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From Design to Execution: Quality-Driven Clinical Trials in ICH E6(R3)

Designing Clinical Trials with Quality in Mind: Applying QbD Under ICH E6(R3)

Dr. Seong Yun Bang

CEO, Chief Consultant at SB SMART Consulting

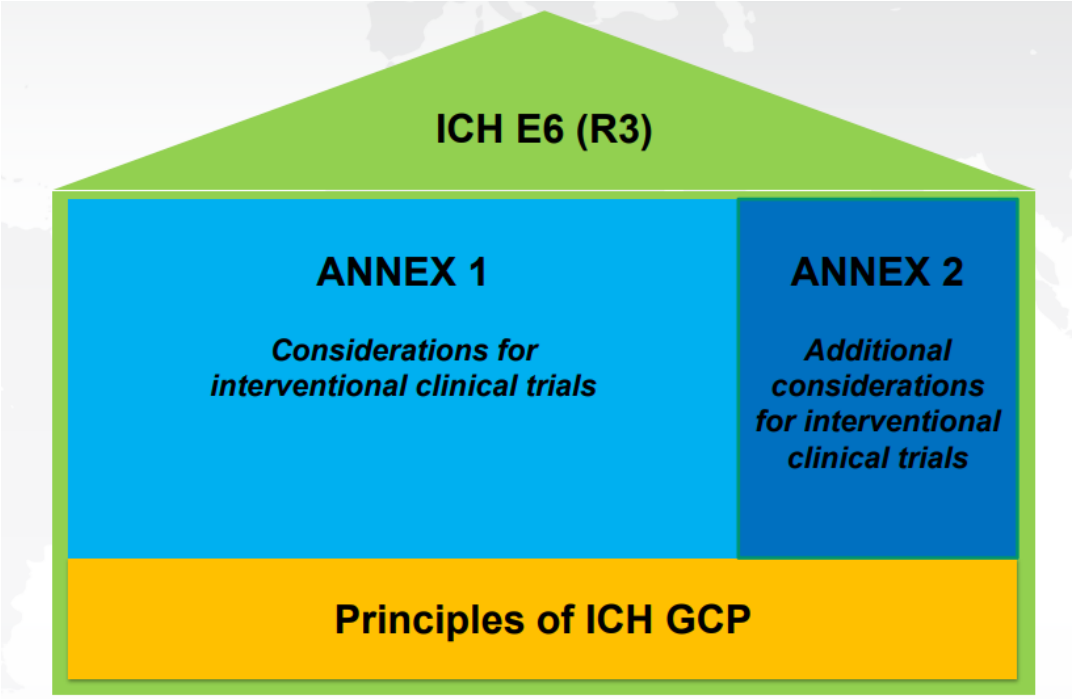
Agenda

- ICH E6(R3)'s updated direction/principles
- Core Concepts of Quality in ICH E6(R3)
- 'Designing Clinical Trial' Applying QbD Under ICH E6(R3) +E8
- Implementing the QbD concept in clinical trial design

ICH E6(R3)'s updated direction/principles

ICH E6 R3 Background & Understanding of New Structure

The ICH E6(R3) guideline is the latest revision of the International Council for Harmonization's (ICH) Good Clinical Practice (GCP) guidelines, focused on modernizing clinical trial conduct.



- Annex 2 is not intended to be comprehensive of all clinical trial design elements or data sources
- It Should be read in conjunction with the ICH E6(R3) Principles and Annex 1 document
- It addresses the GCP considerations that arise from the increased use of a wider range of design elements and data sources.
- It has its foundations in the key concepts of quality-by-design, fitness for purpose and risk proportionality.
- Annex 2 does not endorse specific design elements or data sources

Key Changes in E6(R3) Vs. (R2)

Direction

- It emphasizes a **more flexible, risk-based, and participant-centered approach, while maintaining data integrity and subject safety.**

  - ✓ R2: Focused on monitoring and documentation
  - ✓ R3: Adds patient-centered, flexible, and tech-friendly approach
    QbD explicitly introduced in R3

Key Changes in E6(R3) Vs. (R2)

