Green highlighted text: to be removed as applicable.
Yellow highlighted text: to be customized per protocol
[remove instructions text above when drafting]

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.
Investigational Products	IND/IDE Number: <IND/IDE number or N/A if NSR Device> <Include drug/device name(s), and manufacture(s)> <Include drug/device name(s), and manufacture(s)>
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>
Data Management:	NCI, CCR Office of the Clinical Director, Contractor supporting clinical data management.

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1. Purpose

The purpose of clinical trial monitoring is to ensure:

- 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, Good Clinical Practice (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(R1) 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.

2. Site Monitor

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

Monitors will ensure:

- Data entered on the electronic case report forms (eCRF) are accurate and complete for all fields participant to review.
- Enrolled Participants meet eligibility criteria, including a documented informed consent process that includes a properly signed informed consent form.
- Site essential regulatory documentation is present, current, and complete.
- Investigational study product(s) are stored and handled in accordance with the protocol and Sponsor requirements.
- Investigational study product receipts, use, return, and disposition are controlled and accurately documented.
- Investigational study product dose administration is accurately documented.

- NSR 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 applicable regulations.
- Medical history, assessments and test results, concomitant medications and treatment, non-serious Adverse Events (AEs), Serious Adverse Events (SAEs), Unanticipated Adverse Device Effects (UADE) and Adverse Events of Special Interest (AESI) are recorded and reported in accordance with the protocol.
- Protocol non-adherence/deviations are documented in Participant source records and reported as required.
- Participant withdrawal of consent or Participant status change, e.g., to Off Study or Off Treatment is documented in the Participant records and reported and described on the eCRFs.
- Data corrections, additions, or deletions made to the eCRFs are dated, explained, and attributable to the data originator and the data source.
- Non-adherence/deviations to the protocol, GCP, and regulations are reported, and action taken to prevent a recurrence, as appropriate.

3. 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, April 2023.

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 Visit (SIV)

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.
    - 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) is provided.
    - 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
    - Data Manager
    - Pharmacy Staff representative
    - Non-Pharmacy Staff representative (if the study product is handled in an area outside of the pharmacy)
    - Clinical Nursing representative
- 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.
- 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

The format may be remote, on-site, or hybrid as determined by the Sponsor.

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
- Biorepository for storage or distribution of specimens (e.g., blood, urine, saliva, or hair) for protocol analysis/genetic studies or future research use including,
- Investigational Pharmacy (for non-NIH sites as determined by the Sponsor, if applicable),
- Cell processing area (see section 4.3 for details), or
- Other product manufacturing areas if NCI is responsible for manufacturing (see section 4.3 for details).
- 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 4.3 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 approval.

3.2.4. SIV Presentations

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
- Clinical Data Management Plan (DMP)
- 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
- If applicable, Dose Escalation Determination Documentation
- If applicable, IDE or NSR Device Study requirements
- If applicable, Imaging Products (e.g., radioactive isotopes) 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 a protocol amendment has been approved by the IRB 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

A risk-based monitoring approach will be employed for all studies. Risk-Based Monitoring is an adaptive approach to clinical study monitoring that directs monitoring focus and activities to the pre-defined and evolving areas of greatest need which have the most potential to impact participant safety and data quality.

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

Monitoring visit intervals **and parameters are based on the Perf Score per the Preparation and Review of Clinical Monitoring Plans - 205-S01-W01.**

CMP Specific Risk Score <>

Study Monitoring Milestones Met	Monitoring 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 of enrollment
• Study Participants have entered the active phase.	Within <range> weeks of the last day of the previous IMV
• All Study Participants have entered the Follow-Up phase (i.e., none are being dosed with the study product)	Within <range> weeks of the last day of the previous IMV

- Source Document Review (SDR) is a review of documentation to check quality of source, review protocol compliance and ensure critical processes and source documentation are adequate.
- Source Data Verification (SDV) is the process of reviewing the source document versus the data entered into the eCRF to ensure accurate transcription of data and a match between the source and the eCRF entries.

