

CURRENT TRENDS IN QUALITY ASSURANCE OF CLINICAL RESEARCH

Article Review by Boyina Chaya Devi^{}, Ramesh C^{**}, India
(M.Sc., Ph.D., in Clinical Research Student of Texila American University^{*})
(Adjunct Professor of Pharmacology and Clinical research, Texila American
University, Guyana^{**})*

Email: - chaya_devi06@rediffmail.com

ABSTRACT

Clinical Research 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 Research relies on data consistency and subject safety. Quality control and quality assurance are part of quality management systems. There is an increasing focus on having quality systems in place throughout the planning stages of clinical Research. The regulatory outline for clinical Research 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 Research ought to have a Clinical Research Quality Management Plan (CRQMP) describing the tools that will be used to guarantee study quality. Adoption of quality-by-design (QbD) and quality risk management methods for clinical Research management is the current mantra at FDA.

KEYWORDS

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

INTRODUCTION

Quality is characterized 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 fulfill 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 the clinical Research and contract research organizations to establish, control and monitors 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 Research 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.

QUALITY ISSUES IN CLINICAL RESEARCH

According to Kleppinger (2013), traditionally the quality of clinical Research guided at the investigator site is appraised by sponsor audits and regulatory inspections. Main reasons for the downfall during clinical progression are as follows:

- 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, according to Allen (2012):

- 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. According to survey of *Einstein et al* (2008) In FDA inspections, some of the frequent sponsor deficiencies are:

- 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

Stark (2010) reported that the current time approach of regulatory inspections to guarantee quality in clinical Research is alike to the old- fashioned manufacturing systems: manufacture the product, catch the imperfect ones, and throw them out. Refusal of clinical Research 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 Research and error like empirical testing, patient exposure based assessment of efficacy and adverse events. Clinical Research design followed by clinical Research conduct ensure efficacy and success with early stage decision making, developing drug faster, smaller patient population, lower costs and more certainty , FDA guidelines (2012) identifies traditional surveillance may not be cost effective for the large, multinational Research 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.

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.

According to Duley et al (2008) 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. According to CFR-21, the tasks of the sponsor are being outsourced to third parties, such as contract research organizations. Recent FDA guidelines (2010), supervision of clinical Research is changing toward centralized institutional review board. According to Glickmann et al (2009) the sponsors are more and more involving sites in many countries in a

single clinical Research changing resources and creating consequences for which the full impact may not be felt for many years.

QUALITY-BASED-DESIGN (QbD) IN CLINICAL RESEARCH

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

- 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

According to Barabara Leishmann from Chiltern, 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.

QUALITY ASSURANCE IN CLINICAL RESEARCH

According to QA oncological review, (2008) Quality assurance (QA) is an influential facet of clinical Research, because the data assembled must be acceptable and without any errors and the Research 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.

QA ACTIVITIES DURING THE RESEARCH

There are a number of QA activities throughout the conduct of a Research. 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 Research monitoring is to confirm that the rights and interests of the subjects are protected; the Research data are exact, absolute, and provable from source documents; and the conduct of the Research 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 Research. The monitor should give a written report to the sponsor following each Research-site inspection or Research-related communication.

According to FDA Quality manual (2012), data management of clinical Research 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.

POST-RESEARCH QA ACTIVITIES

Most post-Research QA activities should be dealt by the sponsor with the exception of analysis of left over data queries, summary of the Research results, publication and storing of Research 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 Research source data.

MONITORING OF SITE PERFORMANCE

Although Research necessities are cautiously put forward in such Research documents as an authorized Research protocol, a data management plan, and an attending project plan,

anticipations and requirements can change during the course of a Research. According to Human resource protection groups of FDA, Internal audits of the site selection and management procedures need suitable staff and guarantee that the Research was carried out in compliance with the procedure and suitable regulations. Site performance is assessed by an internal process evaluations following the Research have commenced, taking into regard such Research-related items.

The QA group directs site assessments throughout the course of a Research 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 Research monitors have been solved. According to Marinus (2002), the QA criteria for site selection include high participant registration, high staff turnover and/or abnormal number of adverse events (high/low).

