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Review Article

RECENT ADVANCES IN QUALITY MANAGEMENT OF CLINICAL TRIALS

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ABSTRACT

Clinical trial is an investigation in humans anticipated to decide or confirm the effects of a drug or to identify any adverse reactions with an intention of ascertaining its safety and efficacy. Quality of clinical trials relies on data consistency and subject safety. Quality control and quality assurance are part of quality management. There is an increasing focus on having quality systems in place throughout the planning stages of clinical trials. The regulatory outline for clinical trials has altered in recent years with the addition of thorough controls to guarantee patient protection and data dependability. There is a clear requisite to execute the principles of planned quality management in health research to avoid failure, take full advantage of the utilization of offered resources and guarantee reliability and integrity of results. Ideally, all clinical trial ought to have a Clinical Trial Quality Management Plan (CTQMP) describing the tools that will be used to guarantee study quality. Adoption of quality-by-design (QbD) and quality risk management methods for clinical trial management is the current mantra at FDA.

Keywords: Quality by Design, Quality Management System, Quality assurance, Good clinical Practice.

INTRODUCTION

Quality is characterised by the power to effectively and efficiently provide a solution for the queries about the profits and dangers of a medicinal product or process while guaranteeing safety for human subjects. To fulfil the regulatory anticipations, the sponsors need to enhance quality by improving systems with definite standards for every clinical test procedure. It is compulsory for the sponsors of clinical trials and contract research organisations to establish, control and monitor the quality control and quality assurance systems along with their vital standard operating procedures and other quality documents as well as to provide high quality product and services to full fill the customer need and expectations. Components of quality clinical study include scientifically acceptable and ethically secure experimental design, sufficient protection of subject's privilege, safety and welfare, competent personnel, adequate surveillance, current, complete and exact data.

The regulatory system for clinical trials has become different in recent years with the augmentation of strict controls to guarantee patient security and data credibility. Up to the present moment, quality management was frequently segmented. There is a clear requisite to execute the principles of extremely important quality management in health research to impede downfall, maximize the use of valid resources and guarantee consistency and dependability of outcomes.

DISCUSSION

Good Clinical Practice (GCP) is the general ethical and systematic quality criterion for carrying out clinical trials. The GCP standard practices to all facets of the clinical trial procedure. Under the GCP guiding principle, the quality is a continuous sequence, which commences with designing, is crucial during conducting and recording, and keeps doing during reporting of trials. Clinging to the GCP quality standard throughout the clinical trial procedure give guarantee that the data and reported results are reliable and exact, and that the privileges, reliability, privacy of the trial subjects are watched over.

In spite of the fact that the quality principles for clinical trials have not become different over the years, conformance to these principles have become more demanding to attain, due to the changing scenery of the carry out of clinical trials.

Quality issues in clinical trials

Traditionally, the quality of clinical trial guided at the investigator site is appraised by sponsor audits and regulatory inspections. Main reasons for the downfall during clinical progression are [1]:

- Safety questions
- Be short of efficiency
- Inability to announce in advance failures ahead of human testing or early in progression

Some usual shortages observed throughout site inspections include [2]:

- Inability to go along the investigational program and signed investigator declaration/ consent
- Protocol deviations
- Insufficient record keeping
- Poor quality of being accountable for the investigational product
- Inadequate subject security, including informed consent issues
- Adverse Events recording and reporting

However, the sponsors and its team play an important role in the site performance. In FDA inspections, some of the frequent sponsor deficiencies were [3]:

- Unsatisfactory monitoring
- Inability to ensure investigator conformance
- Inability to submit progress reports
- Downfall to notify FDA
- Deficient investigational product accountability
- Inability to get signed investigator agreement
- Non-performance to obtain FDA or IRB approval

The current time approach of regulatory inspections to guarantee quality in clinical trials is alike to the old- fashioned manufacturing systems: manufacture the product, catch the imperfect ones, and throw them out [4]. Refusal of clinical trial data after the review is not efficient. There is a necessity to modify the focus from review based quality upgrading to planned organized quality management.

Quality – changing scenery

There is a transformation toward a mechanistic based approach including predictive estimation based on a new molecular knowledge about the mechanisms of disease and products from trial and error like empirical testing, patient exposure based assessment of efficacy and adverse events. Clinical trials design followed by clinical trials conduct ensure efficacy and success with early stage decision making, developing drug faster, smaller patient population, lower costs and more certainty [1].