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

- *For protocols with an accrual ceiling ≤90:* 100% review (SDR) of the informed consent and re-consent documents, as applicable (**including screen failures**).
  - If the informed consent includes **an opt-out option** for specimen retention, a sampling of the laboratory specimen retention records will be monitored to confirm disposition of the specimens matches the respective Participant's wishes.
- *For protocols with an accrual ceiling >90:* [25% - 50% - 75% determined by CMP parameters] review (SDR) of the informed consent and re-consent documents, as applicable (**including screen failures**).
  - If the informed consent includes **an opt-out option** for specimen retention, a sampling of the laboratory specimen retention records will be monitored to confirm disposition of the specimens matches the respective Participant's wishes.
- 100% review (SDR) of investigational study product accountability records for Participants dosed.

- First [#] participants, thereafter [#%]% SDV of forms specified in SDV Tier Table below for those enrolled over the course of the study *RAVE studies*
- First [#] participants, thereafter [#%]% SDV of participants enrolled over the course of the study *C3D studies*
- 100% of participants with SAEs will be automatically assigned to Tier 1 *RAVE studies*
- 100% of participants with SAEs will be selected for monitoring *C3D studies*
- SDV Tier Table: [insert SDV Tier Table from Appendix 1] *RAVE studies*

Notes:

- *C3D:* Participant(s) selected for monitoring will be selected at random using a random number generator. Before each monitoring visit, the monitor will randomly select which participants will be monitored. These participants will be documented in the CMP Parameters excel spreadsheet to ensure the percentage of monitored participants does not exceed the above requirements.
- *RAVE:* Participant(s) selected for monitoring will automatically be assigned to a Tier by the RAVE system.
- 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 SAE/UADE.
- The participants selected for SDR and SDV 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, 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.

3.3.2. Facility Monitoring Visits

N/A	Facility	Visit Intervals and Modality[#]		
		SAV/SIV	**IMVs**	**COV**
☐	Department of Transfusion Medicine – CCE/Manufacturing Facility	Onsite monitoring visit will be conducted **prior to the SIV** if not previously visited **within the past 5 years**	Onsite monitoring visit will be conducted **every 5 years**	N/A
☐	Radiology Department / Molecular Imaging	Onsite monitoring visit will be conducted **prior to the**	Onsite monitoring visit	N/A

		SIV if not previously visited **within the past 2 years**	will be conducted **biennially**	
☐	*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.

#Unless otherwise specified by the Sponsor

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

3.3.3. Pharmacy Visits

Risk Score <>

N/A		Visit Intervals and Modality#^		
		SAV/SIV	**IMVs**	**COV**
☐	**NIH Clinical Center Pharmacy** 10 Center Drive Rm 1C230 MSC 1196 Bethesda, MD 20892	Onsite visit will be conducted prior to the SIV	Onsite pharmacy visit will be conducted <> while Participants are being dosed with the investigational product	Onsite visit will be conducted after all participants have completed protocol treatment
	<Other non-NIH locations include pharmacy name and street address>	Onsite visit will be conducted prior to the SIV	Onsite pharmacy visits will be conducted every <> weeks	

	<Other non-NIH locations include pharmacy name and street address>			

#Unless otherwise specified by the Sponsor

^If the protocol uses only commercial products, onsite visit may not be required and the accountability records (if applicable) will be reviewed remotely

*Refer to SROS Monitoring Visits to the NIH Clinical Center Pharmacy Guidance Document

3.3.4. 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 Clinical Site Delegation of Authority and Staff Signature Log is complete and signed.
- Ensure that the PI and site personnel are adhering to the protocol and conducting the study according to regulatory requirements and GCP.
- Ensure 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, HSP, protocol, protocol amendments, and any other protocol-specific procedures.
- Ensure Participants' source records are complete and accurate.
- Ensure the site essential regulatory documents are complete and properly maintained.
- Ensure the participant eCRFs are completed in a timely manner (in accordance with the DMP, if applicable) and data are consistent with source records.

