# Division of AIDS (DAIDS) Site Clinical Operations and Research Essentials (SCORE) Manual: Site Visits

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# Site Visits

DAIDS has a significant regulatory responsibility in the oversight of all its clinical trials. The monitoring and auditing of Clinical Research Sites (CRSs) are activities that DAIDS has in place to:

- Ensure the protection of participants' rights, safety, and welfare.
- Ensure the quality and integrity of reported data.
- Maximize the adherence to the protocol, applicable regulations, policies, and procedures during a clinical trial conduct.

According to the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines "ICH E6" (5.18.3): "Extent and Nature of Monitoring: The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general, there is a need for on-site monitoring, before, during, and after the trial." To fulfill the regulatory oversight obligation, DAIDS (as sponsor) delegates monitoring responsibility to a Monitoring Contractor (Contract Research Organization --CRO), which in turn assigns monitors (also known as Clinical Research Associates – CRAs) to conduct the visits.

ICH E6 (5.0) – Quality Management "requires that the sponsor implement a system to manage quality throughout all stages of the study process" and use a risk-based approach.

As part of this system, DAIDS implements quality assurance activities, and performs different kinds of quality site visits, or GCP audits. Trained, qualified auditors (independent of the clinical trials/systems) are assigned for this purpose, to give an objective, unbiased assessment of the data quality, site adherence to protocol and ICH E6 guidelines.

The Principal Investigator (PI)/Investigator of Record (IoR) must permit monitoring and auditing and ensure that the CRS is adequately prepared before the visit start date.

For double-blinded clinical trials, the Pharmacist of Record (PoR) and/or any unblinded staff must maintain the scientific integrity of studies and take all precautionary measures to prevent unblinding any participant treatment assignments. This includes limiting access to treatment assignment records and study products. Monitors, auditors, and inspectors are typically unblinded and can have access to these documents. Some trials may also have blinded monitors assigned when necessary. If you are not sure if the monitor is unblinded, ask them, "Are you unblinded on this protocol?" before permitting access to any blinded study information. Also, any follow-up letter/report generated that contains unblinded information is to be shared with unblinded staff only, such as the PoR.

Irrespective of the kind of site visit conducted, a site visit log (refer to template in the appendices of this section) must be signed and dated by the monitors and auditors, as well as by a CRS staff member, on each day of the site visit.

## Monitoring Visits

DAIDS uses a risk-based approach to monitoring based on the design, size, and complexity of the clinical trial to develop protocol-specific monitoring plans. These plans outline the type/frequency of monitoring activities, various monitoring visits to occur throughout the course of the study, and the modality to be used (onsite or remote visits). Although the monitoring plan itself is not shared with CRS staff, all the necessary details are shared through monitoring communications, Pre-Visit Letters (PVLs) and Work Orders (WOs).

The types of monitoring visits that typically occur include: Site Assessment Visits (SAVs), Interim Site Monitoring Visits (ISMV), Remedial/For- Cause Visits, and Site Close-Out visits (COVs).

No less than 20 business days before the planned site visit, the CRS staff will receive a PVL and a Site Visit Work Order (SVWO) through the Clinical Site Monitoring (CSM) System. CRS staff must acknowledge receipt in the CSM system. The PVL confirms the visit dates, expected debriefing date, expected participant research records, and planned assessments to be conducted per the SVWO. The SVWO includes:

- Random and custom participant identification numbers (PIDs/PtIDs) for review
- Targeted Source Document Verification (TSDV) protocol(s) list
- Planned assessments to be performed during the visit

The monitor may also ask to review participant research and protocol records not previously requested.

CRSs must prepare for the visit, ensuring that:

- Staff are available to support monitoring activities.
- The data and records are available, complete, and orderly, as requested in the PVL and SVWO (e.g., participant research records, medical records, Case Report Forms (CRFs), regulatory and pharmacy files).
- All follow-up items/issues from prior visits have been resolved.
  Note: Best practice is for CRS staff to resolve any monitoring queries by the end of a visit or before the next scheduled visit.
- Evidence/supporting documentation exists that the CRS has addressed follow-up issues. Resolution documentation should also be ready for the monitor's review.