FDA identifies traditional surveillance may not be cost effective for the large, multinational trials common today. Risk-based approach essential for efficiency and effectiveness. Combinations of methods like central and on-site monitoring, etc. are recommended rather than a single process [5].

***Central monitoring*includes**

- remote data checks for lacking or invalid data, calendar inconsistency, irregular data models
- estimation of rates of data reporting, including adverse events
- estimation of predetermined act indicators
- comparisons with external sources

***Site monitoring*includes**

- On-site visits, the chief support of traditional monitoring, almost certainly cannot be totally ruled out for any monitoring pattern
- Central monitoring, statistical risk resolutions, and/or other methods may give guides as to the reoccurrences and emphasis of visits
- Site visits essential for training on protocol, processes, and relevant regulations, confirmations of site resources, verification of submissions with protocol and regulations

The existing system has also not developed with shifting demands. Studies have turn out to be all the time more multifaceted, leading to enlarged demand for resources [6, 7]. The tasks of the sponsor are being outsourced to third parties, such as contract research organizations [8, 9]. Supervision of clinical trials is changing toward centralized institutional review boards [10]. Sponsors are more and more involving sites in many countries in a single clinical trial changing resources and creating consequences for which the full impact may not be felt for many years [11].

QbD in clinical trials

QbD is a strategic/systemic approach in making better product development to make best use of the success of getting new products to the market faster, safer, and smarter and for less cost. QbD in clinical trials brings out a new product progression toolkit with new predictive tools and new evaluative tools. New predictive tools include enhancing predictability and efficiency along the crucial path by early recognition of product candidate with maximal efficacy versus molecular and biological processes and early estimation of product safety. New evaluation tools are to enhance the performance of clinical trials and medical care.

QbD transits trial and error landscape in clinical trials and researches to a mechanistic based approach, which resulted in a paradigm shift initiated towards learning or verifying structure and inventive trial design or versatile clinical trials. These lead for a new era of drug development with an exploratory step ahead of pre-clinical trials and prior to commercialization [1].

QbD process

- Make more efficient, organized and simplified clinical development of new drugs
- Upgrade understanding the product during an early stage will lead to better science
- Better product dependability and reproducibility
- enhancing efficacy while reducing safety hurdles to patients
- Increase efficiency of production of drug development

From FDA point of view QbD sets up a clear coupling between safety and efficacy of the drug product in the patients. Quality of the product is connected back to the process of its preparation. QbD requires clinical understanding: link between the product and its safety and efficacy in humans, and process understanding: link between the drug product and process characteristics. QbD clinical approaches possible are determining target indication, route of administration, and target patient population and advancing reliable new methodologies to channel the potential of clinical product development [12].

Quality assurance in clinical trials

Quality assurance (QA) is an influential facet of clinical trials, because the data assembled must be acceptable and without any errors and the trial conduct must agree with the protocol. The data are meant for use as an important body of proof when a test article new medicinal product is examined by a government regulatory authority. The industry is unconditionally clear about the regulatory condition and complies with the regulated quality assurance steps to guarantee marketing approval is granted in a timely and undisputable way [13].

QA activities during the trial:

There are a number of QA activities throughout the conduct of a trial. The most significant activity is adverse event reporting by the investigator to the sponsor and, as appropriate, to the EC, verification of data versus source documents, analysis of data queries and drug accountability. The sponsor should facilitate all the reporting to all related investigator(s) and to the regulatory authority of all adverse drug reactions – both critical and unanticipated. Those safety reports should agree with the applicable regulatory requirements. ECs should be communicated about any unexpected and related adverse events that can impact the overall risk-benefit balance.

The intention of trial monitoring is to confirm that the rights and interests of the subjects are protected; the trial data are exact, absolute, and provable from source documents; and the conduct of the trial is in conformance with the protocol, with GCP, and with the appropriate regulatory requirements. Monitors appointed should be suitably trained and be well known with the test article(s), the protocol, the written instructed consent document, the sponsor's SOPs, GCP, and the appropriate regulatory requirement(s). The monitor is the central line of communication between the sponsor and the investigator. The monitor should go along the sponsor's established written SOPs as well as those procedures indicated by the sponsor for supervising a specific trial. The monitor should give a written report to the sponsor following each trial-site inspection or trial-related communication.

