

Design and Conduct of Clinical Studies by Integration of Quality by Design (QbD) into Quality Management System (QMS) - A Pragmatic Approach

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Abstract

Quality is a prerequisite during entire drug development cycle. Clinical studies are required to prove effectiveness of experiment drug and to evaluate its safety profile in humans. To have a smooth design and conduct of clinical studies; Quality-by-Design (QbD) approach can be integrated with Quality Management System (QMS) to ensure the end-to-end quality optimization. Quality by Design is not widely used currently in clinical research.

This manuscript proposes an effective integration of QbD with conventional QMS. We have applied the proposed integrated model in our clinical studies. We have studied elements of QbD thoroughly and identified Critical to Quality (CTQ) factors. These CTQ factors were integrated with QMS components to achieve improved quality. We found the integrated model to be pragmatic for clinical research and it has potential to change the Quality landscape in future.

Keywords: QMS; QbD; Quality; CTQ factors; Clinical study; Data integrity; Clinical study design

Introduction

Clinical studies involve evaluation of therapeutic effectiveness and safety of drugs, biological products, medical devices, and combination thereof in human volunteers. There is an increase in clinical studies due to the current pandemic. Due to revised guidance documents, the complexity of implementing studies has also increased. These changes create new challenges to clinical trial oversight, particularly increased variability in clinical investigator experience, site infrastructure, treatment choices, and standards of health care [1,2]. Thorough science and impeccable quality are absolute necessity throughout clinical study. The sponsors of clinical investigations are required to provide oversight to ensure adequate protection of the rights, welfare, and safety of human volunteers. [3-6].

Although Quality is a cornerstone for any clinical studies, there is also cost involved as a secondary but essential aspect for any organization. Now a days, outsourcing of clinical studies, either full or in part as well as technological advancements changed industry landscape. Globalization of clinical trials in terms of involvement of global stakeholders like CROs, clinical sites and multiple vendors increased the complexity of the clinical studies manifold. As it is associated with many ethical and scientific implications *viz* clinical study protocol compliance, monitoring, volunteer safety and rights, timely reporting, vendor qualification and management, and

stakeholder communication [1,7]. Therefore, a change in quality program has become inevitable to safeguard safety of human volunteers and to ensure data integrity.

The present approach fails to detect the real time assessment of ongoing clinical studies as it evaluates only certain aspects of clinical studies and not consider every stage of it from beginning to its end. In assuring and improving quality, a shift from current retrospective inspection-based quality management system to integrated model of Quality by Design in Quality Management is indispensable. This manuscript offers a framework of effective quality management by integration of Quality by Design (QbD) with conventional QMS that can be tailored to meet the requirements of clinical studies. The proposed integrated approach was successfully applied on conduct of a clinical study of a complex formulation.

QbD Approach for Clinical Study Design

The concept of Quality by Design (QbD) was first described by Juran JM in the early 1990s. In general, it defines quality as freedom from errors that matter. For a clinical trial, this could mean errors in study conduct or inaccuracies in data collection and/or reporting that affect the pre-specified study endpoints (and therefore harm study validity) or that jeopardize a patient's rights or safety [8-11]. In order to ensure quality, it is important to understand nature of non-compliances detected by regulatory agencies. We have evaluated

the database of FDA issued non-compliance observations in clinical studies to understand the trend [7,12]. The major categories of non-compliance over five-year duration (2015-2019) were formulated into a table (Table 1). For better understanding, the observations pattern was plotted into a bar-chart also (Figure 1).

Quality by Design approach consists of defining quality goals at priori-to and develops the essential study documents, procedures to meet the pre-defined quality goals. QbD approach is intertwined with risk assessment and mitigation, hence designing a clinical study with QbD approach helps to eliminate potential risk(s). QbD approach can be divided into two main stages- Design stage and Execution stage [13]. Clinical trial quality ultimately rests on having a well-articulated investigational plan with clearly defined objectives, study methodology, importance of ethics in clinical study and outcomes from the planned clinical study [9,13]. After design phase, protocols, Case Report Forms (CRF) and data collection procedures should be performed in a way, which support the defined design of clinical study. As depicted figure 2, Quality culture of an organization, especially trainings on ethics, data integrity, Good Document Practices are crucial. Moreover, transparent stakeholder communication is an integral QMS component throughout the clinical study, which includes any third-party collaborator (if applicable) as well.

