment Visit (SAV) is or is not required>		
Data Management:	NCI, CCR Office of the Clinical Director, Contractor supporting clinical data management		

2. Purpose

The purpose of clinical trial monitoring is to verify:

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

This document identifies vital 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, 312 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.

3. Site Monitor

Site Monitors are appropriately trained and qualified to monitor clinical trials under an Investigational New Drug Application (IND) or Investigational Device Exemption (IDE).

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

Monitors will verify:

- Data entered into the electronic case report forms (eCRF) are accurate and complete for all fields subject to review.
- Enrolled Participants meet eligibility criteria, including a documented informed consent process that includes a properly signed informed consent document.
- Site essential regulatory documentation is present, current, and complete.
- Investigational study product is stored and handled in accordance with the protocol and Sponsor requirements.
- Investigational study product receipt, use, return, and disposition is controlled and accurately documented.
- Investigational study product dose administration is accurately documented.
- Non-Significant Risk Device study product (including related substances/components) is labeled, stored and handled in accordance with the protocol and Sponsor requirements.
- The clinical trial is conducted in compliance with the protocol, GCP, and regulations.
- Medical history, assessments and test results, concomitant medications and treatment, non-serious Adverse Events (AEs), and Serious Adverse Events (SAEs) are recorded and reported in accordance with the protocol.
- Protocol non-adherence/deviation is documented in Participant source records and reported as required.
- Participant withdrawal of consent or Participant status change to Off Study or Off Treatment is documented in the Participant records and reported and described on the electronic case report forms (eCRFs).

- Data corrections, additions, or deletions made to the eCRFs are dated, explained, and attributable to the data originator.
- Non-adherence to the protocol, GCP, and regulations are reported, and action taken to prevent a recurrence, as appropriate.

4. Procedures

The intensity and modality of clinical site monitoring will be determined by a risk assessment based on multiple factors, i.e., feasibility, research phase, type of research, team experience conducting similar trials, and risk exposure to study Participants and the institution. The intensity of monitoring will vary across studies and among sites. 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.

4.1. Site Assessment

General description:

The goal of the Site Assessment Visit (SAV) is to verify 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 date and distribute a letter describing 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 design, 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. Documentation of a general non-protocol-specific overview of the NIH NCI facility and CCR Research Staff will be maintained in the Sponsor master document files.

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 trial at the same site (same PI and facility), and OSRO SROS is responsible for the monitoring of the other trial.

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 participates in the study.

4.2. Site Initiation Visit (SIV)

Prior to site activation, the site will request a clinical site monitoring Site Initiation Visit (SIV).

SIV Prerequisites:

- Site essential regulatory documents have been submitted to SROS for review; 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.
- Electronic Case Report Form (eCRF) specifications with documentation of Study team approval and sign-off by an authorized team member, or blank eCRFs with documentation of Study team approval and sign-off by an authorized team member.
- The SROS Clinical Site Monitoring Team has finalized 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.

SIV Attendance:

- In addition to the PI, all site research team members should attend the SIV.
- 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.
- If the SIV format is remote, 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.
- Site activation may be delayed if a quorum of Staff are not in attendance at the SIV.

SIV meeting modality:

For single-site studies the format will be remote.

The Monitor will work with the site Staff to schedule an SIV after the OSRO Clinical Trial Records Policy 203 pre-SIV requirements have been met and based on the Site Staff and SROS Staff availability.

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

- Laboratories supporting the study primary or secondary endpoints,
- Laboratory biorepository for storage or distribution of specimens (e.g., blood, urine, saliva, or hair) for per protocol analysis/genetic studies, or future research use.
- Investigational Pharmacy,
- Cell processing area, or
- Other product manufacturing areas if NCI is responsible for manufacturing.
- If an SIV-related onsite facility visit is necessary, the onsite visit activity may be deferred until the first onsite interim monitoring visit.

For multicenter studies (when non-NIH external sites are participating) and as deemed appropriate by OSRO and the NCI CCR Coordinating Center:

- The Monitor will arrange for site-specific onsite SIVs, or
- As deemed appropriate by the Sponsor, a single or multiple remote SIV(s) will be arranged after the participating site(s) have met the OSRO Clinical Trial Records Policy 203 pre-SIV requirements.

SIV Presentations:

The Monitor will draft a PowerPoint protocol presentation and send it to the OSRO Operations Coordinator and the protocol PI for their comments. As appropriate, the Monitor will update the protocol presentation based on feedback received.