Data management of clinical trials is very important and highly controlled, because the data gathered will be utilized for statistical analysis and report writing and will subsequently be put through regulatory review. The data must reflect the actuality, i.e., the source data as collected and stored at the study site. All the data gathered will be examined for missing, solitary or inconsistent values. The data management team will send data queries to the study site and the decisions will be sent back to the data management team by the monitor [14].

Post-trial QA activities:

Most post-trial QA activities should be dealt by the sponsor with the exception of analysis of left over data queries, summary of the trial results, publication and storing of trial documents. The latter is compulsory since a regulatory authority may decide to make an onsite inspection at a later stage in order to examine all the trial source data.

Monitoring of Site Performance:

Although trial necessities are cautiously put forward in such trial documents as an authorized trial protocol, a data management plan, and an attending project plan, anticipations and requirements can change during the course of a trial.

Internal audits of the site selection and management procedures need suitable staff and guarantee that the trial was carried out in compliance with the procedure and suitable regulations. Site performance is assessed by an internal process evaluations following the trial have commenced, taking into regard such trial-related items [15].

The QA group directs site assessments throughout the course of a trial to check for protocol and regulatory compliance, to assure that the safety and welfare of participants are addressed, and to verify that problems reported by trial monitors have been solved. The QA criteria for site selection include high participant registration, high staff turnover and/or abnormal number of adverse events (high/low) [16].

To be successful as a monitor, it is important to build a sense for what should be monitored at every site and how much consideration should be specified to each activity. It helps to be conscious of where

problems are most probable to arise at some stage in the conduct of a trial. The following items get the most shortages during site audits/inspections:

- Failure to follow the procedure;
- Failure to keep satisfactory and exact records;
- Inconvenience with the informed consent form;
- Failure to report adverse events as mandatory by law, regulation, or the sponsor and
- Failure to account for the disposition of study drugs.

Most sponsors have built a set of generic monitoring SOPs. However, in addition, the protocol orders the conduct of the study by setting the procedures that participants must go through and a period of evaluations. The more activities that are carried out throughout a study visit, the more monitoring will be needed and the more likely the monitor is to find defects.

Site monitoring visits are planned on a regular basis – from daily for phase I trials to monthly or less frequently for simple trials such as phase II/III vaccine trials. The monitor concludes a report after each visit, and each report is submitted to the monitor's supervisors – usually a project manager of the sponsor/CRO – and to the investigator. In a recent trend, the institution asks the sponsor to furnish the EC with a copy of each monitoring report for the institution's research sites when the results of the monitor may have an impact on the safety of the trial participants or the conduct of the trial. Some institutions have added this request into the clinical trial agreement, as it forms a part of the institution's/organisation's quality assurance policy [17].

Quality- methods of improvement

The enhancement in the quality of clinical trials requires the use of the organizations approach, tools and patterns. The FDA suggested a four step systems approach [18]:

Say what you do

The sponsor should have a competent and reliable management team to provide control of the whole clinical trial process. There should be a robust supervision of the outsourced trial and harmony between the project team members, to make certain good decisions. The guidelines and SOPs should explain procedures and responsibilities for all significant clinical trial processes, from protocol evolution to preparation of the clinical study report. The SOPs must also focus on the possible expected risks.

Do what you say

This step mainly gives an account of instruction and training of all sponsor staff, CRO staff, and site staff without variation about the trial protocol, study necessities, policies, and procedures. All the team should be conscious of their duties.

For the sponsor and CRO, the monitor is the main source of help for assuring the site quality. Although the GCP defines the training necessities of a monitor, there is a need to make the monitors attentive that monitoring is not just matching data and having a list of documents [19]. Many of the latest FDA warning letters quote monitoring defect as a finding. Most of these findings are in the domain of choice of subjects, protocol conformance, and documentation of clinical estimations in the SD

The quality of a trial demands an assurance of safety subjects.[20] Although that all stake holders are accountable for this ethical obligation, the role of the ethics committee (EC) is very important in guaranteeing subject protection. The EC necessitates training in rules, ethics, and skills of clinical research. However, possibly the most needed is 'take on a week of thorough training in vital thinking [21].

Prove it

This step needs new approaches such as risk-based surveillance and trend examination[18]. Risk-based surveillance focuses on procedure management and substantiation of crucial activities, including quality control, to assure that they are carried out as organized. The trend examination looks at data as compliance information. The trend examination put to use approaches such as statistical monitoring, to estimate data trends across the sites and trials or data mining with an aim of proactively recognizing and estimating conformance signals and not expected risks. The approach of centralized monitoring to direct or target sites for monitoring is coming into view as a useful tool to approve compliance to quality[22].