Critical to quality (CTQ) factors

Any variable critical to the outcome of the study or compromising the safety or rights of the study volunteers are called Critical Quality factors (CTQs) [13]. Sponsor organization should have an SOP in place for identification and documentation of Clinical to Quality Factors. All stakeholders involved in the clinical study are responsible to identify the critical to quality factors. The vital CTQ factors are depicted in figure 3. During study initiation phase, sponsors and investigators should identify the CTQ factors as per established SOP and document the same. This CTQ identification document shall be used further for developing clinical study essential documents. Based on data of 05 years USFDA observations [7] and our experience, we enlisted and elaborate the CTQ factors and their components (Table 2).

Continuous improved by QbD approach

A proven QbD methodology used while study execution is the Plan-Do-Check-Act (PDCA) cycle, to attain continuous improvement. PDCA cycle approach is effective to evaluate system/processes affecting CTQs [14], which is described below (Table 3).

Below is an example, which illustrates usage of PDCA cycle during a clinical study to ensure quality in the process.

Table 1: Major categories of non-compliances for clinical studies over five-years (2014-2019).

Year	Protocol non-compliance	Documentation and its retention	IRB Related	Study Reporting	Investigator Related	IP Management	Personnel Training & JD	QMS Related
2015	171	43	60	11	7	30	30	9
2016	120	29	38	5	3	28	1	10
2017	140	37	21	6	3	22	3	10
2018	118	33	29	11	5	17	3	15
2019	125	31	29	3	3	19	2	7

Source: Bioresearch Monitoring Observations (USFDA website)

