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Clinical Quality Management System: Foundational Aspects, Framework and It's Elements, Benefits

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A B S T R A C T

A comprehensive clinical quality management system (CQMS) includes a framework of guidelines and processes essential for the planning, execution, and assessment of adherence to applicable regulatory standards. Holistic quality management system helps the sponsor or clinical research organization (CRO) to assure that the trial participants, regulatory agencies and stakeholders that the clinical research is of the highest standards. This article will describe the conceptual framework for a Clinical QMS designed to provide a consistent, streamlined and proactive quality approach across all stages of clinical research. In clinical research, adherence to quality standards primarily relies on the commitment of physicians, coordinators, sponsors, contract research organizations (CROs), external service providers, and, crucially, the patients themselves. The diverse array of organizations and participants, along with their respective outputs, is essential to the overall collective quality, which is frequently interdependent. This diversity results in various quality challenges that necessitate tailored mitigation strategies and quality management practices.

Keywords: Clinical Quality Management System, Clinical Quality by Design

1. Introduction

A clinical quality management system (CQMS) is a quality management system exclusively for clinical research. A quality management system encompasses the organizational framework, roles, processes, and resources necessary to ensure and uphold data integrity across the entire data lifecycle. The initial essential step and cornerstone of clinical research involves the creation of scientifically robust and practically feasible clinical trial protocols and procedures for data collection and processing, along with the gathering of vital information necessary for informed decision-making.

Research sponsors should perform a risk assessment and evaluation at both the Quality System level and the clinical study level, following the identification of critical processes. This includes aspects such as trial design, data collection, and the informed consent process.

During the course of a clinical trial, the amount of documentation that must be controlled and coordinated is voluminous and countless associated processes and tasks are required. To be competitive, life sciences companies continually look to increase efficiencies and cut costs at every phase of their clinical trials. Implementing an automated CTMS (Clinical Trial Management System) is a logical first step toward achieving those goals.

The CQMS should use a risk-based strategy, ensuring that the methods employed for quality control (QC) and subsequent quality assurance (QA) of research are aligned with and commensurate to the identified risks. Quality Control (QC) and Quality Assurance (QA) strategies must be meticulously crafted and scheduled to validate and confirm that the design (protocol) is scientifically sound, that the personnel possess the necessary qualifications, and that the execution (including management and oversight of outsourced activities) is effectively regulated.

Clinical Quality by Design (CQbD), in clinical research, refers to a structured methodology aimed at ensuring quality throughout the clinical development process. This approach starts with clearly defined objectives and focuses on essential clinical processes, data integrity, and process oversight, all grounded in robust scientific principles and quality risk management practices.

2. REGULATORY REQUIREMENTS

The main regulatory requirements that organizations will face when conducting clinical research include:

- **Draft guidance on Data Integrity for In Vivo Bioavailability and Bioequivalence Studies (USFDA)**

"Testing sites where BA and BE studies are conducted or analyzed should establish and utilize a quality management system to ensure the integrity of the data"

- **ICH Q10 - Pharmaceutical Quality System**

"An effective pharmaceutical quality system will enhance the quality and availability of medicines around the world in the interest of public health.

