QUALITY ASSURANCE IN CLINICAL RESEARCH

Stake holders in clinical research recognize the benefits of carefully managing the quality of data from their drug development and clinical trials. To ensure clinical data accuracy and integrity, it is necessary to thoroughly review these data, to assess the validity of outlying data points, and to carefully document query identification and resolution throughout a study's duration.

Maintaining accuracy and quality throughout a clinical study is a continual, dynamic process. Although study requirements are carefully set forth initially in detailed documents such as an approved clinical protocol, a data management plan, and an accompanying project plan, expectations and requirements can change during a study. This ongoing process requires revising mechanisms and communicating these revisions clearly to all investigators and support staff.

Defining the Terminology

Quality : The total set of characteristics of a product or service that affect its ability to satisfy a customer's stated or implied needs.

Quality System : The organizational structure, responsibilities, procedures, processes, and resources for implementing quality management.

Quality Audits (QA) : The systematic and independent examination of all trial-related activities and documents. These audits determine whether the evaluated activities were appropriately conducted and that the data were generated, recorded, analyzed, and accurately reported according to protocol, standard operating procedures (SOPs), and good clinical practices (GCP).

Quality Assurance : 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).

Quality Control (QC) : Periodic operational checks within each functional department to verify that clinical data are generated, collected, handled, analyzed, and reported according to protocol, SOPs, and GCP.

Management of Quality

One of the principal requirements of a quality plan is the ability to delegate specific responsibility to individuals and then hold them accountable for their actions. Such an effort requires the definition of every individual’s responsibility and the position the person holds in the organization. This is essential since many responsibilities are allotted to individuals, not by their name, but by the position they hold.

The first activity while setting up the quality system is to define the organization structure and the reporting pathways. Having multiple people doing the same work, brings in the problem of accountability, and this must be avoided. In many organizations there are individuals with extra constitutional authority, but they rarely

are accountable for their actions. The existence of such individuals is highly detrimental to the organizations, and the earlier the managements realize this, the better.

The ongoing challenge in managing the quality of clinical data is to continually monitor data collection procedures and data management practices at every level of the study. This includes :

1. Ensuring that data generated during the study reflect what is specified in the protocol (case report form [CRF] vs. protocol).
2. Comparing data in the CRF and data collected in source documents for accuracy (CRF vs. source documents)
3. Ensuring that the data analyzed are the data recorded in the CRF (database vs. CRF).

Quality surveillance continues after the trial has ended and plays an important role in ensuring that :

- Data presented in tables, listings, and graphs correctly match data in the database.
- Data reported in the clinical study report (CSR) are the data analyzed.
- All aspects of the data management processes are compliant with SOPs and GCPs.

The Quality Plan

The quality plan describes how the quality control and quality assurance processes will be applied throughout the clinical trial. It definitively defines the various quality-related tasks in the study. A quality plan documents specific quality practices, resources, and activities relevant to a specific project. This includes both operational QC and QA activities.

Operational QC

It is critical that trial managers develop a QC plan for each key operational stage of the study that defines standards against which QC will be conducted, including :

1. Sampling plan to be used (if applicable)
2. Data source to be used for QC at each operational stage
3. Metrics to be documented
4. Acceptable quality levels
5. Appropriate methods to report and distribute results.

During the study design phase, QC personnel provide an independent review of the approved proposed protocol. The QC plan includes comparison of the study's CRF to the objectives set forth in the protocol to ensure that it is designed to collect all necessary data. A requirement to review CRF completion guidelines is also an element of the QC plan.