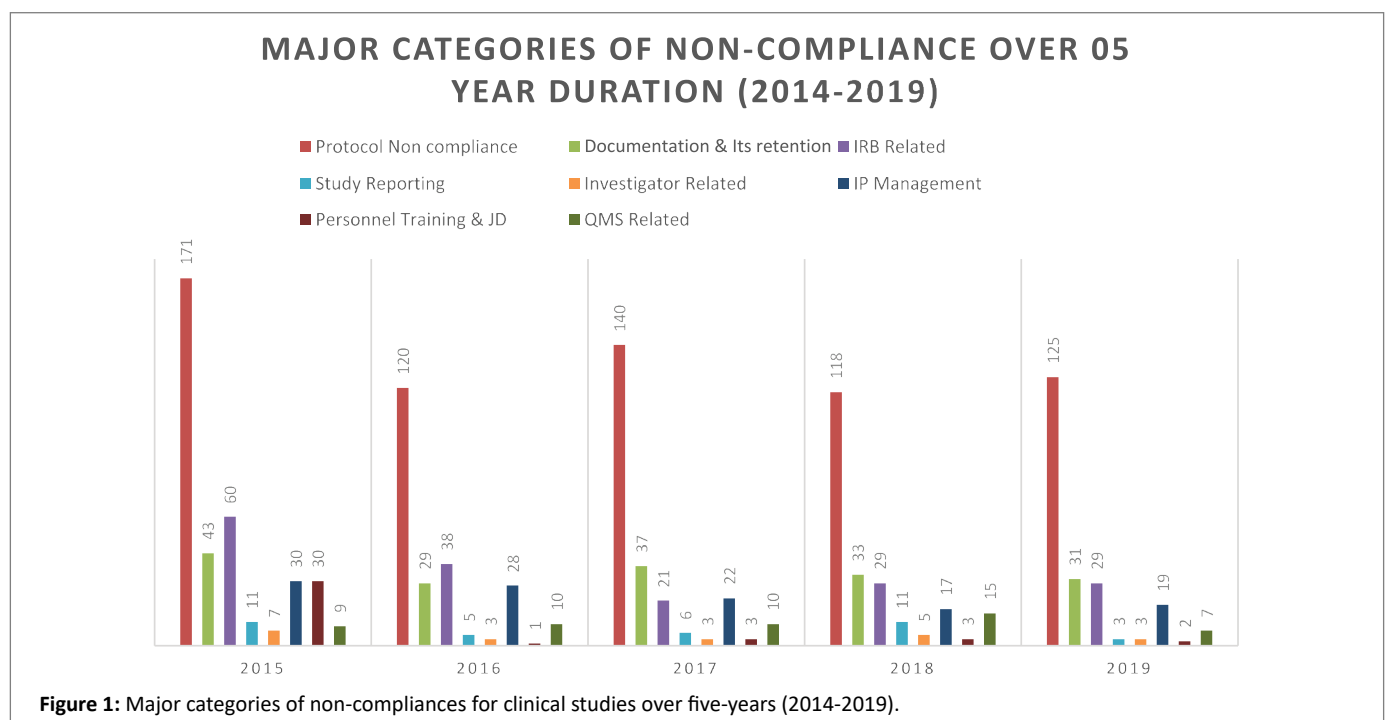
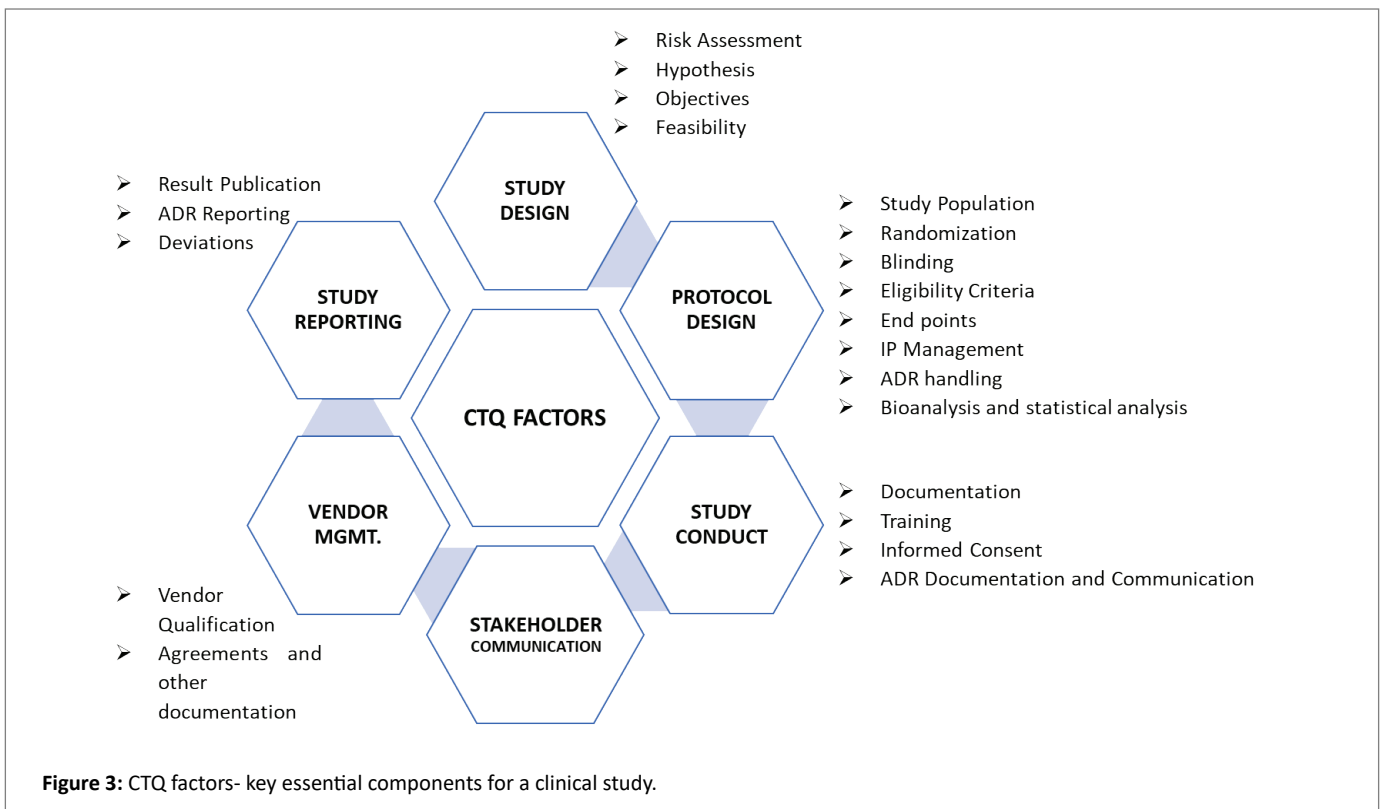