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 Research. 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.

According to Johan, (2010) Site monitoring visits are planned on a regular basis – from daily for phase I Research to monthly or less frequently for simple Research such as phase II/III vaccine Research. 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 Research participants or the conduct of the Research. Some institutions have added this request into the clinical Research agreement, as it forms a part of the institution's/ organization's quality assurance policy.

QUALITY- METHODS OF IMPROVEMENT

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

The sponsor should have a competent and reliable management team to provide control of the whole clinical Research process. There should be a robust supervision of the outsourced Research 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 Research processes, from protocol evolution to preparation of the clinical study report. The SOPs must also focus on the possible expected risks. This step mainly gives an account of instruction and training of all sponsor staff, CRO staff, and site staff without variation about the Research protocol, study necessities, policies, and procedures. All the team should be conscious of their duties.

According to Matzat (2011), 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. 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 Source data. According to Ajay Bhatt (2008), the quality of a Research demands an assurance of safety subjects. 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 as reported by Loff (2004).

According to Morrison et al (2011), the trend examination put to use approaches such as statistical monitoring, to estimate data trends across the sites and Research 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.

The system and processes should be re-evaluated to verify how the troublesome happened. One of the most widely used tools for successive improvement is a four-step quality model — the Deming Cycle plan-do-check-act cycle has been approved by the FDA society for Quality (2014).

ADVANCING NEW TECHNOLOGIES IN CLINICAL RESEARCH [FDA GUIDELINES (2012)]

- 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

According to recent FDAs QMS system, 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. Another more important FDA enterprise is the CTTI (Clinical Research transformation Initiative), 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 Research. The CTTI has made suggestions to build quality into the scientific and operational design and in the conduction of clinical Research. 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 Research 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.

According to Arun Bhatt (2011), 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 Research [26]. 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. Sina Djali (2010) studied and reported about 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 Research operations.

According to FDAs scientific and regulatory committee (2009), 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 Research cost is reduced. The availability of information is the basis of process development by facilitating easier exchange of monitoring information both with a clinical investigator and Research 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. Lewis et al (2009) studied and reported about the combination of processes and systems that enable for early signal detection and the subsequent intervention is the true power of a data-driven QMS (Quality Management System).

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 Research 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-Research reporting of quality management issues: It was suggested that, on completion of a Research, a report should be produced describing any issues found (either with the performance of the Research 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 Research 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 Research so that attention is focused on those aspects that matter to the care of the participants in the Research 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 Research, 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.

REFERENCES

1. Allen Jean Toth: Building quality into clinical Research- an FDA perspective. May 14, 2012. <http://www.fda.gov/downloads/Drugs/.../UCM303954.pdf>.
2. A Guided Self-Assessment for Human Research Protection Programs <http://www.hhs.gov/ohrp/qi/>.
3. Ann Meeker-O'Connell: Enhancing Clinical Research Quality: CDER Perspective. <http://www.fdanews.com/ext/files/Conference/FIS10Presentations/MeekerOConnell-HarmonizingRegulatoryApproaches.pdf>.
4. Ajay S, Bhatt A: Knowledge and skills at the study site - requirements for clinical research professionals in India: A Survey. *CR Focus*. 2008; 19:36–9.
5. American Society for Quality. Project planning and implementing tools. <http://www.asq.org/learn-about-quality/project-planning-tools/overview/pdca-cycle.html>.
6. Arun Bhatt: Quality of clinical Research: A moving target. *Perspectives in Clinical Research*. 2011. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3227329/>
7. Barbara Leishman, F. Hoffmann: Quality by Design in Clinical Projects If you keep on doing what you always did <http://www.chiltern.com/pdf/customers/Chiltern%20v2-%20QRM.pdf>.