During the SIV, the PI (the CCR Lead PI for multicenter studies) will be responsible for the presentation of the protocol. The Monitor will present administrative and procedural topics related to:

- Site Essential Regulatory Documents
- Participant Record Review
- Clinical Data Management Plan
- Sponsor Protocol Non-Adherence/Protocol Deviation Reporting
- Investigational Study Product Storage and Handling
- Research Laboratory
- Monitoring Visit Activities
- End of monitoring visit meeting with the PI
- GCP, HSP, Regulations, and Guidelines
- Source Documentation
- Informed Consent Process
- Sponsor Safety Reporting
- Sponsor Responsibilities
- Investigator Responsibilities
- Site Activation
- Dose Escalation Determination Documentation
- If applicable, IDE or Non-Significant Risk (NSR) Device Study requirements
- If applicable, Imaging Products (e.g., radioactive isotopes) requirements

After the SIV:

- 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 will review and provide feedback on the draft report. Review comments will be resolved by the Monitor and the SIV report finalized.
- Once final, the SIV report will be sent to the PI, the NCI Protocol Support Office, and the Center for Cancer Research Quality Assurance (CCR QA). When the SIV report action items are resolved, the Sponsor will be notified.
- Refer to OSRO Clinical Site Activation Policy (document number 206) for site activation requirements.

4.3. Interim Monitoring

Interim Monitoring Visits (IMVs) may be conducted onsite or via remote secure modalities, e.g., remote access to source documentation/electronic health records, research records, and electronic data capture systems. The feasibility and appropriateness of remote interim monitoring will be assessed by OSRO Operations in collaboration with the SROS Monitoring team.

IMVs may be conducted onsite or remotely unless there are persistent and/or significant issues or concerns that would preclude remote monitoring activities.

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

Study Monitoring Milestones Met	Visit Intervals
• The first interim monitoring visit (IMV) is conducted after the first Participant is enrolled (i.e., a Participant has been consented and deemed eligible by the study team)	Within <range> weeks
• Study Participants have entered the active treatment phase. • Protocol-specific NIH Clinical Center Pharmacy visits will be conducted during the period corresponding to study initiation and periodically during the active treatment phase.	Every <range> weeks
• All Study Participants have entered the post-treatment phase (i.e., none are being dosed with the study product)	Every <range> months

Important note: The frequency of monitoring visits can occur more or less frequently, 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.

4.4. Monitoring Visits

Selection of Participants and Participant Records for Review will include:

- 100% of Participants consented for screening and, or enrollment will be selected for essential monitoring.
- Record review includes:
    - 100% of consent or re-consent documents, as applicable. If the informed consent form includes an 'opt-out' option for specimen retention, a periodic sampling of the laboratory specimen retention records will be monitored to verify disposition of the specimens match the respective Participant's wishes.
    - 100% of eligibility criteria met and unmet
    - 100% of SAEs experienced

Additional selection criteria

- 100% of Participants who met eligibility criteria (excludes screen failures).
- The first <number> Participants enrolled. Thereafter, <number>% of those enrolled over the duration of the study.
- If applicable, the first <number> Participants of each cohort/arm/dosing group.
- Note: The Participants selected and the extent of record review at each visit will be based on the progress of study enrollment, treatment cycles (as applicable), as well as any concerns that may

appear regarding increased risk to the safety of Participants, the integrity of study data or protocol adherence.

- Record review is expanded to include:
  - 100% of consent and re-consent documents
    - If the informed consent includes an opt-out option for specimen retention, a sampling of the laboratory specimen retention records will be monitored to verify disposition of the specimens match the respective Participant's wishes.
  - 100% of investigational study product accountability records for Participants dosed.
  - 100% of primary and secondary endpoint data. Specifically, the data system eCRFs (i.e., compilation of template standard eCRFs and eCRFs that have been modified to capture unique protocol-specific data) to collect data necessary to conduct the primary and secondary endpoint analysis.