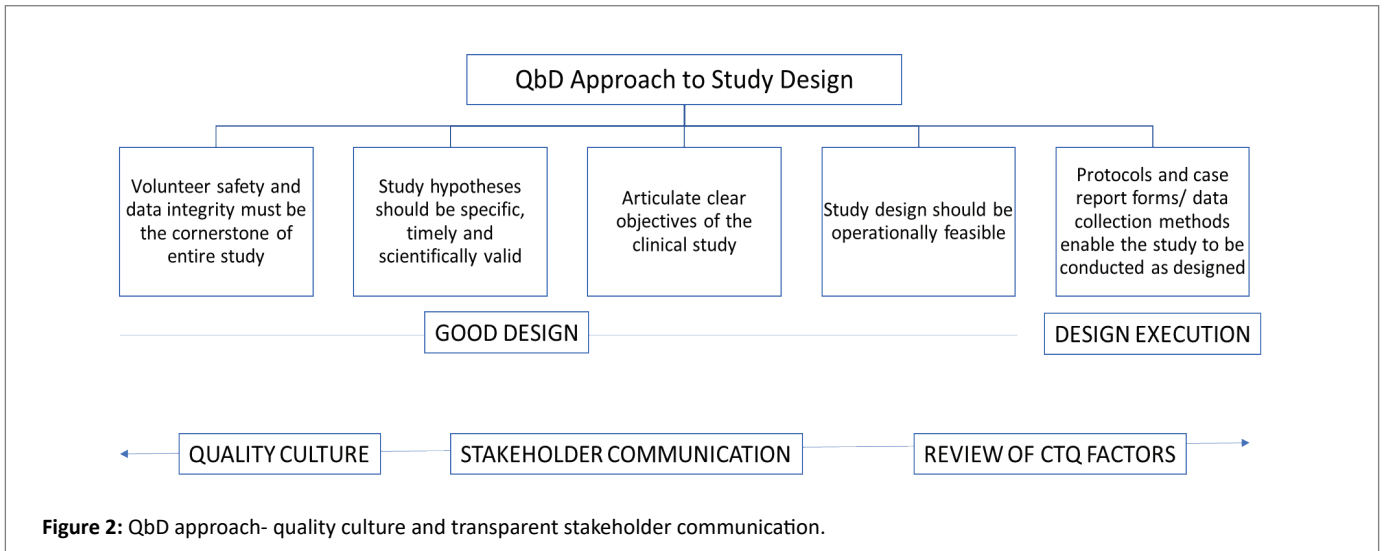