For overall site management, a complete QC plan addresses the following:

1. Investigator selection and qualifications

1. Experience in conducting clinical trials
2. Experience with the specific indication
3. Not on the FDA's restricted or debarred lists (not applicable in India)
4. Adequate staff and facilities
5. Personal involvement

2. Study conduct (monitoring)

1. Subject informed (signed informed consent form)
2. Subject's eligibility (inclusion/exclusion)
3. Protocol compliance
4. Adverse events (AEs) and concomitant medication
5. Drug accountability and storage

3. Source document verification

1. Medical records
2. Lab data
3. Progress notes
4. Diagnostic tests

4. Query resolution

Completed data clarification forms

5. Compliance with regulations

1. ICH/GCP Guidelines (ICH-E6).
2. Schedule Y (Drugs and Cosmetics Rules 1945)

During the data management process, the accuracy of the initial data entry is verified by an independent entry of the same data and a subsequent comparison of both sets of data for non-agreement. The reality of the data is checked with a pre-programmed logic check program and a subsequent manual review. The database entries are then QC'd versus the CRFs. The output that is generated as part of a statistical analysis of the data is also inspected to ensure their accuracy, as is any text in a CSR that refers to the output.

QA Activities

The QA activities to be conducted during a specific clinical trial are included in a QA audit plan. These activities include the number of investigator sites, selection criteria, and vendors to be audited, such as labs and drug packaging and distribution providers. This plan also specifies what internal processes of the study will be audited from initial study design, site and data management, statistical analysis, and the final CSR. It specifies audit team members and auditees for each study stage, as well as the standards against which the audit will be conducted, such as the protocol, CRF completion guidelines, SOPs, ICH/GCP guidelines, Schedule Y.

A thorough QA audit plan also clearly states the documents to be provided by the auditee, as well as the location, date, and expected duration of the audits. Preparation for QA audits should include review of the approved protocol and amendments, SOPs

(both general and study-specific), any specialized training associated with the study, annotated CRFs and the statistical analysis plan (SAP).

Internal process audits are another important QA responsibility. Internal audits review all the drug development processes employed across several studies to determine if there are systemic problems. This includes a review of employee training, compliance with SOPs and regulatory requirements, and documented evidence that QC was appropriately conducted on the output of each internal process, as well as the final deliverable to a client.

Site Management Metrics

Internal audits of the site selection and management processes ensure that qualified investigators are selected, that they have adequate facilities and adequately trained staff, and that the study was conducted in compliance with the protocol and all appropriate regulations. Several metrics commonly evaluated by internal process audits after the study has begun include :

1. Percentage of monitoring visits completed on time.
2. Percentage of evaluable subjects (no protocol violations).
3. Percentage of serious adverse events (SAEs) reported within 24 hours to an Institutional Review Board (IRB) and the sponsor.
4. Percentage of properly executed informed consent forms.
5. Number of queries/CRF pages reviewed.
6. Number of missing data entries/CRF pages reviewed.

Computer Systems Validation

Computer systems validation examines all aspects of the data handling computer systems (hardware and software) to ensure the accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records. This includes initial installation and procedures that document how changes to a computer system are justified, approved, and implemented.

The validation process begins with examining user requirements, the results of the initial hardware installation qualification (IQ) tests, the operational qualification (OQ) tests, and the qualification and training of user personnel. The user acceptance test results (Performance Qualification) are then compared to the user requirements to ensure that these requirements are met. Having assurance that the data handling computer system is validated, data can then be entered.

Data Management QC

Since an average error rate for keying text or numbers is about 1 per 300 keystrokes, the entered data is QC'd by having an independent data entry person enter the same data. Both sets of data are compared electronically, and discrepancies are resolved by a senior data entry person. After all of the data has been entered and all discrepancies and questions resolved, the database is QC'd by comparing the database to the CRFs from which the data was entered.

Data Management Metrics

Examples of data management metrics for QA are :

1. Percentage of database errors.
2. Percentage of queries manually generated.
3. Time from last patient out to database lock.
4. Number of times a locked database is opened.

Data Management QA

Data entry and the database QC process are other critical areas of the data management process that are audited by QA personnel. The audits review the documented evidence that shows the data accuracy and integrity were verified and checked manually, independently, and programmatically to ensure the data were logical. These audits also ensure that all data queries are resolved and that the overall database QC review was conducted according to the QC SOP.