- Copies of requested documents are ready for the monitor at the start of the visit (e.g., Delegation of Duties log, documentation reflecting PI/IoR involvement in the study, Form FDA 1572, etc.).
- Any query raised in Electronic Data Capture (EDC) system has been answered/resolved before the visit begins.

Before the visit ends, the monitor verbally debriefs the PI/IoR and relevant CRS staff of the findings. The CRS Leader and PI/IoR need to attend this final meeting, but if that isn't possible, the monitor will debrief them over the phone preferably within a week.

After the visit, the monitor writes up a report of the relevant information and findings within 15 business days. The report is released in the CSM system, and an email notification is sent to Office of Clinical Site Oversight (OCSO) and the CRS staff. The OCSO Program Officer (PO) and Pharmaceutical Affairs Branch (PAB) representative review the report and enter the monitoring findings or trends identified into the system. The CSM system electronically notifies the CRS of findings requiring action/responses, prompting CRS staff to respond to the findings in the system. The OCSO PO or PAB representative review the respective CRS responses and either:

- Request additional information/implementation and evidence of corrective and preventive actions (CAPA) if the response is considered incomplete/inadequate.
- Mark the issue as "Resolved" if the response is considered adequate/sufficient.

Please refer to the Introduction to DAIDS Systems section for how to obtain access to the CSM system.

### Site Assessment Visits

SAVs evaluate CRSs' facilities for equipment, staffing, training, ability to comply with ICH E6, DAIDS requirements, protocol procedures, relevant Standard Operating Procedures (SOPs), and Manual of Operations/Procedures (MOP) as they relate to clinic, laboratory, pharmacy, or data management operations. DAIDS determines the requirements and timing of a visit before the site is activated. ;

An SAV is typically done by one monitor and takes about one day, depending on CRS structure, and number and composition of additional locations. This can also vary depending on the nature of the protocol, the site setup, and any DAIDS-specific requests. Any issues are entered and resolved through the NIAID CRMS CSM module between the site and the OCSO PO.

In some cases, the Network Leadership and Operations Center (LOC) staff may visit a site to assess its capacity for conducting a particular clinical trial or to ensure readiness to

conduct a specific protocol, and to specifically train staff before its initiation or activation. These visits are separate from DAIDS-directed SAVs.

## Interim Site Monitoring Visit

Interim Site Monitoring Visits (ISMVs) evaluate the conduct of the study by performing source document and other verifications, per DAIDS requirements set in the Protocol-Specific Monitoring Plan (PSMP). The visit requirements are based on ICH E6 and agreed upon between DAIDS and the Monitoring Contractor. These visits are generally scheduled throughout the active phase of the protocol (i.e., from open to enrollment through closed to follow-up) and take place on a schedule previously agreed on by DAIDS and the Monitoring Contractor. The ISMV can also be performed remotely at the request of DAIDS and the usual purpose is to review regulatory documents and EDC data.

The PVL and the SVWO preceding the visit include a list of PIDs/PtIDs for which the monitor(s) will conduct record reviews and a list of assessments to be completed during the visit. Additional PID/PtID review may be performed at the monitor's discretion, time permitting.

A standard ISMV is routinely scheduled quarterly, for three to four days, and may involve more than one monitor. The number of monitors assigned is NOT a reflection of poor CRS performance. CRS performance is a consideration in the assignment of co-monitors; however, co-monitors are assigned to monitoring visits based on a number of other factors including, such as:

- Number of networks and protocols (with risk ranking)
- Number and complexity of assessments or DAIDS-specific requests
- Number of follow-up or quality issues noted
- Enrollment volume and the number of PIDs/PtIDs remaining to meet DAIDS' monitoring requirements

DAIDS may increase the number of visits to a CRS based on protocol priority status or upcoming regulatory inspections.

