Quality by Design in Clinical Trials

The quality of a clinical trial can be assessed by whether the trial meets the needs of its various customers, as well as by its freedom from critical deficiencies or errors. In order to ensure the quality of a clinical trial, it is therefore important to conduct quality planning in parallel with the process to design and prior to the conduct of the trial. Quality planning consists of prospectively establishing quality goals and developing the products and processes required to deliver a quality trial. This article provides an overview of the quality planning process conducted by a pharmaceutical sponsor for a clinical trial.

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The pharmaceutical industry in the past decades has witnessed a positive and successful growth. According to the market study the pharmaceutical companies are going to mark a 15-20 per cent growth rate by 2020-2025. With the technological advancement every passing day, the research and development has reached the levels of intensity to filter down which kind of medicine formulation is useful for which health issue and for how long.

One of the main and most followed practiced is Clinical Trials, the key research tool for advancing medical knowledge and patient care. Clinical trials are essential to the evaluation of promising scientific discoveries, but they are becoming unsustainably burdensome, threatening to deprive patients and healthcare providers of new therapies and new evidence to guide the use of existing treatments. Clinical Trials are only conducted when the doctors do not know whether a new medical formula or process will work well and is safe for the people. The practice of such trials is also done when the doctors are unsure about which kind of treatments will work for which disease. Some trials have given positive results and have been given preference to be recommended to the patients to carry out with the resulted treatment. But not all trials show positive results, some of the trials have proven to be a setback for the patient's health.

With different kind of trials being conducted to detect and determine specific issues and results, the clinical trial is further conducted within four stages for effective outcomes. Patient recruitment, Patient engagement and Patient Retention are the most important stages of a trial. The basic outline about a clinical trial is now understood by almost everyone but one of the most essential part of it has always been unnoticed, ie, the QbD factor. Until there is no quality assurance of such trials the results will not be as effective as they should be. FDA according to the past market study suggested that working on quality-by-design for clinical trials would reduce the industry and regulatory monitoring costs.

Quality by Design (QbD) is an approach that focuses on "errors that matter" for the success of clinical trials. Every trial has certain objectives to meet in order to get the desired outcome and result. These certain objectives are met by going through prolonged process of different stages. The quality of every factor involved in the process matters the most. The negligence in this term might just alter the effect of the trial. It is suitable to take risks to improve quality and outcomes of the trial. QbD enables enhanced process understanding, and a more systematic and scientific approach towards development, so that better controls may be implemented.

QbD cannot be considered without examining validation within a product lifecycle framework. In an inaugural CTTI workshop on "Quality Risk Management: Making Clinical Trials Fit for Purpose" held in August 2011 explored principles of risk management and QbD from other disciplines and examined how such principles could be adapted to enhance clinical trial design and execution. The Qbd approach improves trial efficiency while allowing the sponsors and investigators to meet their obligations to protect individuals who volunteer to foresee the development of the trial.

The purpose of involving the Quality by Design concept in trials was done to have accurate results in time. The companies in the pharmaceutical industry have been

implementing the idea and practice of QbD for the past few decades. The main concern in this concept is the quality generated by framing the design of the clinical trial. Incorporating QbD is one of the few levers that the biopharmaceutical industry can pull to increase its probability of success. The QbD concept has never been the part of the R&D process because the clinical trials are expert-driven rather than process driven. The QbD approach further helps in reviewing case studies demonstrating how these principles are and can be applied in trials sponsored by industry, government, or academia to enhance trial design, implementation, and oversight.

Clinical trials are giving positive results and have indeed marked a good progress in Indian Pharmaceutical sector. The Quality truly matters when we talk about health, and in terms of clinical trials quality is about the process flow and its design framework. A slight negligence can turn up into negative outcome. The key elements- Plan-Do-Check-Act, play a very important role when it comes to risk management in the QbD process. It should always be taken care of while conducting a trial as quality in practice is responsible for effective results and happy healthcare.