- **ICH E6 (R3) - Good Clinical Practice**

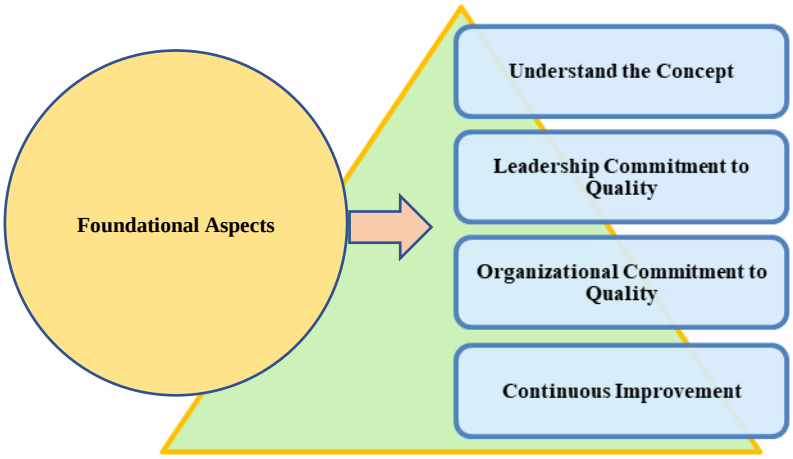
"Good Clinical Practice (GCP) represents a global standard that emphasizes ethical, scientific, and quality considerations in the execution of trials involving human subjects. Adhering to this standard in clinical trials ensures the protection of participants' rights, safety, and well-being.".

- **Regulation (EU) No 536/2014**

"In a clinical trial the rights, safety, dignity and well-being of subjects should be protected and the data generated should be reliable and robust. The interests of the subjects should always take priority over all other interests."

3. CQMS FRAMEWORK

The non-profit organization, TransCelerate BioPharma Inc., partnered with various national health authorities and other industry stakeholders to explore ways and means to improve and streamline quality across the clinical research industry. This initiative resulted in the Clinical QMS Conceptual Framework.



The fundamental aspects are briefly outlined below:

- **Understand the Concept**

Assessment of the factors such as regulations set forth by international regulatory authorities, financial, technical, organizational structure, internal & external stakeholders and the data collected from former development initiatives in which CQMS needs to work needs to be understood first.

- **Leadership Commitment to Quality**

The organization must clearly define the quality standards it expects from its employees. The message of quality should be evident, reliable and consistent.

- **Organizational Commitment to Quality**

When the senior leadership has taken the responsibility of quality, the entire organization will become accountable. All employees must have equal opportunities to discuss about quality, raise concerns and be proactive.

- **Continuous Improvement**

QMS software provides features for automated allocation of tasks, reminders and electronic signatures to put the responsibility on each individual to take ownership of quality regardless of their role and be accountable for the same.

4. THE CORE ELEMENTS OF A CLINICAL QMS FRAMEWORK

A brief summary of six elements which are essential to include in Clinical Quality Management System (CQMS) in accordance with the USFDA Draft guidance on Data Integrity for In Vivo Bioavailability and Bioequivalence Studies (April 2024) is provided below.

a. Data Governance and Data Lifecycle

Data governance encompasses all measures taken to maintain data integrity, ensuring that the data is complete, consistent, accurate, trustworthy, and reliable. The data lifecycle encompasses all stages involved in data collection, which includes generation, recording, modification, processing, maintenance, storage, retrieval, transmission, and eventual disposition.

b. Records Management

Data should be retained in a way that ensures their protection, longevity, easy accessibility, and readability throughout the records retention period, while also adhering to relevant regulations. Testing sites should contemplate the separation of responsibilities across different phases of the data lifecycle, as this could diminish the chances for individuals to deliberately alter data.

- **Computer or Related Systems**

Computer systems and their related documents (such as user manuals and SOPs) can be used for creation, recording, modification, processing, maintenance, storage, security, retrieval, and transmission of data.

- **Collection and Documentation**

Testing site personnel hold the responsibility for ensuring data quality. They are required to document data in a timely and precise manner, along with the relevant metadata. Metadata refers to the contextual information necessary for comprehending data, encompassing any details utilized for identifying, describing, or explaining that data.

- **Sample Analysis**

When sample analysis site and clinical testing site is different, it is important to integrate the elements related to sample analysis into the quality management system. Few important elements are listed below.

