Division of AIDS (DAIDS) Site Clinical Operations and Research Essentials (SCORE) Manual: Clinical Research Site Inspection Readiness

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Clinical Research Site Inspection Readiness

An inspection is an act whereby a regulatory authority conducts an official review of documents, facilities, records, and any other resources that it deems relevant to a clinical trial. There are multiple reasons why a regulatory inspection may be performed at a Clinical Research Site (CRS). These include being part of a marketing authorization application; as part of a for cause investigation to assess significant concerns with study conduct; or part of a targeted scope review of safety data.

Regulatory inspections ensure the:

- Safety and well-being of study participants are maintained.
- Clinical data submitted by DAIDS as sponsor are accurate and complete.
- Clinical trial is conducted according to the protocol, applicable local laws and regulations, and the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) (also referred to as ICH E6) requirements.

Each regulatory agency follows their procedures to conduct inspections, which are available on their respective websites (see “References” section).

The Principal Investigator (PI)/Investigator of Record (IoR) is responsible and ultimately accountable for any regulatory violations and/or protocol non-compliance resulting from failure to adequately conduct and/or supervise the clinical trial.

Additional information and guidance relating to regulatory inspection preparedness are available through training modules offered on the DAIDS Learning Portal (DLP). Refer to the Introduction to DAIDS Systems section of the manual for details on gaining access to the DLP.

How to Become/Remain Inspection Ready

The CRS must remain inspection-ready at all times. To ensure such preparedness, procedures should be in place, applicable staff should possess a thorough knowledge of the study and local regulations, and have good documentation practices to support the study and compliance with all the applicable requirements. CRSs must have a Regulatory Inspection Preparation standard operating procedure (SOP) in place. This may be an institutional or CRS-specific SOP and must be reviewed and approved for use by the Office of Clinical Site Oversight (OCSO) Program Officer (PO). For CRSs that do not have an SOP for Regulatory Inspection Preparedness, an Inspection Preparedness Standard Operating Procedure Template is offered as an appendix to this section.

In addition to having an SOP in place, the CRS leadership must ensure that inspection readiness is incorporated into daily operations and procedures. This can be accomplished

by implementing routine meetings with the study team to identify and address issues as they arise. Careful review of monitoring reports, audit reports, and CRS quality management activities can also help identify areas of concern. Staff must allow adequate time for review of previously identified findings and for properly assessing corrective and preventive actions (CAPA) to ensure all identified findings have been sufficiently resolved. Learning where the potential risks and issues are at the study level can help in evaluating/addressing overarching processes. Engagement with the various functional areas involved in a study will also help staff better understand the different processes and how they may be affected.

Assessment of the CRS is another effective method to determine inspection readiness and help a site prepare for a regulatory inspection. Such assessments should not only focus on study-related risks and issues, but also on the following questions:

- Is this the organization's first inspection?
- Is the study team inspection naïve?
- Are the subject matter experts who will address CRS processes experienced in direct interaction with an inspector?
- Has there been staff turnover throughout the conduct of the study, whereby CRS staff at the start of the study are not the same as at the time of the inspection?
- What is the process for staff transitions when personnel changes occur during the conduct of the study? And how is this documented?
- Are all areas of the CRS clean, well-maintained, and organized?
- Are participant records stored in a locked and secure area to maintain source data integrity and participant confidentiality?

Inspection readiness also requires a CRS to always keep their facility and CRS files well-organized and secure. Regulatory files must be reviewed on a routine basis as per the CRS's Clinical Quality Management Plan (CQMP). These routine quality management activities help to ensure good documentation practices (GDP) and provide the complete story of what occurred during the conduct of the study. Additional guidance on GDP and CQMP is provided in the DLP, DAIDS Clinical Trials Networks Study Specific Procedures, Manual of Operations/Procedures and in the Source Documentation and Quality Management sections of this manual.

Some of the essential documents that a CRS is to include in their regulatory files are:

- Executed (signed) informed consent form(s) (ICFs) for all participants
- Study source documents and participants' research records, as applicable
- All Institutional Review Board (IRB)/Ethics Committee (EC) submissions and approvals
- All key correspondence with DAIDS, IRB/EC, monitors, and study participants

- Letters, faxes, emails, memos, and documentation of telephone calls (with date and summary)
- Screening and enrollment/randomization logs
- Case report forms (CRFs; paper or electronic)
- Study product accountability, storage temperature monitoring, and shipping records
- Current CRS SOPs (all versions used for the study duration are required)
- Documentation of the training and experience (curriculum vitae/resumes) of the CRS staff, as well as job descriptions and delegation of duties logs

For a complete list of essential documents, refer to the Essential Documents Recordkeeping appendix in the Essential Documents section of this manual.

Before the Inspection

Regulatory agencies often confirm an inspection in writing and usually send an announcement letter to the PI/IoR. The United States (U.S.) Food and Drug Administration (FDA) may confirm an inspection in writing or may call the PI/IoR or even arrive unannounced at U.S. locations. FDA will issue a Form FDA 482 (Notice of Inspection) upon arrival.