Generic list of Case Report Forms:

• Eligibility	• Baseline symptoms	• Adverse events	• Off treatment
• Enrollment	• Physical exam	• Concomitant medications	• Follow-Up
• Prior therapies	• Prior radiation	• Extent of disease	• Off study
• Prior treatment	• Prior surgeries	• Response criteria	• Survival
• Medical history	• Laboratory tests	• Procedures	• Investigator sign-off

4.4.1. Site Clinical Site Monitoring Expectations

Before and between each monitoring visit the site Staff will:

- Ensure the site Participant Screening and Enrollment Log is current.
- Ensure that the site Delegation of Authority and Staff 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 GCP.
- Verify that study activities are being performed by the PI or have been delegated to personnel qualified by appropriate education, training, and licensure.
- Ensure Staff training records are current for GCP, Human Participants Protection (HSP), protocol, protocol amendments, and any other protocol-specific procedures.
- Ensure Participants' source records are complete and accurate.
- Ensure the site essential regulatory files are complete and properly maintained.
- Ensure the participant case report forms are completed in a timely manner and data are consistent with source records.

4.4.2. Site Essential Regulatory Documents (ERD) File Review

- The Monitor will ensure that the site essential document files 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.

4.4.3. Informed Consent form (ICF) Review

- Verify the following for all Participants:
  - Original signed consent (not copy version) present on site, all pages 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 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.
    - Note: a monitoring visit to the laboratory responsible for study sample storage is required to verify agreement between Participant consent and laboratory specimen labeling/records/logs/tracking system for appropriate handling/post analysis disposition of Participant specimens.

4.4.4. eCRF Source Data Verification / Source Documentation Review

Verify the following:

- The site has completed the site Source Location Record form.
- Accurate, complete, and current source documentation is maintained.
- Participants' eligibility reviewed and in compliance with protocol.
- All procedures outlined in the protocol were completed.
- Missed study visits, clinical procedures, assessments, and/or tests are recorded appropriately, and deviation reports submitted to the Sponsor and to the IRB per IRB guidelines.
- Licensed investigator assessed all abnormal lab values for clinical significance or as outlined in protocol.
- AEs, SAEs, DLTs, and protocol deviations documented and reported according to the protocol.
- All Participant changes in status (e.g., Withdrawals, Off Treatment, Off Study) are recorded in the source documentation and on the eCRF.
- eCRFs have been completed and verified by authorized study Staff in a timely manner per the established electronic data capture (EDC) system requirements.
- eCRF source data verification must be based on Monitor review of the site's electronic medical records system or certified copies of any source documents provided by the site.
- Data entries in the eCRF pages coincide with the source documentation. The Monitor will note any missing or discrepant data by issuing manual data system queries.
    - Queries will be discussed with the site PI and study Staff during the end-of-visit meeting/debrief.
- Resolution of data queries generated during prior visits. If unresolved, remind the site Staff to address all open queries.
- 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.

- Review all available source documents (e.g., research records, medical records, pathology reports, laboratory reports, radiology/imaging reports, outside medical records) pertaining to the study period for the following:
    - Identification of data that contradict CRF entries,
    - Source data supporting study dose escalation or de-escalation criteria met,
    - Source data supporting study Participant response criteria met,
    - Undocumented non-serious and serious adverse events.
    - Review of key events to ensure that a logical clinical course is reflected by the CRF.

4.4.5. Adverse Events, and Serious Adverse Events

- Verify all newly reported AEs and SAEs against source documentation.
- AE grading is verified according to the following processes:
    - Review is per the NCI Common Terminology Criteria for Adverse Events (most current version, unless otherwise specified in the protocol).
    - The grading criteria met are available in the Participant's source records.
    - If the AE CRF data fields are tracked for completion via a grid/worksheet, then there is adequate information from additional source documentation to confirm the AE grading criteria is met.

- The documentation of grading criteria met is:
  - A descriptive notation/progress note/assessment located in the Participant's source record, and
  - Completed and signed by the PI or sub-Investigator delegated by the PI to assess AEs and SAEs.

  Note:
  - CTCAE grading for a non-serious AE may be completed by a clinician licensed to diagnose at the location.
  - CTCAE grading for a Serious Adverse Event (meets per-protocol SAE criteria) must be completed by a licensed MD.

- Ensure all AEs are reviewed for Participants selected for monitoring to ensure that they are not serious.
- Ensure all SAEs are documented and reported appropriately.
- Follow up on previously reported AEs and SAEs.
- Confirm that all SAEs have been reported to the IRB and the Sponsor, as required.
- Identify any unreported AEs and SAEs in source documentation.
- Review AE and SAE reporting procedures, as necessary.
- If the monitor identifies a previously unreported SAE, instruct the site to report the SAE immediately following the established SAE reporting guidelines.
- The investigator must report the SAE immediately or within 24 hours of notification of the event. The information should be completed as fully as possible. All SAEs should be followed until resolution or permanent outcome of the event.
- Ensure SAEs reported to OSRO are reconciled with the CRF and reported to the IRB.
- Ensure all unreported SAEs and updated SAE information are forwarded to OSROSafety@mail.nih.gov. OSRO Safety will be responsible for follow up, as necessary.