- Samples should be collected as close as possible to the scheduled times specified in the study protocol, and the actual times of collection should be documented accurately.
- Essential instruments and equipment, such as balances, pipettes, etc., should be calibrated, maintained, and serviced in accordance with SOPs and other relevant requirements as necessary.
- It is essential to document and investigate equipment failures to assess their effects on sample stability or on data integrity.
- It is essential to keep logbooks or electronic databases for documenting temperature measurements and calibration records.
- Samples are usually transported to the analytical facility in a frozen state using dry ice for insulation. It is advisable to include a data logger in these shipments, as it offers valuable temperature data during shipment to the analytical location.

The documentation of sample analysis must accurately capture the steps and procedures in real-time, adhering to the principles of ALCOA. Additionally, it should facilitate the reconstruction of the study.

- **Data Storage**

Data should be preserved along with all relevant metadata necessary for reconstructing the study activities.

- **Data Backup**

Data should be backed up in accordance with established procedures, such as a SOP. It is essential to periodically test these backup procedures to confirm their effectiveness in restoring study data to the appropriate software.

Backup file should contain the data along with any relevant metadata. Backups intended for recovery or temporary use do not qualify as archiving data and metadata for the verification of study activities.

- **Archival and Retrieval**

Study data, including both manually recorded and electronic information, must be archived for a minimum of five years within two weeks following the completion of the study, which is defined as the signing of the final study report or the termination of the study.

Testing sites should establish measures to safeguard archived data from damage, alteration, or deletion. It is essential for the management of testing sites to designate a specific individual responsible for overseeing the management of data archives. The retrieval activity should be conducted under the supervision of the archivist.

c. Training

All personnel who involved with BA and BE study data and related activities should be trained on data integrity practices and procedures. This training should cover strategies for preventing and identifying data integrity issues, as well as protocols for reporting any errors or concerns. Emphasis should be placed on the specific job roles, assigned responsibilities, and the pertinent regulatory requirements associated with their functions.

Testing site management should establish procedures for recognizing and regularly evaluating training requirements, along with maintaining records of training and retraining activities. Within a quality management framework, continued training is essential to guarantee that staff members stay skilled in their operational roles and comprehend relevant regulations.

d. Access and Privileges

The quality management system should include documentation that outlines the access rights and privileges assigned to all users, administrators, and other relevant personnel. This framework guarantees that individuals are granted access solely to the functionalities pertinent to their designated roles.

Each personnel should have unique log-in credentials to access systems for clear attribution of actions to specific individuals.

To mitigate the risk of unauthorized access, it is essential for personnel to log off the system upon leaving their workstation. Furthermore, the system should be configured to restrict the number of login attempts and to document any unauthorized login attempts along with the identities of the individuals involved.

The responsibilities of the system administrator, which encompass the authority to modify files or configurations, should be designated to individuals who are separate from those managing the data. The role of the system administrator should be restricted to the fewest personnel necessary, considering the scale and characteristics of the testing site. Additionally, any modifications made by a system administrator to files or settings must be documented in the audit trail.

e. Audit Trails

Testing sites must implement audit trails to accurately document all modifications to the BA and BE study data, while also limiting the capacity of individuals to deactivate these audit trails.

f. Quality Assurance and Quality Control

The quality management system should incorporate both a quality assurance program and a quality control program to effectively address the risks linked to each component of the quality management system.

The quality assurance program should incorporate procedures designed to prevent users from undermining the purpose of the controls, as well as mechanisms to detect breaches of data integrity, whether accidental or deliberate, along with strategies to address and prevent future incidents.

The quality control program should incorporate mechanisms for detecting both unintentional and intentional data compromises. Upon identifying any data integrity weaknesses or issues, the program should ensure that suitable corrective and preventative actions (CAPA) are applied comprehensively across all pertinent activities and systems.

5. BENEFITS

There are numerous benefits when life sciences organization has a quality management system. Brief details about benefits of CQMS is provided below.