Figure 1: Major categories of non-compliances for clinical studies over five-years (2014-2019).



It has been observed that minor documentation details were not completed by study staff personnel. The “plan” aspect of PDCA cycle involves asking questions to answer the root cause of an issue, such as-

- Who is responsible to ensure compliance of documentation?
- Whether there is a pattern in the incomplete documentation of forms?
- How the responsible personnel are trained and assessed before they involve independently in a clinical study?
- Whether other factors are involved for these documentation errors or not.

Once, the cause for an error is found after asking above questions, “Do” aspect determines the further course of action. Suppose in this case, the cause was found to be deficient training to responsible personnel and inadequate assessment, refresher training should be planned for responsible staff and he/she would be allowed to perform the task under observation. During “observation”, data would be collected for documentation compliance and error rate.

Then, “action” aspect would come into play. Actions would be performed, and compliance for documentation [9] shall be continuously monitored. For any non-compliance, CAPA would be taken and PDCA cycle would be repeated to ensure quality. The

Table 2: CTQ factor and QbD approach for clinical study.

CTQ Factor	QbD Approach for Clinical Study
Study Design	<ul style="list-style-type: none"> • Risk assessment for study was documented to outweigh any risks involved in the clinical study • We searched available literature as well as applicable regulatory guidance documents and selected cross-over design, in order to keep lesser number of participants to achieve desired power. • We defined study hypothesis with scientific rationale and primary and secondary objectives • Feasibility of study was performed to determine subject size, estimated cost and evaluation of organizational resources for the study. • We defined that based on the results of pilot study, further decision of pivotal study to be made.
Protocol Design	<ul style="list-style-type: none"> • Based on literature, we defined the study population specific to molecule in study, which was not general population and added more complexity to this clinical study. • We defined randomization scheme in the protocol based on study objectives and also described the procedure to ensure blinding throughout study conduct • We carefully determined inclusion and exclusion criteria to avoid any safety risk to volunteers, and these criteria were defined based on nature of drug investigated nature of study population. • We defined scientific primary and secondary endpoints based on literature. • We describe detailed procedure for study sample collection, transfer to analytical site, analysis methodology as well as statistical analysis for clinical study. • Detailed description was provided in the protocol for adverse drug reaction handling. • Study reporting as well as archival of documents was also captured in line with regulatory guidance requirements.
Study Conduct	<ul style="list-style-type: none"> • Based on study requirements, we designed study specific directives and forms to be used during study conduct. We reviewed templates of CRFs, Statistical Analysis Plan and also defined data collection procedures. • We ensured documentation of roles and responsibility in form of role allocation document. • We ensured training to the investigator as well as key personnel before study initiation and also ensured that trained personnel percolated the training to all personnel, whom role/responsibility is assigned • We asked CRO to provide thorough training to personnel, who have been assigned to perform informed consent aspect of this study.
Vendor Management	We utilized services only from vendors who had been previously qualified by our organization and had shown consistent compliance in services. Moreover, services were obtained only after robust agreements and service-related documentation with qualified vendors.
Communication to stakeholders	We ensured the communication among stakeholders (including vendors) throughout the study conduct and complied with ICH GCP guidance also, in terms of communication to ethics committee, regulatory body.

Table 3: PDCA cycle approach.

Plan: Recognize an opportunity and plan a change.
Do: Implement the plan, execute the process, collect the data, and measure the results.
Check: Review the test, analyze the results, and identify what you've learned.
Act: Act based on what you learned in the study step. If the change did not work, go through the cycle again with a different plan. If you were successful, incorporate what you learned from the test into wider changes. Use what you learned to plan new improvements, beginning the cycle again (Figure 4).

interval for PDCA cycle repetition is determined based on the design and needs of each clinical study.

Quality Management System

Sponsor has the overall responsibility of the clinical study, although multiple sites are involved in a trial to ensure the validity of the data across the population, Sponsor is required to set up a best possible Quality Management System in place to ensure uniformity and integrity of the data. [ICH GCP E6(R2)] QbD integrated QMS ensures compliance in terms of effective documentation and optimized procedures during design and conduct of clinical study [15,16]. In this regard, we have identified critical QMS components, which may

have direct or indirect impact on clinical study either in terms of data reliability and/or safety of clinical study volunteers (Table 4).

Clinical Application

We conducted a clinical bioequivalence study considering the defined integrated quality management approach of QbD and QMS. The study was performed on an anti-cancer drug formulation which belongs to tyrosine kinase inhibitor. The study was executed considering the enlisted CTQ factors such as study design, protocol design, study conduct and vendor management, (Refer table 2) and critical QMS components (Refer table 4). There were many challenges during the beginning of clinical study such as very limited information about the pharmacokinetic characteristics of molecule, drug possess long plasma elimination half-life, and lack of precise information on intra- or inter-subject variability of drug. We assessed the initial risk of clinical study on selected drug considering the integrated QbD and QMS approach. Considering availability of very limited literature, a pilot study was planned in the initial phase of clinical development. The elements of QbD approach to study design depicted under figure 2 and the reported major categories of non-compliance (Table 1) were taken into consideration during clinical study design. The key information on drug pharmacokinetic behavior and inter-subject variability were obtained from pilot study. Moreover, the major learning's from execution of pilot study were implemented in pivotal study (*viz* IMP handling, record and administration; subject inclusion-exclusion criteria, ADR handling, training, stakeholder