4.4.6. Research Laboratory and Specimen Management review

- Assess maintenance of research specimen logs and associated documentation.
- Review handling of laboratory specimens.
- Review specimen storage conditions and maintenance of temperature logs.
- Ensure specimens that are designated and not designated for future use are properly labeled and tracked.
- Ensure organization and storage of specimens in a secure location.
- Ensure appropriate specimen labeling.

Abbreviated Laboratory Review

- Includes a random sampling of lab specimens, to be performed when specimens are onsite. Laboratory specimen "random sampling" as a monitoring activity is defined as follows:
- Independently select a small (< 5) number of Participants from the list of those monitored.
- During a visit to the laboratory, ask the lab personnel to retrieve the specified Participants' samples collected during a given visit and at a specific time point.
- Observe the process of retrieval and the actual specimens noting whether the specimens retrieved were:
- Readily available,
- Appropriately labeled (e.g., label placement, subject identifiers, collection date, future use designation), and

- If the storage conditions met requirements for specimen integrity.
- In addition, conduct a review of:
    - The Protocol and MOP (if applicable) for the requirements for shipping specimens.
    - If there has been a change in the Protocol or MOP for the requirements for shipping specimens, the Monitor should verbally confirm all necessary laboratory training has been completed and up to date and training documentation is present including Dangerous Goods Regulations and IATA as applicable.
    - If the site is actively shipping specimens, and there is any change in the process, discuss the new process and escalate any issues with the transport or handling of the specimens to the CSM.
    - Discuss the process for specimen tracking, including documentation of receipt at processing or storage location.
    - Discuss the means of transport (e.g., air, ground, private carrier)
    - If transport by ground, review:
        - Packaging and labeling
        - Transport by private courier, contract carrier, lab/clinic vehicle
        - If by lab/clinic vehicle, review the training of the site staff, distance and travel time to the destination, and temperature monitoring.
    - If transport by air, review:
        - Packaging and labeling to ensure IATA requirements
        - If the site is not complying with IATA requirements, the site staff should be directed to the IATA website or Dangerous Goods Regulation requirements.
        - Are specimens being retrieved by the air carrier or site personnel transporting the specimens to the air carrier facilities.
        - If site staff are transporting the specimens, review the training of the site staff, distance and travel time to the destination, and temperature monitoring.
- For all days while stored onsite, review storage equipment or ambient temperature logs and, or recordings to check for temperature excursions.
- If temperature logs are unavailable for non-business days, note this within the monitoring visit report.
- Discuss the type of temperature monitoring system and back-up system used. The site should verify which temperature monitoring system and log/report they consider the “official” temperature log and provide that to the Monitor for review.
- Any refrigerator, transport container or freezer temperature excursions should be reported as protocol deviations and escalated to CSM, as indicated, and appropriate action per OSRO direction should be taken.
- A detailed description of the handling, transport, and shipment of lab specimens should be included in the monitoring visit report. Any deviation from the Protocol or MOP should be immediately reported by the Monitor to the CSM for escalation to OSRO.

Full laboratory review

- Conducted as part of the SIV or during an IMV, as part of the COV, and at least once per year; a random sampling of laboratory specimens should be reviewed at all other interim monitoring visits, as long as laboratory specimens remain onsite. Full laboratory review includes all components of an abbreviated review, as well as:

  - Review of laboratory equipment maintenance and calibration status per equipment certification stickers if present, and/or based on site staff report.
  - Review the adequacy of the facility, local laboratory, and any special equipment for the study at the site (e.g., freezer, refrigerator, centrifuge, diagnostic equipment, etc.) The site staff verbally confirms for the Monitor that the calibration records, maintenance records, etc. are on file and up-to-date, and that alarm systems are functioning as required.
- If applicable, confirmation that any lab equipment issues have been resolved and study specific materials are properly disposed of according to the MOP or other written guidance.
- <If applicable, insert> Verification that the <retention records/ Future Use Report> for Participants selected for monitoring match source/informed consent form(s) for future use/long-term storage of specimens. If site staff has questions regarding labeling or destruction of samples, the site staff should be directed to contact OSRO.
- <If applicable, insert> A verbal confirmation from the site staff is required for Participants not selected for monitoring to confirm that the <retention records/ Future Use Report> for those Participants match the source/informed consent form(s) for future use/long-term storage of specimens.
- Verify the site is following appropriate laboratory sample handling, labeling, storage, and shipping procedures per protocol (including preparation for transport in accordance with Dangerous Goods Regulations and IATA guidelines, as applicable) and that the supplies have not exceeded their expiration date.
- Verify that study specific supplies are properly disposed of according to the MOP or other written OSRO guidance, if applicable.
- If laboratory specimens are transferred/ transported between facilities/locations, the Monitor reviews the cold chain documentation and verifies that the cold chain is maintained during the transport (i.e., how, and where are the specimens being moved, any additional requirements the site staff needs to complete for the transport.) The Monitor must document any observations and discussions with the site staff in the monitoring visit report.
- If any critical issues are identified, the Monitor notifies the CSM as soon as possible to allow the CSM the opportunity to address any critical issues with OSRO while the Monitor is onsite.
- Protocol Specific Procedures / Investigations / Assessments
  - Ensure protocol mandated lab test results are recorded and reviewed by PI or a qualified licensed clinician for clinical significance.
  - Ensure protocol mandated radiology test results are recorded and reviewed by PI or qualified licensed clinician.
  - Ensure all other test/assessment results are recorded and reviewed by PI or qualified licensed clinician.

4.4.7. Investigational Study Products review

- Treatment / Administration
  - Ensure the correct dose as outlined in the protocol was administered.
  - Ensure any dose modifications as outlined in the protocol were administered.
  - Ensure compliance is recorded in source documentation.
- Pharmacy Accountability / Documentation

- Appropriate completion and maintenance of accountability records (e.g., receipt, inventory, disposition, transfer, or transport logs, return, or onsite destruction), including documentation of and appropriate action taken for any discrepancies.
- Documentation of and appropriate action taken for any expired, missing, damaged, or wasted study product.
- <if applicable insert the following, delete if study is unblinded> Inspect documents used for back-up randomization and/or for emergency unblinding. IF the documents are inaccessible, i.e., kept at another location, etc., discuss with the appropriate staff member (i.e., unblinded study product administrator/pharmacist) regarding the documents to ensure that no instances of unblinding (either due to an emergency or accidental) have occurred.
- Confirm that investigational study product is stored at the correct temperature in a secure storage area.
- Review temperature logs to confirm stability of storage/shipping conditions. Storage conditions since the last monitoring visit should be reviewed to ensure compliance with protocol requirements, i.e., study product is kept in a secure location with limited access and within the temperature parameters required by the protocol.
- Temperature logs should be reviewed for all days the study product is onsite.
    - If no temperature recordings are available from non-business days, the Monitor should note this within the monitoring visit report.
    - If temperature recordings are documented for non-business days, these should be reviewed by the Monitor to check for any temperature excursions.
    - If there is an alarm system or back-up system in place to monitor the temperature of the storage area, the Monitor should note this along with any details (e.g., temperature range for alarm) regarding the systems in the monitoring visit report.
    - If study product has been isolated or sequestered, the Monitor should review the temperature logs and review the storage location to verify that the product has been properly sequestered and note this within the monitoring visit report.
    - Discuss with site staff the type of temperature log used (e.g., primary source for the temperature). The site should choose which temperature log they consider their “official” temperature log and present that for the Monitor’s review at every visit. Any refrigerator, transport container or freezer temperature excursions should be reported as protocol non-adherence and escalated to CSM/OSRO, as indicated, and appropriate action per OSRO direction should be taken.
- Dose administration records are to be reviewed for the Participants selected for monitoring to ensure consistency (i.e., pill count vs. dispensing records or used vials vs. dispensing records etc.). The study product accountability records must also match the Participants’ source records and CRF data.
    - <If applicable, add:> For any studies involving dosage or dilution calculations, the Monitor should verify that these were completed correctly for the Participants selected for monitoring, or confirm procedures and related documentation has been approved by OSRO.