3.3.5. 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 within the first year of site activation and during the site Close-Out visit (COV).
    - The Monitor will perform the full ISF review within the first year of site activation regardless of site enrollment (i.e., if no IMV is scheduled to occur by one year post-activation, the Monitor will perform a full ISF review remotely).
      - The Monitor will utilize the TMF Index as a reconciliation tool to confirm if the ISF is complete and accurate.
    - ERDG reviews documents for pre-activation and at routine IMVs at the internal NIH sites. For external sites, [insert if ERDG or Monitor is performing]
      - Refer to the SROS Essential Regulatory Document Review Form for list of documents and the respective review criteria and information that should be verified during the IMVs.
    - 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.

3.3.6. 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.
- **Note**: a monitoring visit to the laboratory responsible for study sample storage is required to confirm agreement between Participant consent and laboratory specimen labeling/records/logs/tracking system for appropriate handling/post-analysis disposition of Participant specimens.

ICF review of any enrolled participants should be prioritized and reviewed at the subsequent IMV from the enrollment and prior to continuing with review of subsequent eCRFs for that participant. If it is not possible to review the ICF of a newly enrolled participant at the subsequent IMV to enrollment, then it should be tracked and flagged for review at the next IMV possible. ICF review of screen failures should be prioritized after ICF review of enrolled participants.

3.3.7. eCRF Source Data Verification / Source Documentation Review

SDV will exclude documents created and/or signed within 12 business days of the monitoring visit.

- Verify the following:

  - The site has completed the site SLR 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, UADE, AESI, 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 eCRFs 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.

- SDR 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 eCRF 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 eCRF.

3.3.8. Adverse Events, Unanticipated Adverse Device Effects, and Serious Adverse Events

For Participants selected for full monitoring:

- SDV all newly reported AEs and SAEs/UADEs against source documentation.
    - Note: The current list of SAEs/UADEs reported to the Sponsor is available in the Spotfire line listing reports.
- AE grading is verified according to the following processes:
    - Review is per the NCI Common Terminology Criteria for Adverse Events (CTCAE). Refer to the protocol for the specified version.
    - The grading criteria met are available in the Participant's source records.
    - If the AE eCRF 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/ UADEs.

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/UADE criteria) must be completed by a licensed physician listed on the study Delegation of Authority Log.

- Ensure all AEs are reviewed.
- Ensure all SAEs/UADEs are documented and reported the IRB and the Sponsor, as required.
- If the monitor identifies a previously unreported SAE/UADE, instruct the site to report the SAE/UADE immediately following the established SAE/UADE reporting guidelines.
- Follow up on previously reported AEs and SAEs/UADEs, if needed.
- Identify any potentially unreported AEs and SAEs/UADEs in source documentation.
- Review AE and SAE/UADE reporting procedures, as necessary.
- The investigator must report the SAE/UADE within 24 hours of notification of the event. The information should be completed as fully as possible. All SAEs/UADEs should be followed until resolution or permanent outcome of the event.
- Ensure SAEs/UADEs reported to OSRO (refer to the SAE/UADE line listing report in Spotfire) are reconciled with the CRFs and reported to the IRB.
- Advise the PI that all unreported SAEs/UADEs and updated SAE/UADE information should be forwarded to OSROSafety@mail.nih.gov, as applicable.
  SAE/UADE review should be prioritized for review at the subsequent IMV from the initial SAE/UADE report for that event. If it was not possible to review the SAE/UADE at the subsequent IMV, then it should be tracked and flagged for review at the next IMV possible.

3.3.9. 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.

3.3.9.1. Abbreviated Laboratory Review

Conducted as part of an IMV and at least once per year. For NIH sites, the IMV may be associated with another protocol utilizing the same laboratory, but the report of the laboratory visit will be provided as an addendum to the subsequent IMV for each protocol utilizing the lab.