Improve it

Improving quality will always need actions i.e., effective CAPA. For CAPA to be effective there should be a thorough examination of the root cause and its effect on the quality, and look for an action plan that can grant long-term and endurable solutions [18]. The system and processes should be re-evaluated to verify how the troublesome happened [4]. One of the most widely used tools for successive improvement is a four-step quality model — the Deming Cycle plan-do-check-act cycle[23].

***Advancing new technologies in clinical trials*[1]**

- Biomarkers/surrogate markers
- Special clinical study design
- Adaptive design
- Micro dosing study
- Modern statistics
  - Simulation experiments
  - Bayesian adaptive designs
  - Data-mining in crucial path of research
- Investigating safety and efficacy

Quality – new regulatory accesses and initiatives

Up to now, quality management was often uneven. For example, there was quality verification at the beginning of a novel research development in the grant selection procedure, and one more at the closing stages through peer review publications. But throughout the balance of the research procedure, quality management was repeatedly left to researchers and their institutions[24]. The regulatory authorities concerns on quality problems in trials and are forcing them to think over new approaches to evaluate the quality of a clinical trial conduct.

The FDA is developing new approaches of risk-based evaluation planning[18]. This would include:

- Center for Drug Evaluation and Research (CDER) risk-based site selection tool
- Institutional Review Board (IRB) inspection model
- Bioequivalence examination model
- Sponsor / CRO surveillance review model

The FDA is programming to switch its inspection focus, which is presently post New Drug Approval (NDA) submission, to clinical trial inspection and supervision in real-time. This would indicate surveillance inspections of sponsors and clinical investigators when the trial is in progress. The FDA will also suggest appraisal of the sponsor quality systems and the sponsor quality management plan at the completion of phase II trials. The FDA and EMA would cooperate in joint, parallel, and consecutive inspections and contribute to information on the finest practices. The agency's other plan is to make use of data as knowledge to inform inspection prioritization, organizing, scheduling, and scope.

Another more important FDA enterprise is the CTTI, which was set up in 2008, by the FDA and Duke University, as a public–private partnership. The purpose of the CTTI is to recognize practices that, through broad adoption, will augment the quality and competence of the clinical trials [25]. CTTI comprises more than 60 organizations such as government agencies, industry representatives, patient and consumer representatives, professional societies, investigator groups, academic institutions, and other interested parties. The CTTI has launched several projects to identify practices that will enhance the quality and efficiency of clinical trials. The four major areas for research are: Design principles, data quality and quantity (includes monitoring), study start-up, and adverse event reporting.

Some of the important CTTI projects are:

- Effective and efficient monitoring as a part of quality
- Improving unanticipated Serious Adverse Event reporting to investigators
- Making better the public interface for use of collective data in clinical trials
- Site metrics for study start-up
- Practice of central IRBs for multicenter clinical trials

The CTTI has made suggestions to build quality into the scientific and operational design and in the conduction of clinical trials. Some of these are:

- Concentrate on what matters — it is the absence of errors that matter, that is, errors that have a meaningful impact on patient safety or interpretation of results
- Develop a quality management plan focusing on the areas of serious risk for generating errors that matter
- Prospectively measure the error rates of critical parameters
- Monitoring approach — visits, central, statistical — tailored to the trial design and key quality goals
- Improve training and procedures
- Report quality problems found, actions taken, converse their effect on the analysis and explanation of results

The FDA's recent steps highlight the significance of prospectively building quality into the scientific and operational design, and the conducting and monitoring of clinical trials [26].

Data driven QMS in clinical trials

A greater part of data presented to global regulatory agencies during the endorsement stage of an investigational product is gathered in the course of its clinical development. Any concern about the integrity of clinical data, conformance with GCP, or ethical standards during regulatory examination can lead to costly delay in the fulfilling of a marketing authorization. This risk can be reduced to smallest possible extend if proper metrics are used for continuum monitoring of the quality of the contributing research operations. As highly cost-effective tools, metrics can be used to check operations during this phase of development. With continuum monitoring, proactive measures can be put into effect to prevent issues from aggravating into regulatory concerns. Combined with an electronic information management system, the aim of data driven quality management is to monitor and manage cost and timelines while assuring the quality of clinical trial operations[27].

Processing the data maintained in various operational and clinical databases versus a pre-defined set of standards and metrics in a systemic way, is the first step in development of a plentiful source of both historical and current conformance information. This helps in developing metrics to further derive key performance indicators (KPI) for each parameter.

