

Arun Bhatt

*President, Clininvent Research
Pvt. Ltd., Everest Chambers,
Mumbai, India*

Address for correspondence:

Dr. Arun Bhatt,
President,
Clininvent Research Pvt. Ltd.,
A-103, Everest Chambers, Marol Naka,
Andheri-Kurla Road, Andheri (E),
Mumbai - 400 059, India.
E-mail: arunbhatt@clininvent.com

Abstract

Quality of clinical trials: A moving target

Quality of clinical trials depends on data integrity and subject protection. Globalization, outsourcing and increasing complexity of clinical trials have made the target of achieving global quality challenging. The quality, as judged by regulatory inspections of the investigator sites, sponsors/contract research organizations and Institutional Review Board, has been of concern to the US Food and Drug Administration, as there has been hardly any change in frequency and nature of common deficiencies. To meet the regulatory expectations, the sponsors need to improve quality by developing systems with specific standards for each clinical trial process. The quality systems include: personnel roles and responsibilities, training, policies and procedures, quality assurance and auditing, document management, record retention, and reporting and corrective and preventive action. With an objective to improve quality, the FDA has planned new inspection approaches such as risk-based inspections, surveillance inspections, real-time oversight, and audit of sponsor quality systems. The FDA has partnered with Duke University for Clinical Trials Transformation Initiative, which will conduct research projects on design principles, data quality and quantity including monitoring, study start-up, and adverse event reporting. These recent initiatives will go a long way in improving quality of clinical trials.

Key words: Data integrity, inspection, quality systems, risk-based monitoring, subject protection

INTRODUCTION

In recent years, the global pharmaceutical industry is facing challenges of increase in cost and delay in drug development. The twin objectives – saving of cost and time – have resulted in globalization of clinical trials to developing countries. However, the differences in regulatory processes, ethical issues, medical expertise, clinical practice, and health infrastructure, between

developed and developing countries, makes the third objective – compliance to global quality – difficult and demanding. To manage such complex multi-country clinical trials, the pharma industry strategy has been to outsource the clinical trial process. The globalization and outsourcing of clinical trials have made the target of achieving global quality trying and tough. This article is a brief review of the emerging scenario of complying with international quality standards for clinical trials.

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CONCEPT OF QUALITY IN CLINICAL TRIAL

Good Clinical Practice (GCP) is the universal ethical and scientific quality standard for conducting clinical trials. The GCP standard applies to all aspects of the clinical trial process. Under the GCP guidelines, the quality is a

continuum, which begins with designing, is critical during conducting and recording, and continues during the reporting of trials. Hence, a deficiency in the quality of protocol or a case record form (CRF) would increase the number of monitoring findings and data queries. Adherence to the GCP quality standard during the clinical trial process provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of the trial subjects are protected.

The GCP concept of quality has now been upgraded to include the notions of benefit: Risk of a new medicinal entity (NME). The Clinical Trials Transformation Initiative (CTTI) has characterized quality as, ‘the ability to effectively answer the intended question about the benefits and risks of a medical product (therapeutic or diagnostic) or procedure, while assuring protection of human subjects.’^[1,2] Although the quality standards for clinical trials have not changed over the years, compliance to these standards have become more challenging to achieve, due to the changing landscape of the conduct of clinical trials.

QUALITY – THE CHANGING LANDSCAPE

Traditionally, the system of quality assurance has relied on audits and inspection of the clinical trial sites. This system has come under pressure because of several factors.