Category	ICH E6(R2)	ICH E6(R3)
Purpose of Revision	Integration of a risk-based approach	Emphasis on patient-centricity, adaptation to the digital era, and strengthened quality by design
Quality Concept	**Mention of Quality Management System**	**Clear introduction and emphasis on Quality by Design (QbD)**
Critical to Quality (CtQ) Elements	**Not clearly defined**	**Identification and strong emphasis of CtQ elements**
Risk Management	**Focus on risk-based monitoring**	**Risk-based quality planning initiated from the design stage**
Continuous Quality Improvement	**Mentioned minimally**	**Introduction of the concept of continuous improvement**

Key Changes in E6(R3) Vs. (R2)

Category	ICH E6(R2)	ICH E6(R3)
Patient-Centricity	Limited mention	Explicit description of patient-centricity
Adoption of Technology	Indirect mention; lacks specificity	Promotion of digital tools, including eConsent and eSource
Vendor Management	Oversight emphasized	Strengthened procedures for vendor selection, contracting, and ongoing management
Flexibility	Document-centered, procedure-oriented	Permits output-oriented and flexible processes
Documentation Requirements	Emphasis on SOPs, reports, etc.	Flexibility allowed through “necessary documentation”

Core Concepts of Quality in ICH E6(R3)

What is ‘Quality’ in Clinical Trials?

- **Quality is ultimately about maintaining data integrity, participant protection, and protocol compliance during/in clinical trial.**

- ICH E6(R3) emphasize **more proactive approach** to avoid deviations, violations, errors and to minimize unexpected events and results **; Quality starts at the design phase, not just monitoring.**

- Most of all, data integrity, participant protection, and protocol compliance are interconnected and mutually reinforcing. (interconnectedness)

Proactive Approaches in Clinical Trial

What are the proactive approaches in clinical trials ?

- **1. Risk Assessment and Planning:**
  - Identify Potential Issues
  - Develop Preventative Measures
  - Plan for Contingencies
- **2. Clear Communication and Training:**
  - Communicate Expectations
  - Provide Comprehensive Training
  - Foster Open Communication

Proactive Approaches in Clinical Trial

What are the proactive approaches in clinical trials ?

3. Continuous Improvement:

- Monitor and Evaluate
- Analyze Deviations and Errors
- Implement Corrective and Preventative Actions (CAPA)
- Regularly Review and Update

4. Human Factors and Culture:

- Consider Human Limitations
- Promote a Culture of Safety
- Leadership Commitment

What is QbD(Quality by Design) ?

In ICH E6(R3),

Quality by Design (QbD) is a fundamental principle that emphasizes building quality into clinical trials *from the outset, rather than relying on retrospective checks.*

- ✓ **It involves proactively identifying and addressing critical-to-quality (CtQ) factors that are essential for participant safety and the reliability of trial results.**
- ✓ **This approach promotes a more efficient, reliable, and regulatory-aligned trial design.**

Core Elements of QbD in Clinical Trials

- **Proactive Quality Management:**

QbD shifts the focus from reactive quality control to proactive quality planning and management.

- **Identifying 'Critical to Quality' Factors:**

Sponsors are expected to identify, prospectively, the factors that are essential for ensuring the quality of a clinical trial.

- **Risk-Based Approach:**

QbD aligns with a risk-based approach, where trial oversight is tailored to the complexity and risk level of the trial.

Core Elements of QbD in Clinical Trials

- **Fit for Purpose:**

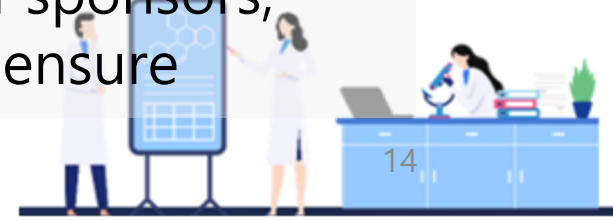
ICH E6(R3) encourages a "fit for purpose" approach, where trial designs are tailored to the specific objectives of the study.

- **Flexibility and Adaptability:**

The guideline recognizes that not all trials are the same and encourages flexibility in trial design, methodology, and technology.

- **Stakeholder Collaboration:**

QbD principles emphasize the importance of collaboration between sponsors, researchers, and other stakeholders to optimize trial execution and ensure quality.



What is ‘Critical to Quality’ Factors ?

Critical to Quality (CtQ) factors, as defined in ICH E8(R1),

CtQ Factors are aspects of a clinical study that are essential to **its integrity, reliability, and ethical conduct.**

It emphasizes the importance of integrating quality into all aspects of the clinical trial process, from initial planning to final reporting.

