cQRM (clinical Quality Risk Management)
cQRM is a risk management methodology that applies quality risk management to clinical trials. It focuses on proactive risk management in clinical research and helps in completing clinical trials successfully within the timelines and budget. Applying cQRM principles to clinical research from the early stages of drug development can expedite the process of bringing quality drugs from bench to market, addressing regulatory challenges and patient safety.

Quality risk management guidelines were established for GMP and medical devices; however there were no guidelines available on handling of risk in clinical trials. cQRM is a holistic approach to clinical quality management that incorporates risk management principles of ICH Q8 and ICH Q9. cQRM helps in identifying critical activities and potential risks involved in clinical trial conduct, which reduce or eliminate the risks and minimize the likelihood of errors and prevent their reoccurrence.

PRINCIPLES OF cQRM:

1. Risk evaluation based on scientific knowledge and experience of process
2. Dynamic QRM, iterative and responsive to change
3. The level of effort, formality and documentation of the QRM process should commensurate with the level of risk
4. Continual improvement and enhancement

OBJECTIVES OF cQRM:

The key objectives of the cQRM included the following:

- Proactive Risk Management
- Provide guidance on regulatory requirements of Quality Risk Management in clinical trials
- Regulatory Compliance
- Focus on Patient Safety
- Rights and wellbeing of trial subjects
- Ethical conduct of trial
- Data Integrity & Quality
- Budgeting & Timely completion of trial
- Continual Improvement
- Provide guidance on relationship of QRM to clinical quality systems

QUALITY RISK MANAGEMENT PROCESS:

Effective QRM implementation helps in identifying potential risks, root causes, assessing possible consequences and their prevention. QRM should be appropriately defined in the organization’s quality management system. Executive Management should be involved in the identification and implementation of QRM principles within the organization. QA is responsible for training and implementation of QRM in
the organization. Project managers are responsible for developing project specific risk management plans prior to start of trial in association with concerned project stakeholders and the same should be verified and approved by QA and Sponsor. The QRM process should be reviewed at regular intervals as part of the quality systems review (along with Customer feedback, complaints, deviations, violations etc.).

Risk Management (RM) is the process of measuring or assessing, risk and developing strategies to manage it. All risks can never be fully avoided or mitigated simply because of financial and practical limitations. In other words, organization has to accept level of residual risks. In ideal RM, a prioritization process followed whereby risk with the greatest loss and the greatest probability of occurring are handled first. Risks with lower probability of occurrence and lower loss are handled later applying clinical risk management. Need to perform the following minimal steps: Identify > Analyze > Plan> Control> Track> Communicate.

KEY ATTRIBUTES OF RISK ASSESSMENT:

Clearly identify the process being assessed and what it is attempting to achieve, what the risk is and what the impact could be on the clinical trial.

- systematic identification of possible risk factors
- take full account of current scientific knowledge
- QRM by people with experience in the risk assessment process and the process being risk assessed
- use factual evidence supported by expert assessment to reach conclusions
- do not include any unjustified assumptions
- identify all reasonably expected risks – simply and clearly along with a factual assessment and mitigation where required
- QRM documentation and control
- ultimately be linked to the protection of the patient
- risk mitigation plans should be objective

Risk Assessment Fig. 01
cQRM (clinical Quality Risk Management)

Risk Analysis criteria Fig.02

Risk Communication

Initiate Quality Risk Management (QRM) Process

Risk Assessment
- Risk Identification
- Risk Analysis
- Risk Evaluation

Risk Control
- Risk Reduction
- Residual Risk Evaluation/Acceptance

Output of the QRM process

Risk Review
- Review Events

Unacceptable or new risks

Life cycle approach
Based on process knowledge
Standardised first step to ensure consistency of approach
Transparent system
Streamlined and iterative
Flexible tool choice depending on scenario
Initiation of a site wide risk register
Automatic roll up of risk from the ongoing RA’s to the Risk dashboard

Quality Risk Management Process Fig.03
cQRM IN CLINICAL TRIALS:

cQRM implementation in clinical trials will result successful completion of clinical trials. Prior to start up of any clinical trials, concerned project manager and QA should facilitate QRM meeting with concerned stakeholders to identify potential risks, search for and locate risks before they become problems. Make sure risks are broken down to sufficient degree and potential root causes are identified. Risk identification will be performed using following methods:

- reviewing metrics from prior studies
- brainstorming sessions
- review warning letters and other reports of inspectional findings

Using above risk identification methods, Project Manager will prepare the project specific Risk Management Plan along with the risk mitigation and contingency plans. Typical clinical project risk management plan should address the following risk indicators:

Risk indicators:

- **Regulatory approvals**
  Ensure dossier preparation as per the regulatory requirements, if any substantial amendments should be implemented after Regulatory approvals

- **IRB/IEC approvals**
  IRB/IEC approval timelines for CTA (Clinical Trial Application) review and approval

- **Enrollment**
  Assess patient enrollment challenges involved in the clinical trial prior to site initiation

- **Patient safety**
  Ensure the patient safety throughout the trial and provide alternative treatments or standard of care to patients in case of any safety issues

- **Reporting of SAEs (Serious Adverse Events)**
  Ensure prompt reporting of any serious or unexpected risks or problems to the IRB/IEC and applicable regulatory bodies. Investigation and follow-up of all possible study-related adverse events

- **Data and safety monitoring**
  Appropriate oversight and monitoring of clinical trials to ensure patient safety and integrity of the data

- **Monitoring**
  Ensure subject safety and wellbeing. Monitoring should be commensurate with risks and complexity of the trials

- **Deviations/violations**
  All deviations and violation should be notified to IRB/IEC within the stipulated timelines, as applicable the same should be notified to applicable Regulatory Agencies

- **Timelines & milestones**
  Ensure project timelines are realistic and adequate to complete the study

- **Resources**
Ensure adequate resources and duties are allocated to qualified personnel

- **Data management**
  
  Ensure validated data management plan is in place

- **IP (Investigational Product) Management**
  
  Ensure Investigational Product shipment, storage, dispensing, retention/destruction in compliance with study protocol and applicable regulatory requirements.

- **Audits**
  
  Ensure validated QA plan is in place to conduct study audits and/or to facilitate regulatory inspections

- **Study compliance**
  
  Forecast possible protocol deviations and violations prior to start of clinical trial and develop risk management plans to handle them

- **Finance & Accounts**
  
  Ensure clinical trial budget is adequate

- **Increased variability in:**
  
  - Investigator experience
  - Ethical oversight
  - Site infrastructure
  - Treatment choices/standard of care
  - Site geographic dispersion

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**Risk indicators covering key quality issues**

cQRM “Risk indicators” in Trial Management Process Fig.04
INTEGRATION OF cQRM WITH QMS:

Recent regulatory requirements mean that organizations are now expected to integrate Quality Risk Management (QRM) into their current quality system. QRM can be used to either help with making decisions about events that have happened in the past or to evaluate change and come to a decision (i.e. reducing the level of validation). In each case, the outcomes should be based on data and any other relevant information.

Integration of QRM into QMS is a novel approach, it is extremely important that QRM is properly integrated into your current quality system and not used in isolation. QRM procedures should be integrated with the quality system and apply to risk assessments. The QRM standard operating procedure (SOP) should define how the management system operates and its general approach to risk management. It should include scope, responsibilities, controls, audits, diagnostic tools, approvals, management systems, applicability.

BENEFITS OF cQRM:

- cQRM increases the clinical data quality and reduce non-conformances, deviations, CAPA, rework, scrap, complaints, etc
- Is an iterative and continuous process where prior risks that became problems are either mitigated or recognized and reviewed in a predictive manner for the future.
- Provides a mechanism for risk communication (formalized vehicle/process) and exposure to management
- Provides a framework to better understand processes, what is critical and why
- Helps provide rationale for not spending time on low risk activities, process events, or systems, rather focusing resources and time on the things that are really important

CONCLUSION:

cQRM is a proactive approach to identify potential risks, systemic issues early before they become problems and tracks the data over time, which allows for addressing issues. It helps in reducing overall costs by enabling qualified decision making in the planning stage.

REFERENCES:

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7. GAMP Good Practice Guide ISPE, 2005- A risk-based approach to compliant electronic records and signatures
8. ISO 14971:2007 - Application of Risk Management to Medical Devices