The clinical trial protocols have become increasingly complex.^[3] According to a study of over 10,000 protocols, Dr. Getz observed that between 1999 and 2005, the number of unique study procedures grew by 6.5% annually. During the same period, the average number of inclusion criteria increased nearly thrice. This caused a significant increase in the investigator site burden. The annual increase of the site burden was 10.5%. The length of CRF increased from an average of 55 pages in 1999 to 180 pages in 2005 — a rise of 227%. Dr Getz concluded that such a significant increase in the investigator site burden would adversely impact the site performance.^[3]

The other major factor is globalization of clinical trials. According to Glickman *et al.*, since 2002, there has been a 15% annual growth in the number of active FDA-regulated investigators based outside the US.^[4] The number of countries outside the US, which have participated in clinical trials, has increased two-fold between 1995 and 2005.^[4] As many of these clinical trials are in the developing countries, there is a concern about the ethical and scientific implications of the globalization of clinical trials.^[4] The large disparities between developed and developing countries in education, socioeconomic standing, and healthcare systems, and the differences in medical training, clinical practice patterns, and health

infrastructure standards of care can have an impact on the quality of trials.

The current strategy and models of outsourcing add to the complexity of quality management. Getz and Vogel’s survey of global outsourcing showed that pharma companies outsource a wide variety of activities and functions. There was also a trend toward the use of multiple outsourcing partners and in-sourcing of clinical research professionals, as also the use of different relationship structures.^[5] The pharma sponsors use multiple clinical research organizations (CROs) — a mix of full service and niche CROs. They also prefer to use functional CROs in outsourcing. This means that the whole clinical trial process may be shared by multiple CROs managing diverse functions — regulatory approval, protocol preparation, site management, monitoring, data management, statistics, and medical writing. This could mean multiple CROs using multiple standard operating procedures (SOPs) or the sponsor asking each one to follow the sponsor’s SOPs. The fragmentation of outsourcing can lead to deficits in documentation, unclear division of responsibilities between CROs and sponsors, and limited real-time assessment of the CRO function. It will also be difficult to carry out a comprehensive root cause analysis and corrective actions.^[6] The FDA is concerned that many third parties involved in the clinical trials can impact data integrity and / or human subject protection.

QUALITY ISSUES IN CLINICAL TRIALS

Traditionally, the quality of a clinical trial conducted at the investigator site is assessed by sponsor audits and regulatory inspections. Over the last several years, routine FDA inspections have been Voluntary Action Indicated (VAI) 59%, No Action Indicated (NAI) 40%, and Official Action Indicated (OAI) 1%. In For Cause inspections, the proportion of OAI is 23%.^[7] In India, out of 23 site inspections, 12 (52%) were NAI and 11 (48%) were VAI.

Some common deficiencies observed during site inspections include:^[8,9]

- Failure to follow the investigational plan and signed investigator statement / agreement
- Protocol deviations
- Inadequate record keeping
- Inadequate accountability for the investigational product
- Inadequate subject protection, including informed consent issues
- Adverse Event (AE) recording and reporting

Over the years, these have remained the areas of deficiencies at the investigator sites.

However, the sponsor and its team — monitors — play a significant role in the site performance. In FDA inspections, some of the common sponsor deficiencies were:^[10]

- Inadequate monitoring
- Failure to secure investigator compliance
- Failure to submit progress reports
- Failure to notify FDA, investigators or Internal Review Boards (IRBs)
- Inadequate investigational product (IP) accountability
- Failure to obtain signed investigator agreement
- Failure to obtain FDA or IRB approval
- Unqualified monitors

The FDA warning letters also cite deficiencies in monitoring.^[11] Some findings were:

Study monitors failed to identify that subjects who did not meet eligibility criteria were enrolled

- To ensure that the investigation was conducted in accordance with the investigational plan
- To identify that no physical examination, assessment, or overall clinical assessment was documented in study source data (SD) or CRF
- To identify that study documents contained conflicting information regarding accountability of the drug

As the quality of a clinical trial depends on ensuring protection of human subjects, the functioning of the IRB also needs to be reviewed.^[8,12] In the FDA inspections, The IRB deficiencies were:

- Inadequate meeting minutes
- Inadequate / not following written procedures
- Failure to have a majority of members present during convened meetings
- Inappropriate use of the expedited review
- Failure to conduct a continuing review
- Failure to have a non-scientific member during the IRB meetings
- Failure to maintain IRB member rosters
- Failure to make risk determinations

The present approach of regulatory inspections to ensure quality in clinical trials is similar to the old-fashioned manufacturing systems: Produce the product, catch the defective ones, and throw them out.^[2] Rejection of clinical trial data after the inspection is ineffective and wasteful. There is a need to change the focus from inspection-based quality improvement to planned systematic quality management.

