Division of AIDS (DAIDS) Site Clinical Operations and Research Essentials (SCORE) Manual: Quality Management

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Quality Management

DAIDS requires that all Clinical Research Sites (CRSs) have a Quality Management System (QMS) in place that defines Quality Management (QM) tools, activities, and processes to ensure work quality. QM includes the CRS procedures, forms, and templates: Quality Control (QC), Quality Assurance (QA), and Corrective and Preventive Actions (CAPA) processes as well as continuous improvement activities required to ensure complete, accurate study data.

QC processes verify the completeness and accuracy of a final product/output against its original specifications. In clinical trials, QC serves to verify that activities and documents are complete and accurate, in real time, or at least prior to the clinical trial's next critical step.

QA processes analyze a sample of the product/output using a retrospective, objective, systematic, and periodic review to verify that the process/system that generates the product/output complies with stated specifications. In clinical trials, QA is a review of a sample of clinical trial documents to verify that the CRS processes and systems generating the clinical trial data are performing per the required specifications.

CAPA is a structured approach to investigating, correcting, and preventing a deficiency/issue in a process/system.

The main elements of a DAIDS required QMS are:

- Standard Operating Procedures (SOPs)
- Clinical Quality Management Plan (CQMP)
- CRS QA Summary Reports

Clinical Research Site Standard Operating Procedures Management

CRSs standardize clinical trial processes by establishing SOPs that document clinical, administrative, and management activities and processes. CRS Leaders or their designees must ensure that each SOP includes sufficient details to guide CRS activities, and that SOPs are revised to incorporate changes, as necessary.

CRS Leaders must also align SOPs to International Council for Harmonisation (ICH) Good Clinical Practice (GCP) requirements ("ICH E6"), and any other applicable local laws, regulations and institutional policies.

Standard Operating Procedures Requirements

- CRSs must have a master SOP that describes minimum requirements for developing, reviewing, approving, implementing, and revising CRS SOPs. SOPs

should be reviewed and revised at least every three years or as needed when a current process changes.

- At a minimum, all CRSs that conduct DAIDS clinical trials must establish the SOPs listed in the List of Required SOPs at DAIDS CRS appendix of this section, to ensure standardized CRS processes. This section's appendix includes an SOP Template to help CRSs create and maintain the required SOPs in a consistent format.
- CRSs must also implement any clinical trial-specific SOPs required by protocol or the DAIDS Network Manual of Operations/Procedures (MOP).

DAIDS does not review and approve all CRS required SOPs, but reserves the right as sponsor to assess SOPs to ensure compliance and address issues (e.g., require the CRS to develop additional SOPs to address an identified process issue).

CRSs may combine more than one process/activity into an SOP to meet the multiple requirements of studies, DAIDS Network and/or DAIDS.

All CRS staff must review the applicable CRS SOPs and affiliated Network MOP(s) as part of their CRS orientation, before clinical trial initiation and/or before conducting any tasks on an ongoing clinical trial. They must also review any revisions to applicable CRS SOPs and/or Network MOP(s) during the clinical trial. Please refer to the CRS Personnel Qualification, Training and Responsibilities section of the SCORE Manual for detailed training documentation requirements.

CRSs must file all current and obsolete SOP versions according to DAIDS clinical research records storage and retention requirements described in Essential Documents section of the SCORE Manual. Copies of obsolete versions should be retained for historical reference, but they should be clearly marked as obsolete to ensure staff use current, approved documents. SOPs must include a version history table to document the change date, version number, and reason for the update. Staff must train on any non-administrative SOP changes and document their training accordingly.

All versions of SOPs and Network MOP(s) used during the clinical trial must be available for review to DAIDS staff, DAIDS representatives (monitors, auditors, etc.) and regulatory inspectors during monitoring visits, audits, or inspections.

Clinical Quality Management Plan

All CRSs conducting DAIDS clinical trials must develop and implement a CQMP to guide required QM activities, ensure participants' rights and safety are protected, the data collected at CRSs are Attributable, Legible, Contemporaneous, Original, Accurate, and Complete (ALCOA-C), and that clinical trial conduct complies with applicable regulations.

For Pharmacy and Laboratory Quality Management Plans, refer to the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* and *Good Clinical Laboratory Practice Guidelines* respectively.

Clinical Quality Management Plan Requirements

At minimum, DAIDS requires the CQMP to:

a. Describe roles and responsibilities of key personnel involved in developing, implementing, and evaluating the CQMP.
b. Determine Key Indicators (KIs) for QA/QC review, including:
    - Informed Consent Form (ICF) and Process
    - Assessment of Understanding of ICF, as applicable
    - Eligibility Criteria and Process
    - Protocol-Required Tests and Procedures
    - Visits/Missed Visits
    - Concomitant/Prohibited Medications
    - Study Product Administration/Dosing
    - Adverse Events (AE), Serious Adverse Events (SAE), and DAIDS-Expedited Adverse Events (EAE) identification and reporting
    - Protocol-defined endpoints identification and reporting, as applicable.
    - Source Documents, Signatures, Initials, Dates
    - Investigator File Review Deficiencies
c. Describe QM Activities:
    - QC review activities verify tasks were performed according to designated instructions and/or requirements. QC is conducted in real time, immediately after a task is performed, or at least before the next critical step of clinical trial. These activities support compliance with ICH E6, Human Subject Protection (HSP), protocol directives, and CRS requirements. Examples of QC activities include:
        - Re-reviewing eligibility checklists before enrolling a participant onto study and performing additional protocol procedures.
        - Verifying that visit checklists are completed at the end of participant visits, before participants depart the CRS.
        - Re-reviewing ICF documents for accuracy and completeness before participants depart the CRS (i.e., verify the correct version was used; ensure all required dates, entries, and signatures are recorded; etc.).
    - QA activities are conducted retrospectively, periodically, systematically, and independently for a specified time-period, on a defined subset of a CRS's clinical trial-related activities and documents. QA audits function as an independent examination for adherence to ICH E6, HSP, protocol, and all other DAIDS and regulatory requirements. QA activities include:

- Periodic evaluations to determine agreement between key elements of source documentation and completed Case Report Forms (CRFs). (See Appendix Participant Chart Review Tool of this section.)
- Periodic regulatory file document assessments to ensure current and complete content. (See Appendix Protocol Regulatory File Review Tool of this section.)

d. Describe QA and QC process tools, including visit reminder checklists, data entry query reports (from the Data Management Center), Clinical Site Monitoring Reports, and "Participant Chart and Protocol Regulatory File Review Tools".

   Please note: DAIDS requires CRSs to use the "Participant Chart and Protocol Regulatory File Review Tools" to conduct bi-annual QA reviews. CRSs may use additional tools to supplement the required DAIDS tools and increase review frequency to suit CRS and clinical trial needs.

e. Describe the frequency of QM activities. As examples, high- and/or fast-enrolling clinical trials may need more frequent QA reviews to mitigate risk. Similarly, complex clinical trials may require QA reviews for a higher volume of tasks/actions than routine clinical trials.
f. Designate a minimum percentage of participant research records for review during QA audits. Sample size should be adequate to represent a valid assessment of clinical trial activities based on factors such as risk level, accrual numbers, and clinical trial phase, and CRS staff experience.
   - DAIDS may set a minimum required percentage of participant records for QA audit for a particular clinical trial or for a CRS.
g. Describe required QA activities that will ensure complete, current regulatory files. Example: list regulatory file review tools and review frequency.
h. Document QM activities with the following minimum identifiers:
   - Reviewer name and role;
   - Review date;
   - Participant identification (PID) numbers reviewed;
   - Specific indicators reviewed;
   - Time period covered by the review;
   - Findings/results of review;
   - Root cause analysis (as applicable);
   - Corrective actions;
   - Preventive actions;
i. Describe the CQMP Evaluation Process. The CQMP must describe how the CRS staff conducting the QA reviews will analyze, evaluate, and communicate QA/QC findings to other CRS staff. The CQMP must also describe CAPA and continuous improvement criteria and processes that may necessitate changes to CRS practices and the CQMP.

j. Describe how CRSs will retain CQMP-related QM files (e.g., QA/QC review tools, CQMP, QA summary reports, DAIDS-CRS correspondence, etc.) and make these files available to DAIDS staff or their representatives for review.

The Clinical Quality Management Plan Template appendix in this section helps CRSs create the required CQMP. Please refer to DAIDS CQMP, Frequently Asked Questions for answers to additional CQMP-related questions.

Clinical Quality Management Plan Review and Approval Requirements

CRSs must submit draft CQMPs for review and approval to the Office of Clinical Site Oversight (OCSO) Program Officer (PO) during site activation and any subsequent, non-administrative changes. As per the Guidelines for Preparation of the Bi-annual QA Summary Report the existing CQMP will be reviewed bi-annually with the QA Summary Report preparation. If the findings in the CRS QA summary report trigger a need to revise the site CQMP, the CRS must submit the revised CQMP to the OCSO PO for review. Once the OCSO PO reviews and provides comments on the new draft or revised version of the CQMP, CRSs must address the comments and submit a revised version for approval. Once the OCSO PO approves the CQMP, the Principal Investigator (PI)/Investigator of Record (IoR) or CRS Leader must sign/date the CQMP, after which it may be implemented at the CRS. CRSs must provide a copy of the signed/date CQMP to DAIDS.

Quality Assurance Summary Reporting Requirements

CRSs must use the CRS QA Summary Report Template, an appendix of this section, to report QA findings to the OCSO PO bi-annually. The CRS QA Summary Report may identify problems, possible root causes, any CAPAs implemented, and if the CQMP needs to be revised.

If CRS staff identifies an unreported SAE during QA activities, they must report the event immediately to the Institutional Review Board (IRB)/Ethics Committee (EC) and DAIDS per protocol, DAIDS EAE policy, and institutional requirements.

DAIDS may require more frequent QA reporting based on CRS performance, protocol enrollment rate, or other factors. “Guidelines for Preparation of the Bi-annual QA Summary Report” (appendix in this section) guides CRSs on completing the report.

Quality Management Document Retention Requirements

All documents related to QM activities must be stored in a separate folder/binder and accessible to DAIDS upon request. These documents include:

- Signed versions of CQMPs.
- Completed *CRS QA Summary Reports*.
- *Participant Chart Review Tools*.

- *Protocol Regulatory File Review Tools*.

Please refer to the “Essential Documents*”* section of the SCORE manual for document retention timelines.

Appendices

1. Standard Operating Procedures Template
2. List of Standard Operating Procedures Required at DAIDS Clinical Research Sites
3. Clinical Quality Management Plan Template
4. Guidelines for Clinical Research Site staff on Preparing the Bi-annual Quality Assurance Summary Report
5. Clinical Quality Management Plan: Participant Chart Review Tool
6. Clinical Quality Management Plan: Protocol Regulatory File Review Tool
7. Clinical Quality Management Plan: Clinical Research Site Quality Assurance Summary Report
8. Clinical Quality Management Plan: CRS QA Summary Report - Section 4 – Additional Lines