Research Laboratories handling Participant Samples and Storage

The onsite visit may include: 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 protocol-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, participant 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.

- If a participant withdrew Informed Consent, review:
  - The collected specimens were properly disposed of according to the MOP or other written guidance.

- 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 confirm 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.

3.3.9.2. Full Laboratory Review

Conducted as part of the SIV or COV. 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.
- Confirm 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.
- Confirm 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.

3.3.10. 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 protocol 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 access limited to authorized pharmacy staff only 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 quarantined, the Monitor should review the temperature logs and review the storage location to confirm 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.
    - All maintenance and calibration records should be reviewed to ensure the equipment is properly certified and calibrated routinely.
- 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 confirm 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.

3.3.11. 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 the NSR Device(s) are being used according to the protocol (e.g., detection of specific mutation).
- Confirm the NSR Device(s) are properly labeled in compliance with FDA Guidance.

3.3.12. 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.

3.3.13. Imaging Study Products Review

- Radiology Department Visit Activities
  - Review accreditations/equipment maintenance related certification (if applicable).
  - Review manufacturing process (if applicable).
  - Review accountability records.

3.3.14. Protocol Non-Adherence/Deviation Reports

- 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) or protocol deviation/non-adherence log (non-NIH/external sites). Protocol deviation predating (December 2022) PDTS will not be captured in the system.

3.3.15. 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/UADEs
- Protocol Non-adherence/deviations
- Scheduling of the next Monitoring Visit

3.3.16. 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 OSRO Operations within the same business day. OSRO Operations 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. Centralized Monitoring

Centralized monitoring activities are conducted by The SROS Centralized Monitoring team as detailed in the SROS Centralized Monitoring and Data Quality Review Plan. The SROS Centralized Monitoring team will share the proposed reviews with SROS Monitoring and OSRO for their review and approval prior to implementing.

SROS Centralized Monitoring team will conduct data reviews as detailed in the "Centralized Data Review Checks.xlsx" file along with the review frequency and mode, as shown in Table [x] below. This file will be stored in the "CCRS SROS Portal" SharePoint Site (https://triinc.sharepoint.com/sites/CCRSROS

[insert table from SROS Centralized Monitoring Team]

The SROS Centralized Monitoring Team will add queries to the EDC system, and send a notification to the site PI and Research Nurse with cc OSRO Operations. If the SROS Centralized Monitoring Team needs to contact the site aside from the notification of queries, the SROS Site Monitor will communicate with the site. The SROS Centralized Monitoring team will document the review statuses in a Data Quality Review Log to capture what was reviewed and if a query was issued.

During IMVs, the SROS Site Monitor will discuss the status of open data review queries from the SROS Centralized Monitoring team.

3.5. Close-Out Monitoring

SROS Monitoring will periodically perform an assessment of the site readiness (e.g. if the CMP paraments have been met) for a COV and notify OSRO Operations. A closeout visit (COV) may be requested by the site 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:

- Ensure the completion of outstanding eCRFs and resolution of data queries.
- 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 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 participant informed consent for future use/long-term storage, if not previously completed.
- 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 SAEs/UADEs have been reported appropriately.

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 protocol 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.

3.6. 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. 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.

3.6.1. 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.

3.7. 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/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 elem ents 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.

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 https://www.fda.gov/media/121479/download
- 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
- 203 Clinical Trial Records Policy
- 206 Clinical Site Activation Policy
- 205-S01-W01 Preparation and Review of Clinical Monitoring Plans
- OSRO Lexicon https://ccrod.cancer.gov/confluence/display/CCRCRO/SOPs?preview=/196477356/281346877/1A%20R2%20Lexicon.pdf
- Source Location Record (SLR)
- SROS Monitoring Visits to the NIH Clinical Center Research Laboratory Guidance
- SAE/UADE line listing report in Spotfire https://analytics.tech-res.com/spotfire/wp/analysis?file=/NCI-SROS/Argus/By%20Case%20and%20By%20Event%20Report&waid=ghcMvv6j4kiRtblbc4gDl-311017e8ffjfhH&wavid=0
- SROS Centralized Monitoring and Data Quality Review Plan