Regardless of which regulatory authority is going to conduct the inspection, the CRS must:

- Notify DAIDS OCSO PO, Contract Research Organization (CRO) (if applicable), and other stakeholders of inspection dates (within one business day for scheduled inspections and as soon as possible for “for-cause” inspections).
- Review applicable regulatory guidance, regulations, and relevant CRS inspection procedures (e.g., Inspection Preparedness SOP).
- Provide refresher training on Inspection Preparedness SOP.
- Ensure that the PI/IoR and key staff will be available for the entire inspection.
- Identify an appropriate workspace for the inspectors. Workspaces should have ample room for reviewing documents, be clear of all unrelated study materials (e.g., documents relating to other studies not within the scope of the inspection), and be away from busy/noisy areas to ensure confidentiality and privacy for any ongoing research activities going on at the same time.
- Check availability of all study-related documents.
- Ensure the ability to photocopy documents on site to be prepared for requests by inspector(s).
- Decide on the roles and responsibilities each CRS staff member will have before, during, and after the inspection and ensure staff are aware of their roles.
- Provide training on interview techniques and conduct mock interviews with staff designated to participate in the inspection.

- Request an independent translator to be available (if requested by Regulatory Agency).
- Complete the CRS Inspection Preparation Checklist available as an appendix of this section.
- Create storyboards for any significant issues that may have occurred during the study. A storyboard is a high-level summary of a sequence of events, escalations, and actions for a significant issue; it is used as a roadmap to connect events and issue-related documents. It should reference where additional details can be found and not replace any existing documentation (such as CAPA) that provides a full explanation of the issue and its resolution. The following is a storyboard example:

  Issue: Ongoing concerns with open data queries

  - 20Mar2019 - CRA brought overdue data queries to the attention of the PI/IoR – see Monitoring Report dated 13Apr2019 in Section 5 of Regulatory Binder.
  - 25Mar2019 – PI/IoR met with the study staff to discuss the issue and sent an email to all attendees at the site with a summary of the discussion – see email dated 27Mar2019 in Section 6 of the Regulatory Binder.
  - 23May2019 - CRA brought ongoing overdue data queries to the attention of the PI/IoR; this required extra escalation and a CAPA was initiated at the site – see CAPA #123
  - 15Jun2019 – CAPA was closed after all actions were complete 01Aug2019 – PI/IoR confirmed that there have not been any further overdue data queries.

Depending on the time available and the CRS's prior experience with inspections, their OCSO PO may request a Pre-Inspection or Mock Inspection visit by a DAIDS contractor to help prepare the site.

During the Inspection

The PI's/IoR's involvement in the inspection is essential, and their presence is required at the opening and closing meetings and intermittently throughout the course of the inspection.

The CRS staff should follow their institutional policy for visitors, sign-ins, and visitor badges, and escort inspector(s) at all times. For security purposes, CRS staff are to verify the inspector's badge against the letter announcing the inspection.

It is also the responsibility of all CRS staff to keep all passwords (electronic CRF, database, or Electronic Medical Record [EMR] access) as well as personal access codes

secure, and never share these with an inspector. If the inspector requests to see the database or EMRs, the CRS staff must access the system on behalf of the inspector and remain with the inspector at all times during access.

The following activities typically take place during an inspection:

- An opening meeting to introduce CRS staff and confirm the type and scope of the inspection
- A facility tour where the inspector will pay attention to the adequacy of space; the secure limited access to offices, laboratories, computers, documents, and study product storage; the presence of study-related equipment and maintenance logs; and the use of electronic systems
- Interviews with CRS staff based on their expertise and assigned role at the CRS. The PI/IoR must always be prepared to describe the roles and responsibilities of study staff.
- A review of study participant ICFs and other documentation to verify the safety and well-being of study participants was maintained throughout the study, and that CRS staff followed the protocol and all applicable regulations
- Documents reviewed to verify CRS processes, staff qualifications, training, and study conduct. All documents requested during the inspection must be copied and the request tracked by using a Log of Copied Documents. This log should record the order in which documents were requested for copying by the inspector. A shadow file of all documents provided to the inspector should be created and kept at the CRS to aid in the response to inspection findings (if any).
- Some documents contain sensitive information (e.g., contractual agreements, sponsor audit reports, etc.). As such, these should only be provided to the inspector after consultation with DAIDS.
- Daily debriefing sessions with the PI/IoR and relevant team members (CRS Leader, CRS Coordinator, Pharmacist of Record, etc.).
  Note: Inspectors are not required to hold a daily debriefing; therefore, the PI/IoR needs to discuss/request these during the opening meeting.
- A formal close-out meeting with the PI/IoR at the end of the inspection. The PI/IoR can invite other relevant staff members (CRS Leader, CRS Coordinator, Pharmacist of Record, etc.) to attend the close-out meeting.