Assessments differ based on protocol requirements and specific requests from DAIDS, and may also be conducted during an SIV, Remedial or For-Cause Visit, or a COV. The monitors may conduct the following assessments.

***CRS Files Review***

- Protocol-specific regulatory file review
- Annual site-specific regulatory file review

The above assessments differ in scope but verify compliance with Institutional Review Board (IRB)/Ethics Committee (EC)/other regulatory entity requirements for the study under review. The Protocol-specific regulatory file review includes at least the following:

- Protocol registration email, de-registration email
- All IRB/EC communications, submission packets, and approval letters
- IRB roster and documentation of voting abstention
- Form FDA 1572 or DAIDS IoR Form
- Delegation of Duties/Study Personnel Signature Log
- Current manuals/policies and procedures (all DAIDS, Network, CRS required)
- All protocol versions, Letters of Amendment, Clarification Memos, and IRB approved Informed Consents
- Study-specific procedures manual and/or Network MOP
- Investigator's Brochures and/or Package Inserts
- Safety Memos/Reports
- Screening/Enrollment Logs

The annual site-specific regulatory file review includes staff curriculum vitae (CVs), professional licenses, required training, laboratory certifications, and normal reference ranges.

***Pharmacy Assessments***

Upon PAB request, the following assessments may be performed:

- Protocol-specific Investigational Drug Audit (PSIDA)
- Investigational Pharmacy Inventory and Storage Assessment (IPISA)
- Global Pharmacy Services (GPS)

The PSIDA includes at least the following:

- Assessment of investigational pharmacy personnel
- Verification of pharmacy records and documents, including dispensation and preparation documentation
- Follow-up of unresolved, previously identified or new unreported issues

The IPISA includes at least the following:

- Assessment of investigational pharmacy personnel
- Verification of study product inventory and accountability, as well as storage records and review of shipping documentation
- Follow-up of unresolved, previously identified or new unreported issues

The IPISA reports may contain unblinded information and must not be shared with blinded staff.

The GPS is a comprehensive pharmacy assessment that may include a full review of all pharmacy personnel, equipment, facilities, as well as all processes and procedures. The GPS reports contain unblinded information and must not be shared with blinded staff.

***Operations Assessments***

Operations Assessments are conducted as directed by DAIDS at a CRS and/or other locations used to recruit and follow study participants. The assessment, of both the clinic and the pharmacy, will be completed on an annual basis or as DAIDS directs. The average length of the Site Operations Assessment Visit is approximately two hours, depending on the size of the CRS and number of locations, and is conducted by one monitor.

A Site Operations Assessment encompasses:

- DAIDS- and non-DAIDS workload at the CRS
- All CRS locations (including Additional Locations and/or any changes in location)
- Accessibility to DAIDS-required guidelines and manuals
- CRS supervision, including day-to-day management of the site and communication channels among CRS staff
- Quality management activities and adherence to the CRS's Clinical Quality Management Plan (CQMP)
- Facility and equipment used for DAIDS clinical trials

An Annual Pharmacy Operations Assessment (APOA) encompasses:

- Investigational pharmacy personnel documentation, including CVs, applicable licenses, registration, and any other applicable training records
- Pharmacy facilities and equipment, including controlled room temperature, refrigerators, and freezers, continuous and manual temperature monitoring and recording devices, and notification systems
- Aseptic compounding, including verification of compounding area/equipment and review of pharmacy staff aseptic technique training and assessment documentation
- Chain of custody procedures

***Laboratory Specimen Verification***

Laboratory Specimen Verification (LSV) is completed at the request of DAIDS and includes a laboratory specimen facility visit, review of sample tracking and retrieval, and assessment of sample storage space(s).

## Remedial or For-Cause Visit

In response to continual (or pervasive), documented accounts of noncompliance, data discrepancies, or concerns over the study's ethical conduct (e.g., suspicion of scientific misconduct or fraud), For-Cause Visits may be conducted.