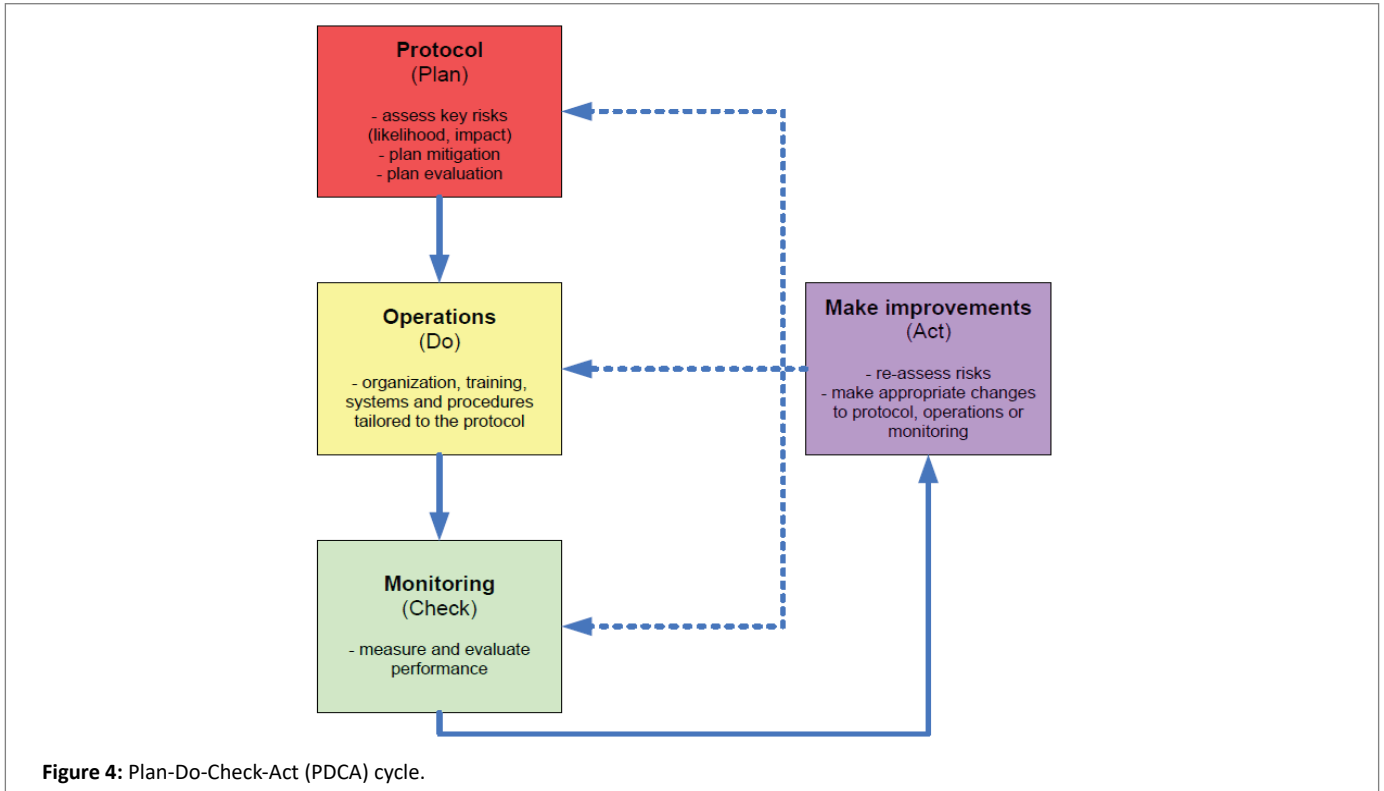


Table 4: Critical QMS components.