QUALITY — SYSTEMATIC APPROACH

The regulatory authorities expect the industry to focus on developing quality systems during the planning and

conducting of clinical trials. Such systems depend on the development and implementation of standards for each clinical trial process.^[2,6] The quality system requirements include:^[2]

- Personnel roles and responsibilities
- Training
- Policies and procedures
- Quality assurance and auditing
- Document management, record retention, and reporting
- Corrective and preventive action (CAPA)

There are four types of errors likely to occur in clinical trials: Design, procedural, recording (both random and fraudulent), and analytical.^[2] The quality system should deal with each of these.

The sponsors are also advised to apply risk management principles to effectively target resources to activities that present a greater risk to data integrity and human subjects' protection.^[6] There is also a need to define controls to prevent errors, identify potential problems, and intervene before the problems become serious.

QUALITY — METHODS OF IMPROVEMENT

The improvement in the quality of clinical trials requires the use of the systems approach, tools, and models.

The FDA recommended a four-step systems approach, as follows:^[6]

- Say what you do
- Do what you say
- Prove it
- Improve it

Say what you do

The sponsor should have a qualified and responsible management team to provide governance of the whole clinical trial process. There should be a robust oversight of the outsourced trial and excellent coordination among the project team members, to ensure good decisions. The policy and SOPs should define procedures and responsibilities for all key clinical trial processes, from protocol development to preparation of the clinical study report. The SOPs should also focus on the potential anticipated risks.

Do what you say

This step largely describes education and training of all sponsor staff, CRO staff, and site staff uniformly about the trial protocol, study requirements, policies, and procedures. All the teams should be aware of their responsibilities.

For the sponsor and CRO, the monitor is the main resource for ensuring the site quality. Although the GCP defines the training requirements of a monitor, there is a need to make the monitors aware that monitoring is not merely matching data and having an inventory of documents.^[13] Many of the recent FDA warning letters cite monitoring deficiency as a finding. Most of these findings are in the area of selection of subjects, protocol compliance, and documentation of clinical assessments in the SD. As per an Association of Clinical Research Professionals (ACRP) survey, 66% of the CRAs were from a non-medical background. Hence, there was a gap in familiarity with the medical practices and their documentation.^[13] This means that a monitor should go through study-specific monitoring — protocol specific requirements, therapeutic areas, standard of medical care, and source data verification (SDV).

The quality depends a lot on how the site conducts the study. As most sites, in an emerging country, such as India, are on the learning curve of clinical research, they need in-depth training in regulatory requirements, ethics, consent process, and protocol compliance.^[14] Most of the sites in India are high in recruiting; hence, the site has less focus on documentation. The sites should understand that documentation is the heart of GCP compliance.

The quality of a trial requires an assurance of protection of subjects. Although all stake holders are responsible for this ethical responsibility, the role of the ethics committee (EC) is vital in ensuring subject protection. The EC requires training in regulations, ethics, and science of clinical research. However, perhaps the most essential is ‘undertaking a week of intensive training in critical thinking.’^[15]

Prove it

This step requires new approaches such as risk-based monitoring and trend analysis.^[6]

Risk-based monitoring focuses on process management and verification of critical activities, including quality control, to ensure that they are carried out as planned.