- Authorized final disposition of used and unused study product/packaging and any ancillary supplies to be specified in written correspondence to the site by the responsible OSRO personnel/representative or other approved written guidance. The final disposition of study product (i.e., empties, un-used) retained for monitoring and at the end of the study should be determined during the study. Insert plan for disposition if applicable.
- Confirm that investigational study product is being dispensed according to protocol.
- Confirm that study product accountability records are accurate, current, and reconciled.
- Ensure no discrepancies exist between study product accountability log and Participant data on eCRF.
- Ensure study product accountability log documentation is completed in chronological order and is current.
- Ensure all transactions are documented on study product accountability log.
- Ensure the balance on the study product accountability log matches the inventory balance.
- Ensure all study product shipment receipts are retained.
- Ensure product is returned/destroyed as mandated by protocol.
- Ensure no product is returned/destroyed prior to Sponsor authorization to proceed.
- Ensure product return/destruction documents are retained.
- Ensure the study product returns (e.g., pill count, doses taken or missed) process is well documented in Participant source (e.g., the Participant drug diary is retained as source in the research or medical record) and consistent with eCRF data.

4.4.8. Non-Significant Risk (NSR) Device Study Products review

- NSR Laboratory Visit Activities
  - Review any changes (to the Procedures, Equipment, Chain of Custody, etc.) implemented after the SIV
  - Confirm that laboratory reagents are being used according to the protocol (e.g., detection of specific mutation).
  - Verify the reagents are properly labeled in compliance with FDA Guidance.

4.4.9. Cell Manufacturing Study Products review

- NIH Department of Laboratory Medicine Center for Cellular Engineering (CCE) Visit Activities
  - Review any changes (to the Procedures, Equipment, Chain of Custody, etc.) implemented after the SIV
  - Ensure the equipment maintenance records are up to date
  - Review the chain of custody of received specimens (e.g., tumor tissue) and engineered cells

4.4.10. Imaging Study Products review

- Radiology Department Visit Activities
  - Review any changes implemented after the SIV
  - Review accreditations/equipment maintenance related certification (if applicable)
  - Review manufacturing process (if applicable)

- Review accountability records

4.4.11. Protocol Non-Adherence/Deviation Reports

- Verify that all protocol non-adherence/deviations is 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.

4.4.12. Data Review

- Confirm all data is verifiable against source documentation.
- Confirm no transcription errors have been made.
- Ensure corrections are appropriately entered and documented and/or tracked in the electronic data capture system audit trail.

4.4.13. 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
- AEs and SAEs
- Protocol Non-adherence/deviations
- Scheduling of the next Monitoring Visit

4.4.14. Issue Escalation

- 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
- 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.

4.5. Close-Out Monitoring

The Monitor may conduct close-out visit procedures in conjunction with the final monitoring visit or later depending on site/study timelines. In preparation for the closeout visit the monitor will review and assess readiness for a closeout visit (COV). During the close-out visit, the Monitor will perform the following:

- Ensure the completion of outstanding eCRFs and resolution of data queries.
- Verify the resolution of all outstanding prior visit action items, including unresolved Onsite Monitoring Discrepancy Forms, if applicable.
- Ensure all previous monitoring corrections have been addressed.
- Ensure the return or destruction of the investigational study product (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 subject informed consent for suture use/long-term storage, if not previously completed.
- Collect outstanding logs and study forms (ex. screening 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 SAEs have been reported appropriately.
- Ensure the PI has notified the IRB of the site closure.
- Ensure OSRO has been formally notified of site closure.
- 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
- Prepare the final close-out monitoring visit (COV) report and submit the draft COV report to OSRO Operations for review and acceptance.

4.6. 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.
- 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 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.

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.

Monitor Assignment

- SROS monitoring team members will be assigned to specific protocols.
- 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.
- 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.

4.7. 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 non-serious or serious adverse events e.g., failure to report AEs/SAEs 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.

5. References:

- E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R2) Good Clinical Practice, FDA Guidance
- Guidance for Industry – Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf
- 21 CFR Part 50, Protection of Human Participants
- 21 CFR Part 54, Financial Disclosure by Clinical Investigators
- 21 CFR Part 56, Institutional Review Boards
- 21 CFR Part 312, Investigational New Drug Application
- 21 CFR Part 812, Investigational Device Exemptions

6. CMP Review log:

Review Date	Updates required (Y / N)	SROS Clinical Study Manager Reviewer	OSRO Operations Coordinator Reviewer	Summary of changes
DDMMMYYYY	Yes or no	Name	Name	If yes, provide summary. If no, leave blank.