The monitor performs the visit to further investigate what prompted the need for such a visit and may make recommendations about the following:

- Corrective actions
- Training needs assessment
- CRS CQMP evaluation
- Future CRS visits for contingencies follow-up

A standard Remedial or For-Cause Visit lasts three to four days on average, depending on the scope of work. Remedial Visits include assistance for CRS staff in the development and implementation of CAPAs for identified deficiencies.

# CRS Closeouts

## Study-Specific Closeout

For study-specific closeouts, CRSs must follow Network-specific MOPs.

## CRS Closeout

A closeout takes place once all CRS activities have ceased: that is, no currently active clinical trials are happening, no research-related activities or interactions with participants are ongoing, and all data cleaning activities are completed with no future activities planned. CRSs can be closed due to performance, administrative, and/or other compliance issues. CRSs may also be closed by DAIDS at the end of a grant cycle when not selected for future funding.

DAIDS will determine the need for an onsite COV based on CRS operations complexity and compliance with closeout procedures. The activities performed during a COV confirm that all participants have completed study visits, withdrawn from the study, or been transferred to another CRS. The COV takes about one day and is conducted by one monitor.

As part of the close-out process, the OCSO PO requests the CRS to complete the *OCSO CRS Close-out Checklist*. The OCSO PO follows up with a designated CRS point of contact until the checklist is complete (e.g., no outstanding items).

The overall site closeout proceeds according to DAIDS instructions/direction, verifying that:

- The study product has been returned to the Clinical Research Products Management Center (CRPMC) or transferred/destroyed, as appropriate.
- The on-site study specimens have been accounted for and subsequently shipped, transferred, or disposed of/destroyed.
- All essential documents have been stored or transferred, including but not limited to the following:
    - Source documents (original research records, clinic notes, and hospital notes)
    - IRB/EC and regulatory submissions and approvals
    - Protocols and related documents, such as amendments
    - Paper CRFs (if applicable)

  **Note:** When local and/or institutional requirements exceed these storage/retention requirements, the local/institutional requirements must be followed. Please refer to the Essential Documents section of this manual for more information on retention of records.

## Quality Management Audits

According to ICH E6 5.19.1: “The purpose of a sponsor’s audit, which is independent of, and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, Standard Operating Procedures (SOPs), GCP, and the applicable regulatory requirements.” DAIDS Quality Management is responsible for the conduct of all site audits.

DAIDS together with the auditing team determine an audit’s scope and purpose following these considerations:

- The importance of submitting the clinical trial results to regulatory authorities
- The number of participants
- A clinical trial’s type and complexity
- The risk level for participants
- Any significant and/or recurrent deviation(s) identified during the study conduct

CRSs will receive a confirmation letter outlining the purpose and scope for the audit, with a listing of what should be available for review. The PI’s/IoR’s presence during these visits is mandatory, for interviewing and debriefing at least.

Preparation for these types of visits typically include:

- Delivery of the confirmation letter and schedule to the CRS staff

- Review of follow-up issues from monitoring visits for completion; Contact with the OCSO PO and PAB representative for assistance with (or clarification of) any follow-up action items outstanding
- Verification that participants' research records, case report forms (CRFs), and CRS files are all complete and available before the visit start date
- Allocation of adequate space for the auditor(s) to work in
- Communication that CRS staff are expected to attend the debriefing

Based on study complexity, number of participants enrolled, number and types of issues at the CRS, and other considerations, DAIDS and the contractor together determine the audit's length and the number of auditors required.

During the audit, an auditor reviews participant records, perform interviews, tours the facilities, and finalizes the assessment with a debrief meeting. Afterward, they will provide DAIDS with a detailed report, including any deficiencies that were identified, and an audit certificate (when applicable). The PI/IoR must ensure that audit observations are addressed, by identifying each issue's root cause and implementing adequate CAPAs.