- **Patient and consumer safety:** This is assured by the generation of reliable data that organization, its partners, regulatory and healthcare authorities and other stakeholders can use for improving the lives of patients. Furthermore, the end-users of the results of clinical research are assured that the medications/treatments that they receive are based on proper research.
- **Regulatory compliance:** Organization will be able to systematically and universally manage quality through the entirety of clinical research in compliance with all the applicable regulatory requirements. This will range from first-in-human trials to post-marketing studies.
- **Quality assurance:** Organization will reduce or eliminate repetitive quality issues such as intentional/unintentional non-compliance, insufficient staff training, reduction in resources, insufficient supervision by management, lack of protocol clarity and insufficient quality control in the collection and recording of data. All of which threaten patient safety/data integrity.

- **Promoted continuous improvement:** Continuous improvement within the organization is an ongoing task, it can be a challenge to track and manage all the changes and processes. QMS software enables organizations to create, approve, track and manage changes accordingly. It can ensure that all the necessary changes are implemented on time, thereby promoting continuous improvement.
- **Developed Operational Consistency:** Being consistent is an important concept for any organization. Only when operations are standardized, organization can be sure of the quality of products/services. To build trust, establish awareness among stakeholders and market products/services efficiently and profitably, organization are required to be consistent. In its absence, the organization will likely fail.
- **Improved Decision-Making:** Both ISO 9001:2015 and ISO 13485:2016 emphasize the significance of this review process. It is crucial for senior management to conduct regular assessments of the QMS to ensure its suitability, adequacy and effectiveness. QMS software can help the organization to quickly analyze the data, draw meaningful insights, and present the same to the relevant stakeholders for review. This will help senior management make better decisions that are data-driven and in line with the organizational goals.

- **Improved Company Culture:** The highest moral of the organization should be quality. The senior management committed to quality is essential. They should establish quality principles that can be disseminated throughout all departments, ensuring that every employee is aligned with and trained in the fundamentals of quality management. This culture within the organization is routed through the QMS at all levels through its policies, processes, and procedures.
- **Increased Profits:** A robust quality management system will help the organization in boosting profits by increasing the efficiency, reducing the wastage, lowering of operational and administrative costs. It also increases market share, as well as an increased possibility to access new markets. QMS software in particular can cut costs related to the manual processes in QMS. This will enable staff to focus on other areas of improvement and not get hindered by tasks like chasing signatures for document approvals, finding the right documents and version control and so on.

6. CONCLUSION

An efficient, dynamic and adaptable CQMS emphatically assure the patients, other stakeholders of the organization and the regulatory agencies that the clinical research/clinical trial that the organization is conducting are of the highest standards. Well-structured clinical QMS will help the organization to reduce errors, time and costs. GCP provides overarching recommendations regarding the qualifications and expertise required for individuals involved in the creation of study protocols, case report forms (CRFs), and analysis planning, such as biostatisticians, clinical scientists, and physicians. However, to make sure these experts come up with a scientifically valid and practical protocol, a strong CQMS is essential. This involves proper risk assessment and management, along with validated quality control and assurance processes to meet GCP standards and relevant ethical guidelines. With the help of a CQMS, organizations will be able to implement the applicable regulatory standards and methodologies needed to achieve the goals of clinical research. A robust clinical quality management system (CQMS) will improve the oversight of all protocols, documentation, and audits conducted throughout the clinical trial process. This system enables organizations to optimize necessary procedures and ensure compliance with relevant international regulatory standards. Additionally, it enhances organizational efficiency by refining risk management strategies, promoting effective risk mitigation, and expediting the achievement of key objectives, specifically determining the safety and efficacy of new drugs, treatments or medical devices.

Finally, Regulatory Authorities (RAs) have integrated Good Clinical Practice (GCP) into legislation to safeguard public health by establishing standards that protect research participants and uphold the integrity of research findings and data. These authorities implement these regulations through continuous monitoring and inspections, taking enforcement actions when necessary. Consequently, the role of RAs is multifaceted; they ensure public safety during clinical trials by providing regulations and enforcing compliance as required, while also serving as one of the “customers” for the outcome of clinical research and the data which the RA assesses against scientific and quality criteria.

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