General Tips for Implementing Clinical Quality Management

Background: The National Institute of Allergy and Infectious Diseases (NIAID) Division of Microbiology and Infectious Diseases (DMID) policies and standards are established to ensure quality control and quality assurance processes are in place at clinical research sites conducting DMID-funded clinical research. The International Council for Harmonization (ICH), Good Clinical Practice Guidelines E6 (R2) and the complementary U.S. Food and Drug Administration (FDA) E6(R2) Guidance for Industry, E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) defines quality assurance as, "All those planned and systematic actions that are established to ensure that the trial is performed, and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s)." (ICH GCP E6 1.46)

All DMID-funded clinical sites should develop and implement a CQMP as an on-site management tool to internally evaluate and document the site's performance of the protocol procedures; incorporating key quality indicators and operational steps for assuring protections are in place for human subjects, the research data is reliable, timely quality reviews are established to determine adherence to the protocol, GCP guidelines, and applicable FDA and local regulations.

General Tips:

1. **Maintain a quality risk management culture and process – PLAN, DO, CHECK, ACT**
   - **Plan** for risk-based quality management *prior to* initiating protocol activities
     - Identify and assess risk *prospectively*; at the system level (e.g., standard operating procedures, computerized systems, site capacity and resources), and the clinical trial level (e.g., trial design, data collection and source documentation, informed consent process, study product management, specimen processing/shipment).
       - Likelihood: What is the likelihood risks might occur?
       - Impact: What is the extent to which risks could impact human subject protection and reliability of study results?
       - Mitigation: Define acceptable or unacceptable levels of risk, and associated actions planned to mitigate unacceptable levels of risks.
   - **Do** – implement steady state clinical quality management activities according to the plan; manage risk *throughout* the protocol lifecycle
   - **Check** – analyze measurable observations/results from documented clinical quality management activities
   - **Act** – conclusions from the analysis of metrics prompt actions toward issue management, continuous improvement, and evaluation of the clinical quality management plan for effectiveness

General Tips for Implementing Clinical Quality Management

2. Establish and Implement a CQMP

- Define processes, quality review tools, checklists and reports summarizing quality management activities to drive and determine CQMP effectiveness
  - Internal sources (quality measurement tools, checklists, i.e., documentation of quality reviews of subject charts, study product/pharmacy accountability, laboratory results reports, site essential regulatory documents and regulatory files).
  - External sources (i.e., data entry, query/error or transmission reports from the data coordinating/management center; clinical site monitoring reports; external audits (third party, FDA, IRB, OHRP).

3. Organize all records for ease of access, maintenance and review

- All records in any form; including, but not limited to, written, electronic, magnetic, optical records, scans, x-rays, and electrocardiograms, that describe or record the methods, conduct, and/or results of the research, the factors affecting a trial, and the actions taken
- Be prepared to trace issues/findings to the root causes

4. Real time quality control inspection of documentation

- The real time ("day to day") observation and documentation of the study data collected
- Site's follow work processes and approved protocol-directed procedures
- Source data and source documentation i.e., Case Report Forms / data entry / electronic health records; refer, below, to A.L.C.O.A./C principles and references in ICH Guidelines and FDA Guidance for Industry
- **A.L.C.O.A.C**: Per ICH GCP E6 (R2), Integrated Addendum, 4.9.0, source data should be
  - **Attributable**: it is obvious who wrote/entered the information.
  - **Legibility**: the information is readable.
  - **Contemporaneous**: the information is current, dated and signed at the same time, and in the correct time frame.
  - **Original**: the information is the first recording. It is not a copy* or altered.
    - *Refer to ICH GCP E6 1.63, *Certified Copy*
  - **Accuracy**: source documentation of source data is accurate; no discordant data is recorded elsewhere.
  - **Complete**: trial data are complete, verifiable and reliable.
- **A.L.C.O.A**: Per FDA Guidance for Industry, Electronic Source Data in Clinical Investigations
- **A.L.C.O.A**: Per FDA Guidance for Industry, Use of Electronic Health Record Data in Clinical Investigations: Applying A.L.C.O.A principles can eliminate duplication, transcription errors, promote real-time access, accuracy and completeness
- Issue Management: A periodic summary of actionable items, prompting corrective and preventive action toward continuous improvement and effectiveness
- Be prepared to trace issues/findings to the root causes

General Tips for Implementing Clinical Quality Management

5. Periodic quality assurance processes described in the CQMP

- Systematic, objective, and comprehensive examination of the total work effort to determine the level of compliance with Good Clinical Practice (GCP) standards
- Sample size is adequate to represent a valid assessment based upon enrollment, protocol-driven procedures, and data collected
- Issue Management: summarize findings and review periodically toward continuous improvement and effectiveness
- Be prepared to trace issues/findings to the root causes

6. Timely communication

- To promote, document, and maintain effective communications across staff and departments (i.e., clinical, pharmacy, laboratory, diagnostics), applicable clinical sites (multi-site protocols), operations entities managing data collection, processing, analysis; pharmacovigilance; study product issues)
- To Sponsor as per protocol
- To IRB as per protocol, and institution processes

7. Corrective Actions

- Maintain corrective action preventive action (CAPA) standard operating procedures
- Document corrections, decisions made, and actions taken to prevent recurrence of errors / deviations, and adverse trends. Examples:
    - Internal quality review and external monitoring findings
    - Validation of established test systems (laboratory equipment calibration)
    - Criteria for proper study product management
    - Eligibility criteria
    - Subject enrollment
    - Deviation from approved protocol (subject or non-subject related impact)
    - Subject consent for storage of their specimens for future use
    - Required training per sponsor/DMID
- Implement corrective actions as defined in the protocol and study Manual of Operational Procedures (i.e., deviations to the protocol, SAEs, AEs, study product issues, specimen shipments)
- Timely reporting /communication to site staff, sponsor, and to the IRB, when indicated

8. **Continuous Improvement – Assessing the site's success**

- Review the CQMP annually, at a minimum
    - Review summaries of past performance improvement data and activities.
    - Assess the overall effectiveness of the CQMP and integrate improvements to past performance and recent quality review findings.
- Revise the CQMP, if indicated, integrating data from issue management