The key elements of QbD concept are further defined in "Plan-Do-Check-Act" work-frame pattern. The first key element of the Quality By Design approach is to plan. This phase involves planning an appropriate design that focuses on proactive quality of risk management and scientific risk assessments. Ensuring safety of the recruited patients via carefully determined inclusion and exclusion criteria, validating the assessments and procedures that will generate the data collected are to be looked after in this planning stage. Operational risk assessments (eg, can appropriate and sufficient investigational sites be secured?) and operational risk (eg, supply chain issues, procedures such as imaging, patient reported outcomes, lab assays, data integrity) in this stage should focus on the feasibility considerations for the trial. The planning is done but how will this plan be carried out? All we need to do is build a strong team and train them to focus on the quality outcomes. And the second stage "Do" revolves around team management and training them to understand the importance of quality by design in clinical trials.

Training investigational sites, principal investigators, monitors, and clinical trial educators is the first step. Once the training is done, then comes the need to set up a rigorous process for overseeing trial execution, including prospective alerts, triggers, and risk mitigation plans that deliver against iterative project management plans. These 'Do' stages can be classified as setting up the basic outline of Quality by Design approach of a clinical trial. The "Check"and "Act" stage will further help in analyzing the pathway of outcomes in a trial.

The "Check" phase employs sophisticated reporting software housed in a central data-operations centre to provide near-real-time access to blinded data at the participant level. This enables visualizations of core study indicators such as enrolment site, site performance, and monitoring performance. The technology investments are critical as they enable visualizations of core study indicators that can support real time decision making. Dashboards displaying expected versus actual enrolment, for example, are potent tools that provide detailed information in a readily assimilated manner. The final proactive stage of the QbD approach is the "Act" phase which involves pre-emptive project management and proactive risk mitigation using the information gleaned from the check phase. Re-forecasting is conducted based on information gained to date. The success of QbD in manufacturing site of clinical trials is motivator for those on the R&D side of it. Pharmaceutical industry has marked a positive growth with the involvement of QbD approach in the trials.

Why QbD in Clinical Trials?

- Using Quality by Design helps to avoid major errors that matter most of the decision making process.
- QbD ensures human subject protection as appropriate information and timely consent are passed to all stakeholders and human subject at each and every stage of the clinical trial.
- QbD program is designed in such a way that investigational products are safely administrated and monitored on regular basis by trained professionals and technologists.
- With QbD the clinical trials are planned in a way that the safest study procedures & investigations are selected to reduce the errors that matter for the patient's safety or credibility of the results
- QbD also helps in unbiased treatment allocation for investigational products or procedure and subject selection and routine follow up of the designed programme.

QbD and Human Subject Recruitment

- Inclusion criteria for subject selection involves risk to benefit ratio analysis, how much relevant the target population is for investigational therapy.
- Human subject protection is of most importance along with focus on co morbidity, concomitant m ation, consent. Human subje ee to withdraw from the trials a if he/ she feels uncomfortable longer wants to be part of the stud
- Feasibility checks are of quite importance as medications must fit with routine care and practice as clinicians are busy and patients are ill.

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Challenges in Implementing QbD in Clinical Trials

Quality by design is a new, upcoming and developing concept in the field of clinical trials. It lacks Standard operating protocols and no standard practices are evolved yet, making it quite difficult to follow and regulate. Imbalance and lack of sound knowledge experience has reduced its acceptance among majority of developers, CRO and sponsors. Qbd concepts are not yet fully matured compared to the traditional clinical trial processes.

As the success stories or positivity is less not all stakeholders are motivated to get engaged with this concept of clinical trials. Generally in majority of cases clinical trials are outsourced. Implementing QbD approaches with outsourced partners is in itself a challenging task as CRO and sponsors should have a balanced knowledge, experience and expertise about QbD in clinical trials. Unequal understanding and involvement among sponsors and investigators affects outsourcing of clinical trials using QbD approach. Cultural and behavioural challenges are also minimising the implementation of QbD.

Merits of Quality by Design in Clinical Trials

Clinical trials by QbD are practical and sustainable. It gives sponsor a competitive edge over the players following the traditional approach in clinical studies. Even cost incurred with this method is comparatively low. QbD improves quality and safety of the entire clinical study with affecting the subjects involved. The QbD approach in clinical studies improves integrity of collected data, information, observations and facts. This will lead to more quality submissions of investigational products and more product approvals at faster rate without affecting the quality of subjects taking part in the study. ■

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