Critical QMS Component	Advantage on clinical study conduct
Organizational policies and procedures	SOPs, Quality Directives, Policies and manuals decide quality framework for any organization. Such documents should be clear, concise, written in a language which can be understood by all study personnel in order to have a harmonized, smooth conduct of clinical study.
Training system	Training on regulatory guidance documents, data integrity aspects and necessary study documents ensure that study personnel perform the allotted task with thorough understanding and clarity of regulatory requirements.
Personnel roles and responsibilities	Clear role and responsibility allocation bring clarity for personnel to carry out work. Allocation of role and responsibility allows the user to get proper training before involvement in the study. Documentation of role and responsibility helps to reconstruct the study activity against personnel.
Quality Assurance audits	Appropriate sample size for auditing- either online or retrospective helps to ensure data reliability. Timely audit helps to resolve issues in timely manner, and scope of QA audit can be widened based on observations found.
Quality Control Unit	Thorough QC check and corrections help to resolve issues online and in general, QC check is performed for 100% study, which helps to remove any risks to data credibility.
Communication between stakeholders	Transparent communication and information flow help to operate a study without hindrance. Moreover, it also allows evaluation of study as an ongoing basis.
Human Factors (quality culture, personnel motivation)	Quality culture and an environment which encourages personnel to work motivated, ensures that responsible person contribute in best possible way to ensure quality.
Vendor/Supplier management	Evaluation of services provided any different vendors help to determine the right vendor for clinical study. Vendor Qualification prior to service agreement ensures desired quality throughout the study.
IT infrastructure and Computer System Validation	This factor assures that a computer-based resource used in the clinical study has been in compliance state in line with regulatory requirements.
Document management and Archive	Design of essential documents as well as pre-defined chain of custody for clinical study documents along with its archive in line with regulatory requirements ensure reconstruction of study at a later phase and retention of documents in unaltered manner.
Facilities and equipment	Facility design in such a way that different operations do not present any hindrance with each other and facility design should ensure that independence of critical operations like QA, Archive is achieved. Moreover, movement of material should not create any risk of contamination in case of laboratory operations.

communication, bioanalysis, subject sensitization to compliance with study protocol and visit for ambulatory sample draw). The CTQ factors for pivotal study were further strengthened based on key learning's and areas where we found the scope for further optimization (Table 2). Pharmacokinetic blood sample collection time point and duration were optimized to adequately characterize the maximum plasma concentration (C_{max}) and Area Under Curve (AUC). Study sample size for pivotal study was computed based on the inter-subject variability obtained in pilot study and considering pivotal study power of at least 80%. The key advantages we observed through implementation of this integrated approach in our clinical study include:

- » Initial risk assessment to determine CTQ factors provided better picture of clinical study and enabled stakeholders to evaluate all aspects in a holistic manner.
- » Each milestone was achieved in the pre-defined timeframe which ultimately lead to effective conclusion of study in a timely manner.
- » Due to clear communication channel, issues were resolved promptly.
- » Personnel involved in the study did not deviate from the procedure defined in SOPs due to timely and thorough training beforehand.
- » Our pivotal study was completed without any protocol deviation as study personnel were clear for assigned job and a transparent communication among different stakeholders.
- » There were no regulatory observations found for this clinical study and we received authorization for the investigational drug.
- » We did not face any issue while document reconciliation due to robust data management and pre-defined chain of custody for documents.
- » We concluded a complex study with relative ease due to better study design and procedural controls in place.

Conclusion

In current manuscript, we enlisted the critical QMS components which ensured high quality standard across overall clinical development program (Table 4). The integrated approach of QbD into QMS was successfully implemented into a clinical study program to evaluate overall impact on quality and data integrity and subject safety. We concluded the clinical studies and found that QbD integrated QMS approach led to better data quality and compliance throughout the clinical study program. We humbly believe that this integrated approach is a scientific, risk-based, holistic and proactive approach to ensure safety of human volunteers and data integrity. We hope this article will initiate further discussions in the industry over this integrated approach for clinical studies.

Conflict of Interest

The authors have no conflict of interests.

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