Abbreviations

AE/SAE	Adverse Event/Serious Adverse Event
AESI	Adverse Event of Special Interest
eCRF	Electronic Case Report Form
eTMF	Electronic Trial Master File
CCR QA	Center for Cancer Research Quality Assurance
CMP	Clinical Monitoring Plan
COV	Close-Out visit
CSM	Clinical Site Manager
CTCAE	Common Terminology Criteria for Adverse Events
DMP	Clinical Data Management Plan
EDC	Electronic Data Capture
ERD	Essential Regulatory Documents
ERDG	Essential Regulatory Documents Group
FDA	Food and Drugs Administration
GCP	Good Clinical Practice
HSP	Human Participants Protection
IATA	International Air-Transport Association
ICF	Informed Consent Form
ICH	International Council of Harmonization
IDE	Investigational Device Exemption
IMV	Interim Monitoring Visit
IND	Investigational New Drug
IRB	Institutional Review Board

MOP	Manual of Operations
NCI CCR	National Cancer Institute Center for Cancer Research
NSR	Non-significant Risk
OSRO	Office of Sponsor and Regulatory Oversight
PI	Principal Investigator
RFS	Request for Services
SAV	Site Assessment Visit
SDR	Source Document Review
SDV	Source Data Verification
SIV	Site Initiation Visit
SLR	Source Location Record
SOP	Standard Operation Procedure
SROS	Support for Regulatory and Sponsor Oversight
UADE	Unanticipated Adverse Device Effect

Appendix 1

Safety/Dose Finding (Phase 1) SDV Tiers

Notes: Participants with SAEs are manually moved to Tier 1. Forms that do not collect critical data for primary or secondary analysis are excluded from all tiers, e.g., Research Sample Collection, Prior Radiation/Therapy/Surgery Supplement, etc. If PK is a primary outcome the PK CRF should be in both Tiers 1 and 2.

Tier # and Name	% of pts randomized to tier (x=SDV level from perf. Score)	Forms
1-Primary and Secondary forms	x/2	Tier 2 forms plus: Course Initiation (after DLT evaluation period) Course Assessment (after DLT evaluation period) Study Meds Admin (after DLT evaluation period) Concomitant Measures/Medications (after DLT evaluation period) PK Procedure Participant Enrollment Radiation Treatment Response Assessment Extent of Disease Follow-up Off-Treatment Off-Study
2-Primary forms	x/2	Enrollment Arm and Cohort Assignment Course Initiation (only DLT evaluation period) Course Assessment (only DLT evaluation period) Study Meds Admin (only DLT evaluation period) Adverse Event

Tier # and Name	% of pts randomized to tier (x=SDV level from perf. Score)	Forms
		Concomitant Measures/Medications (only DLT evaluation period) Physical Exam Vital Signs Labs
3-No SDV	100-X	n/a

Efficacy (Phase 2) SDV Tiers

Notes: Participants with SAEs are manually moved to Tier 1. Forms that do not collect critical data for primary or secondary analysis are excluded from all tiers, e.g., Research Sample Collection, Prior Radiation/Therapy/Surgery Supplement, etc. If PK is a primary outcome the PK CRF should be in both Tiers 1 and 2.

Tier # and Name	% of pts randomized to tier (x=SDV level from perf. Score)	Forms
1-Primary and Secondary forms	x/2	Tier 2 forms plus: Adverse Event Concomitant Measures/Medications PK Physical Exam Procedure Participant Enrollment Vital Signs
2-Primary forms	x/2	Arm and Cohort Assignment Enrollment

Tier # and Name	% of pts randomized to tier (x=SDV level from perf. Score)	Forms
		Course Initiation Course Assessment Study Meds Admin Radiation Treatment Response Assessment Extent of Disease Follow-up Off-Treatment Off-Study
3-No SDV	100-X	n/a