Presently monitoring is used as a communication tool with an investigator. However, because of the large volume of the data generated by monitors, sponsors have difficulty fully using the potential of this data. Using a simulation model and by decreasing the monitoring frequency and using central monitoring, total trial cost is reduced [28].

Using data from several sources focuses on the finding of signals for concern so that early interference becomes an effective tool. Through importance on transparency, QMS aids a collaborative environment on related compliance issues at all level of the organization. The availability of information is the basis of process development by facilitating easier exchange of monitoring information both with a clinical investigator and trial sponsor. It also assist forward focus on relevant issues and providing input to make better training programs at all levels of the organization, while rejecting minor issues. Combination of processes and systems that enable for early signal detection and the subsequent intervention is the true power of a data-driven QMS [29].

Conclusions and future directions

Guidance from FDA: It would be helpful if FDA were to clarify that it is not necessary to follow any particular monitoring method. In general, guidance documents should emphasize the key principles (ensure human subjects protection, data quality, and compliance with regulations) without specifying any particular method, and should give examples of various approaches by which these have been achieved.

Integrated quality management plans: Sponsors should develop an integrated quality management plan (QMP) in parallel with the protocol. This should provide evidence that the risks have been appropriately assessed and that mitigation plans have been put in place. The emphasis should be on key high-level issues rather than an in-depth description of monitoring activities, the details of which may, and often should, evolve over time. This approach would encourage trial sponsors to do their thinking in advance (e.g., about critical factors, risk mitigation, and quality control measures). Sponsors should also consider engaging in more discussion with FDA reviewers and inspectors regarding the QMP. (FDA is currently piloting such interactions, although it may need to increase its staffing to accommodate demand.)

End-of-trial reporting of quality management issues: It was suggested that, on completion of a trial, a report should be produced describing any issues found (either with the performance of the trial or with the QMP itself) and explaining how any issues identified might affect the analysis and interpretation of the results. This could be included in regulatory submissions and in publications of the trial results.

Sharing quality management knowledge, methodologies, and data: Number of different approaches to quality management is being developed by industry, academia, and regulators. Greater collaboration would accelerate these developments.

Education and awareness: It is important that all stakeholders understand the critical elements of a high-quality clinical trial so that attention is focused on those aspects that matter to the care of the participants in the trial and the reliability of the results that are produced. This applies to those that are involved in the design, implementation, analysis, interpretation, regulation, and inspection of clinical trials, as well as to those who use the results, such as healthcare providers, doctors, and their patients. The meeting highlighted a need for increased education and awareness of these issues.

International adoption: International adoption of basic principles of clinical trials and harmonization of regulations would facilitate global adoption of the proposed changes[32].

Potential role for CTTI

The CTTI, a public-private partnership relating industry, government, patient advocates, trade organizations, professional societies, academia, and non-academic investigators, was shaped in November 2007 to recognize practices that will enhance the quality and competence of clinical trials [33]. The CTTI has considered quality as "the capacity to efficiently answer the intended question about the benefits and risks of a medical product or process, at the same time as assuring security of human subjects" [34]. One of the first projects designed and accepted under this initiative is "Effective and Efficient Monitoring as a Component of Quality Assurance in the Conduct of Clinical Trials." Even though present regulations need sponsors to guarantee proper monitoring of clinical investigations of products subject to Investigational New Drug Applications and Investigational Device Exemptions, monitoring process that are unsuccessful and overly burdened may unintentionally give to poor data quality [35].

It is possible that CTTI could provide a forum for the development of a sample quality management plan for vetting and dissemination among stakeholders. CTTI might also consider creating an online forum for lessons learned and convening a roundtable to accelerate the adoption of this approach.

CTTI is well placed to increase awareness of the importance of appropriate quality management in clinical trials. A position paper will be written for a leading medical journal, explaining the need for this change of emphasis. Other educational activities could be considered as part of future projects [32].

Adherence to quality requirements is the cornerstone of a scientifically valid and ethically secure clinical trial assuring data consistency and subject safety. The twin objectives of quality — data integrity and subject safety — can be met by a systematic approach to the whole process of a conduct of clinical trials. The new regulatory approaches of risk-based inspections and real-time supervision, linked with a spotlight on the quality systems, claim continuous alertness and continuous process improvement from the key stakeholders — investigators and sponsors.

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