Statistical Analysis QC

After a study database has undergone a QC review, it is exported into a SAS (Statistical Analysis System) to develop analytical programs that create data that are to be included in a CSR. The data are QC'd and validated by having independent programmers create programs for the same data, and all discrepancies are then resolved.

Statistical Analysis QA

QA of the statistical analysis process ensures SAS programs are validated for the generation of all tables and graphs by checking that all the requirements were met and boundary conditions were tested. QA also verifies that the SAP was developed according to the processes defined in the SOPs and that all statistical analysis plans are approved by the appropriate authority.

In addition to reviewing the statistical analysis process, QA also inspects a predetermined sample of tables and graphs. Numbers are checked against database listings, and tables are reviewed against format requirements specified in the SAP. The QA report will document the following information:

1. Percentage of tables and graphs with numerical or formatting errors.
2. Percentage of SAS programs adequately validated.
3. Time from database lock to final generation of tables and graphs.

Study Site Audits

Audit is the systematic and independent examination of trial related activities and documents to determine whether trial related activities were conducted according to the protocol, sponsor's SOPs, GCP and applicable regulatory requirements. An audit of a clinical trial provides the research sponsor with an independent appraisal of the quality and completeness of the trial and identifies potential problem areas in order to implement solutions to avoid situations when corrective action is no longer an option. It provides a snapshot overview of clinical trial conduct.

For commercially sponsored studies, the Sponsor will employ independent auditors who will review the study in detail at a chosen site. Alternately, the QA group conducts site audits throughout the course of a trial to assess protocol and regulatory

compliance, to ensure that the safety and welfare of subjects are addressed and to confirm that problems reported by study monitors have been resolved. QA's criteria for site selection for audits include :

1. High patient enrollment.
2. High staff turnover.
3. Abnormal number of AEs (high and low).
4. High or low subject enrollment rates that are unexpected given the research site's location and demographics.

Site audits ensure adequate documentation of case histories (source documents), such as medical records, progress notes, hospital charts, drug accountability records, ECGs, laboratory test results, SAEs and informed consents. Audits examine whether all clinical tests were performed at the time specified in the study protocol, and review specimen collection, storage and shipping packages (if applicable), and the timeliness of review of clinical test results.

QA site audits evaluate the timeliness of entering data into a CRF, and examine the accuracy of the data by comparing them to their respective source documents mentioned above. Audits also ensure that all investigational product received by a site is adequately accounted for.

Corrective and Preventative Action Process

The purpose of a corrective and preventative action process is to ensure that complaints, discrepancies, and non-compliances are visible, prioritized, and tracked, and that the root cause is determined and resolved. It also provides a system to track issues of nonconformity that have not been resolved. This process requires identifying a person responsible for defining and implementing corrective action.

Continual Improvement Process

QA also has a critical introspective role to continually monitor and evaluate its own activities and to improve all drug development processes. This continual process of improvement tracks and reports on metrics for key activities and deliverables of drug development, keeping in mind the adage that "what gets measured, gets managed." Other inputs to process improvement include a formal debriefing after project close, client and employee satisfaction surveys, and client audits.

Inspections

Inspection is a particular type of audit carried out by a competent authority where clinical trials involve drugs or devices. Inspection is an official review of documents, facilities, records, and any other resources that are deemed by the authorities to be related to the clinical trial. An inspection is carried out to ensure a clinical trial is being conducted in compliance to GCP and appropriate regulatory legislation.

The competent authority in the UK is the Medicines and Healthcare Products Regulatory Agency (MHRA). European Agency for the Evaluation of Medicinal Products (EMEA) who oversee clinical trials in Europe or other regulatory authorities such as the Food And Drug Administration (FDA) are the authorities that conduct inspections in areas where they exercise regulatory control.