The trend analysis looks at data as compliance intelligence. The trend analysis employs approaches such as statistical monitoring, to assess data trends across the sites and trials or data mining with an objective of proactively identifying and evaluating compliance signals and unanticipated risks. A recent survey conducted by the CTTI revealed that the majority of all sponsor organizations utilize centrally available data to assess site performance; however, only one-third or less always use a centralized monitoring process to guide, target, or supplement site visits. The CTTI members perceive that on-site clinical trial monitoring is

not efficient in improving the quality in clinical trials.^[16] The approach of centralized monitoring to guide or target sites for monitoring is emerging as a useful tool to confirm compliance to quality.

Improve it

Improving quality will require actions — effective CAPA. For CAPA to be effective there should be an in-depth analysis of the root cause and its impact on the quality, and a search for an action plan that can provide long-term and sustainable solutions.^[6] The system and processes should be reassessed to ascertain how the problem occurred.^[2]

One of the most widely used tools for continuous improvement is a four-step quality model — the Deming Cycle plan-do-check-act cycle.^[2] This model can be applied to a quality issue in the following manner:

- **Plan:** If the audit finds that subjects are not dating a consent form, first step would be to identify the error in the process. The root-cause-analysis would consider the process employed by the personnel authorized and their training. The plan would focus on re-training the persons who have committed the error.
- **Do:** This step would require applying the planned changes. This means re-training the persons who have committed the error.
- **Check:** This would require monitoring of the consent process, to check whether the errors continue, by observing the staff during the consent process and auditing a select number of consent forms.
- **Act:** If all consent forms are signed and dated, then the plan could be applied to the whole team. If the errors persist, the cycle is repeated

QUALITY — NEW REGULATORY APPROACHES AND INITIATIVES

The regulatory authorities’ concerns about quality issues in trials are compelling them to consider new approaches to assess the quality of a clinical trial conduct. The FDA is developing new approaches of risk-based inspection planning.^[6] This would include:

- Center for Drug Evaluation and Research (CDER) risk-based site selection tool
- IRB inspection model
- Bioequivalence inspection model
- Sponsor / CRO surveillance Inspection model

The FDA is planning to shift its inspectional focus, which is currently post New Drug Approval (NDA) submission, to clinical trial inspection and oversight in real-time. This would mean surveillance inspections of sponsors and

clinical investigators when the trial is ongoing. The FDA will also propose evaluation of the sponsor quality systems and the sponsor quality management plan at the end of phase 2. The FDA and EMA would collaborate in joint, parallel, and sequential inspections and share information on the best practices. The agency's other strategy is to use data as information to inform inspection prioritization, planning, and scope.

Another major FDA initiative is the CTTI, which was established in 2008, by the FDA and Duke University, as a public-private partnership. The aim of the CTTI is to identify practices that, through broad adoption, will increase the quality and efficiency of the clinical trials.^[1] CTTI includes 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 initiated several projects to identify practices that will increase the quality and efficiency of clinical trials. The four priority 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 component of quality
- Improving unexpected Serious Adverse Event reporting to investigators
- Improving the public interface for use of aggregate data in clinicaltrials.gov
- Site metrics for study start-up
- Use of central IRBs for multicenter clinical trials

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

- Focus 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 highest risk for generating errors that matter
- Prospectively measure the error rates of important parameters
- Monitoring approach — visits, central, statistical — tailored to the trial design and key quality objectives
- Improve training and procedures
- Report quality issues found, actions taken, discuss their impact on the analysis and interpretation of results

The FDA's recent initiatives highlight the importance of prospectively building quality into the scientific and operational design, and the conducting and monitoring of clinical trials.

CONCLUSIONS

Compliance to quality requirements is the cornerstone of a scientifically valid and ethically sound clinical trial. The twin objectives of quality — data integrity and subject projection — can be met by a systematic approach to the whole process of a conduct of clinical trials. The recent regulatory approaches of risk-based inspections and real-time oversight, coupled with a spotlight on the quality systems, demand continuous vigilance and continuous process improvement from the key stakeholders — investigators and sponsors.

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