8. Clinical Research Transformation Initiative (CTTI): Conducting Multicenter Clinical Research: New Recommendations and Tool for Research. <https://www.ctti-clinicalResearch.org/>.
9. Code of Federal Regulations Title 21. US Food and Drug Administration, Department of Health and Human Services. Subchapter D: drugs for human use. Investigational New Drug Application Subpart D—responsibilities of sponsors and investigators. Sec. 312.50. General responsibilities of sponsors. <http://frwebgate.access.gpo.gov/cgi-bin/getcfr.cgi?>
10. Duley L, Antman K, Arena J, et al: Specific barriers to the conduct of randomized Research. *Clin Research* 2008; 5:40-48
11. Eisenstein EL, Collins R, Cracknell BS, et al: Sensible approaches for reducing clinical Research costs. *Clin Research* 2008; 5:75-84.
12. FDA ORA Quality Manual. <http://www.fda.gov/AboutFDA/CentersOffices/ORA/UCM135836.htm>.
13. Glickman SW, McHutchison JG, Peterson ED, et al: Ethical and scientific implications of the globalization of clinical research. *N Engl J Med* 2009; 360:816-823
14. Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors FDA Inspections of Clinical Investigators. <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126553.pdf>.
15. Johan PEK, Marjorie AS, Reviewing Clinical Research: A Guide for the Ethics Committee. March 2010. www.pfizer.com/files/research/...Research/ethics_committee_guide.pdf.
16. Kleppinger CF, Ball LK: Building quality in clinical Research with use of a quality systems approach. http://cid.oxfordjournals.org/content/51/Supplement_1/S111.full.
17. Lewis DD, Yang Y, Rose T, Li F. A new benchmark collection for text categorization research. *J Machine Learn Res*. 2004; 5:361–397.
18. Loff B, Black J: Research ethics committees: What is their contribution? *Med J Aust*. 2004; 181:440–1.
19. Marinus A. Quality assurance in EORTC clinical Research. European Organisation for Research and Treatment of Cancer. *Eur J Cancer* 2002; 38(Suppl 4):S159-S161
20. Matzat J: Educating and training CRAs for the field. *Monitor*. 2011:32–5.
21. Mirowski P, Van Horn R: The contract research organization and the commercialization of scientific research. *Soc Stud Sci* 2005; 35:503-548.
22. Morrison BW, Cochran CJ, White JG, Harley J, Kleppinger CF, Liu A, et al: Monitoring the

- quality of conduct of clinical Research: A survey of current practices. ClinResearch. 2011; 8:342–9.
23. Pharmaceutical Research and Manufacturers of America. White paper on acceptable approaches for clinical Research monitoring. Office of Scientific and Regulatory Affairs; March 2009.
 24. Preparing for an FDA medical Device Sponsor Inspection. <http://www.fda.gov/downloads/Training/CDRHLearn/UCM176843.pdf>.
 25. Quality Assurance and Educational Standards for Clinical Research Sites. J Oncol Practice 2008; 4(6):280–282. <http://jop.ascopubs.org/content/4/6/280.full?sidpa9e414cd-8327-47cc-87aa-89959172e375>.
 26. Research needs quality management. Article, quality management. http://www.therqa.com/assets/js/tiny_mce/plugins/filemanager/files/Committees/Quality/Research_needs_quality_managemeny_system.pdf.
 27. Stark Yafit: Clinical Quality by Design (QbD) & the Critical Path. May 2010. <http://apps.pharmacy.wisc.edu/esp/prog/IsraelQBD/handouts/Starck%20Yafit.pdf>.
 28. Sina Djali, MS: How a Data-Driven Quality Management System Can Manage Compliance Risk in Clinical Research. Drug Information Journal, Vol. 44, pp. 359–373, 2010 • 0092-8615/2010. www.diahome.org/productfiles/8357/diaj_36269.pdf.
 29. TITLEp21& PARTp312&SECTIONp50&TYPEpTEXT.
 30. Wechsler: Central vs. local: rethinking IRBs. Applied Clinical Research Online 2007. <http://appliedclinicalResearchonline.findpharma.com/appliedclinicalResearch/Regulatory+Articles/Central-vs-Local-Rethinking-IRBs/ArticleStandard/Article/detail/401619>.