Mandatory GCP inspections for all commercial and non-commercial clinical trials became law under the Medicines for Human Use (Clinical Trials) Regulations 2004. All Principal Investigators (PI) must agree to provide access to source records and clinical trials documentation to the Sponsor, Research Department personnel or designee and regulatory authorities for the purposes of monitoring, audit or inspection. Patients are required to permit access to their data to auditors and inspectors, though this data is provided without any identifiers. This requirement should be clearly stated in the Patient Informed Consent Form.

US FDA has set up an office in India (at Gurgaon) to conduct inspections of sites involved in studies conducted under a US IND. FDA conducts site inspections to determine if the PIs are operating in compliance with current FDA regulations and statutory requirements. PIs who conduct FDA regulated clinical investigations are required to permit FDA investigators to access, copy and verify any records or reports made by the clinical investigator with regard to the disposition of the product and subject case histories. FDA personnel typically perform this oversight function through on-site inspections designed to document how the study was actually conducted at the clinical investigator's site. PIs are required to retain records for a period of two years following the date a marketing application is approved for the product or, if no application is filed or if the application is not approved, until two years after the investigation is discontinued and FDA is notified. FDA conducts both announced and unannounced inspections of clinical investigator sites:

- Routinely to verify data that has been submitted to the Agency;
- As a result of a complaint to the Agency about the conduct of the study at the site;
- In response to sponsor concerns or termination of the clinical site;
- At the request of an FDA review division; and
- Related to certain classes of investigational products that FDA has identified as products of special interest in its current work plan (i.e. targeted inspections based on current public health issues).

During an inspection at the site of a clinical investigator, FDA personnel typically verify :

- Who performed various aspects of the protocol (e.g., who verified inclusion and exclusion criteria, who obtained informed consent, who collected adverse event data);
- The degree of delegation of authority (e.g., how the clinical investigator supervised the conduct of the investigation);
- Where specific aspects of the investigation were performed;
- How and where data were recorded;
- Accountability for the investigational product;
- The monitor's communications with the clinical investigator; and
- The monitor's evaluations of the progress of the investigation.

Following the inspection, the FDA personnel who conducted the clinical investigator inspection prepare a written Establishment Inspection Report (EIR). The EIR, 483 (if issued), copies of any materials collected during the inspection, and any clinical investigator response are forwarded to the appropriate FDA Center for further

evaluation. After this review, one of the following types of letters is typically sent from the Center to the clinical investigator :

(1) A letter that generally states that FDA observed no significant deviations from the regulations. Note that a letter is not always sent when FDA observes no significant deviations.

(2) An *informational or untitled letter* that identifies deviations from statutes and regulations for which voluntary corrective action is sufficient. Occasionally, such letters request a response from the clinical investigator.

(3) A *Warning Letter* that identifies serious deviations from applicable statutes and regulations. A Warning Letter generally requests prompt correction by the clinical investigator and a formal written response to the agency.

In addition to issuing these letters, FDA can take other administrative action against clinical investigators for non-compliance with applicable statutes and regulations. For example, FDA may initiate a process to disqualify the clinical investigator from receiving investigational products in the future if the investigator has repeatedly or deliberately failed to comply with applicable statutory or regulatory requirements or has submitted false information to the sponsor or FDA in any required report.

The FDA is authorized to inspect IRBs too, though such inspections have not yet taken place in India they are routine elsewhere.

Managing the quality of clinical data does the following :

1. Ensures management of compliance with the protocol, SOPs, and GCPs.
2. Enables systemic problems to be resolved before the end of the study.
3. Helps reduce data queries (industry average = $150/query).
4. Identifies ways to reduce cycle times for various processes.
5. Ensures data integrity throughout the study's course and that the data collected are the data required by the protocol.
6. Ensures the accuracy and consistency of data from entry into the CRF to final datasets reported in the final CSR.
7. Plays a critical role in dealing with instances of nonconformity while carrying out clinical trials.

In conclusion, it should be remembered that quality is never the result of an accident; it always results from sustained serious efforts.

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