The following recommendations may benefit the CRS during an inspection:

- Remind all participating staff to remain calm throughout the inspection. Do not rush a response or a document to the inspector. Refer to the information provided in the Guidance on Site Regulatory Inspection appendix to this section.
- Assign a staff member to take notes throughout the duration of the inspection.

- Designate at least one CRS staff member as the point of contact (POC). The POC must stay with the inspector(s) at all times and be familiar with the clinical trial and CRS activities.
- Be prepared (CRS leadership) to hold daily debriefings (by phone or via email) with the OCSO PO on request.
- Never argue with an inspector, even if there is disagreement with a citation/deficiency. The CRS will have an opportunity to respond afterwards in writing. It is best to provide evidence with the response.
- Questions or requests for DAIDS documents should be referred to the OCSO PO promptly. The OCSO PO monitors CRS communication more frequently during an inspection to answer any questions in a timely manner.

After the Inspection

At the close-out meeting, the inspector will provide the PI/IoR with instructions to formally respond to the findings along with a timeline.

The inspector will complete a written inspection report after the completion of the inspection. The timeline to finalize and distribute the report varies among the regulatory agencies and will be communicated to the PI/IoR during the close-out meeting. The PI/IoR will receive a copy of the inspection report and should immediately forward it to the OCSO PO. The PI/IoR can consult with DAIDS on preparation and submission of responses to inspection findings, as per the regulatory agency timeline, and the implementation of corrective and/or preventive actions as necessary. Responses to inspection findings include the following:

- Detailed description/explanation of the finding.
- Root cause for the finding, if applicable.
- CAPA implemented or planned as a result of the finding.
- Source documentation to support CAPA implementation
- Timeline for all deliverables (implementation of CAPAs).

Typical Regulatory Agency timelines for responses to inspection findings are as follows:

Regulatory Agency	U.S. FDA	(European Medicines Agency) EMA
Typical response timelines	15 business days	15 calendar days

Note: The U.S. FDA requests that the response be included with the official inspection results as part of the public record.

Refer to the "Guidance on Site Regulatory Inspection" provided as an appendix to this section for additional information on preparing and hosting an inspection.

U.S. FDA Inspection Reports

If the U.S. FDA inspector(s) find practices or situations that significantly deviate from the regulations and/or ICH E6, they will provide the inspection findings verbally as well as in writing on Form FDA 483 (Inspectional Observation) during the close-out meeting. The CRS staff must understand all the observations listed in the Form FDA 483 and ask for any clarifications needed to be able to provide adequate responses, when required. A warning letter is issued when there are more significant issues. The Form FDA 483 is used for less severe issues. The FDA inspector will provide timelines for response and further reporting and actions. The FDA will later issue (within 45 days) an Establishment Inspection Report (EIR) which is the full inspection report that includes all observations, discussion items, a summary of the areas reviewed, and the final classification. The classification will be one of the following:

- **NAI (No Action Indicated):** No objectionable conditions or practices were found during the inspection (or if found do not justify further regulatory action).
- **VAI (Voluntary Action Indicated):** Objectionable conditions or practices were found, but the agency is not prepared to take or recommend any administrative or regulatory action.
- **OAI (Official Action Indicated):** Regulatory and/or administrative actions will be recommended.

European Medicines Agency Inspection Reports

After an inspection the EMA inspector(s) will conduct a closing meeting to verbally communicate any findings detected and to ensure that the results of the inspection are clearly understood and that there is no misunderstanding by either the inspector(s) or CRS staff. Typically, within 15 calendar days following the completion of the inspection, the EMA inspector will issue a GCP Inspection Report that includes a summary of the activities inspected and the findings graded as follows:

- **MI (Minor):** The inspector(s) identified conditions, practices, or processes that would not be expected to adversely affect the rights, safety, or well-being of the participants and/or the quality and integrity of data.
  Numerous minor observations might indicate poor quality data and the sum might be considered equivalent to a major finding.

- **MA (Major):** The inspector(s) identified conditions, practices, or processes that might adversely affect the rights, safety, or well-being of the participants and/or the quality and integrity of data. Major observations are serious deficiencies and are direct violations of ICH E6 principles.

Observations classified as major may include a pattern of deviations and/or numerous minor observations.

- **CR (Critical):** The inspector(s) identified conditions, practices, or processes adversely affecting the rights, safety, or well-being of the participants and/or the quality and integrity of data. Critical observations may include a pattern of deviations classified as: major, poor quality of the data, and/or absence of source documents. Manipulation and intentional misrepresentation of the data would be classified as critical.

Appendices

1. Inspection Preparedness Standard Operating Procedure Template
2. Guidance on Clinical Site Regulatory Inspection
3. Clinical Research Site Inspection Preparation Checklist
4. Log of Copied Documents

References

1. FDA: Program 7348.811 Chapter 48 - Bioresearch Monitoring Clinical Investigators and Sponsor-Investigators
2. EMA: Procedure for Conducting GCP Inspections Requested by the EMEA
3. SAHPRA Guidelines for Clinical Trials