**Note:** Related documents, such as the audit report and audit responses document (CAPA), are **not** to be maintained in the study-specific files.

As per ICH E6 5.19.3(d): "To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case-by-case basis when evidence of serious GCP non-compliance exists, or in the course of legal proceedings." Therefore, it is recommended that the CRS maintains such documents in a separate file.

Types of CRS audit visits that DAIDS may request follow here.

## Routine Investigator Site Audit

Routine Investigator Site Audits are the most common type conducted as part of DAIDS' quality management program. They assess the study conduct and compliance with the study protocol, procedural documents, GCP, DAIDS' and other applicable regulatory requirements.

Such visits are typically performed for a single protocol, a risk-based selection of the CRS, or are triggered by poor performance.

Routine Investigator Site Audits are typically proactive visits that can happen at any stage but usually early on or midway through the clinical trial.

### For-Cause Investigator Site Audit

For-Cause Investigator Site Audits investigate reported serious and/or persistent noncompliance with the study protocol, procedural documents, GCP, applicable regulatory requirements, and/or DAIDS directives. They can also happen when scientific misconduct (e.g., fabrication and/or falsification of data) is suspected.

Such visits are typically reactive, responding to a reported concern, and the auditor's review focuses on issues at hand.

For-Cause audits are not announced as such to allow for adequate investigation of reported concerns.

## CRS Regulatory Inspection Readiness Visits

### Site Inspection Readiness Visit (SIRV)

Site Inspection Readiness Visits prepare CRS for Regulatory Authority inspections. Preparation is investigator-centric and may be either on-site or remote. On-site visits may include an educational presentation, high-level review to verify the presence of study documents, and a spot check of certain criteria that DAIDS and the contractor will define before the visits, including but not be limited to PI/IoR oversight, review of study endpoints documentation, and serious adverse event reporting. Remote preparation does not consist of remote review of study documentation; it includes only an educational presentation to the CRS staff. Readiness activities will be adapted to the CRS's needs and the nature and scope of the inspection(s), once known.

The visit is usually performed for a unique clinical trial but may address multiple clinical trials at a CRS, for possible inclusion in a marketing application.

SIRVs can be proactive, to prepare the CRS for an inspection related to a planned or potential submission of a regulatory marketing application. They can also be reactive, to respond to a regulatory agency inspection announcement, when feasible.

### Mock Inspection Visit

Mock inspection visits train CRS staff by providing a simulation of an actual inspection experience, as nearly as possible. Staff learn how to host the visit and respond to an inspector's questions via simulated interviews. Approach and verification activities including documentation/data review, interview of key personnel, and direct observation of facilities and equipment will be adapted to DAIDS requirements. Mock inspections provide the CRS with a "dry run" experience in preparation for a potential regulatory inspection.

Mock inspection visits can be proactive, to prepare the CRS for a planned or potential inspection related to a regulatory marketing application submission. They can also be reactive, to respond to a regulatory agency inspection announcement, when feasible.

**Note:** To ensure inspection readiness, CRS staff can benefit of the information on how to prepare for and maintain a state of readiness for a regulatory inspection described in the Clinical Research Site Inspection Readiness section of this manual.

## Appendices

1. Clinical Research Site Visit Log Template

## Version History

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|---|---|---|
| V1.0 | 1/19/2021 | Original Version |
| V2.0 | 6/10/2024 | Pg 3 – Updated timeframe for release of Pre-Visit Letter and Site Visit Work Order from 15 to 20 days prior to scheduled visit.<br><br>Updated terminology from Announced Work Order to Site Visit Work Order to align with current terms.<br>Removed SIV and amended the SAV section as SIV/SAV visits are now combined under the heading of SAV. |
| V3.0 | Nov 2024 | Pg 4 – minor edits to the SAV section.<br>Pg 9-11 – edits to the "Quality Management Audits" section to update terminology and types of visits.<br>Pg 11 – Added "CRS Regulatory Inspection Readiness Visit" section. |