These factors, when properly identified and managed, ensure that the study can reliably answer its research questions, protect participants, and support sound decision-making based on the study's findings.

Examples of CtQ Factors(1)

- **Protocol Design:**

A well-defined protocol that clearly outlines the study objectives, methodology, and procedures is crucial. ; including the selection of appropriate endpoints, inclusion/exclusion criteria, and statistical analysis plan.

- **Investigational Product:**

The quality, characterization, and stability of the investigational product are critical, particularly in later-stage clinical trials.

- **Data Management:**

Robust data management processes, including data collection, storage, and analysis, are essential for ensuring data integrity and reliability.

Examples of CtQ Factors(2)

- **Participant Safety:**

Adequate safety monitoring plans, including the identification and reporting of adverse events, are vital for protecting participants.

- **Training and Qualification:**

Proper training and qualification of study personnel are essential for consistent and accurate execution of the study protocol.

- **Monitoring and Auditing:**

Regular monitoring and auditing of study sites and data are necessary to ensure adherence to the protocol and identify potential issues.

How to Identify and manage CtQ Factors

- **Define the Primary Objective:**
  - Clearly articulate the main goal of the clinical trial. ; What are you trying to prove or demonstrate?

- **Identify Critical Data and Processes:**
  - Determine which data points are crucial for assessing the primary and key secondary endpoints.
  - Identify processes that are critical to generating reliable data and ensuring participant safety.

- **Understand Stakeholders Needs:**
  - Consider who the “stakeholders" of the clinical trial are. This includes patients, physicians, regulatory bodies, and sponsors.
  - What are their expectations regarding the trial's outcome, safety, and conduct?

How to Identify and manage CtQ Factors

- **Engage Stakeholders:**
  - Involve various stakeholders (investigators, site staff, patients, regulators, sponsors) in the identification process.
  - Their input can provide diverse perspectives and help identify potential risks and challenges.

- **Risk Assessment**
  - Conduct a thorough risk assessment to identify potential hazards that could impact data integrity or patient safety.
  - Use tools like Failure Mode and Effects Analysis (FMEA) to identify potential failure points and their impact.

- **Develop Quality Tolerance Limits (QTLs):**
  - Establish specific thresholds for key parameters (QTLs) that, if exceeded, may indicate a significant issue.
  - QTLs should be defined early in the trial and monitored throughout its duration.

How to Identify and manage CtQ Factors

- **Document CtQ Factors:**
  - Create a document that outlines all identified CtQ factors, their rationale, and associated risks.
  - This document should be used to guide trial planning, execution, and monitoring.
- **Incorporate CtQ Factors into Study Documents:**
  - Integrate the identified CtQ factors into essential documents like the protocol, informed consent, and monitoring plan.
  - Continuous Monitoring and Improvement:
  - Regularly monitor the trial against the defined CtQ factors and QTLs.
  - Use the monitoring data to identify trends and areas for improvement.

‘Designing Clinical Trial’

Applying QbD Under ICH E6(R3)+E8

- ICH Efficacy guidelines are an integrated set of guidance covering the planning, design, conduct, safety, analysis, and reporting of clinical studies.
- Relevant Guideline : E6(Good Clinical Practice), E8(General consideration for clinical studies), E9(Statistical Principles for Clinical trial)

What is ‘Designing Clinical Trial’ ?

The primary goal of clinical trial design IS

- To rigorously assess **the efficacy and safety of a new intervention (drug, treatment, device, etc.) while minimizing bias and maximizing the potential for generalizable results.**

- The critical pathway involves **a series of interconnected activities** that, when executed effectively, ensure the trial proceeds efficiently and yields reliable data.

* By carefully managing the critical pathway activities, clinical trial design can optimize the research process, minimize risks, and ultimately contribute to the development of new and effective treatments for diseases.

Key Goals of Clinical Trial Design

- **Efficacy Assessment:**
  - Determining whether the intervention produces the intended effect and is superior, non-inferior, or equivalent to a standard treatment or placebo.
- **Safety Assessment:**
  - Identifying potential adverse effects and characterizing the safety profile of the intervention.
- **Risk-Benefit Ratio Evaluation:**
  - Determining if the benefits of the intervention outweigh its risks, guiding clinical decision-making.
- **Generating Knowledge:**
  - Contributing to the broader understanding of the disease, its treatment, and human biology.
- **Guiding Further Research:**
  - Providing evidence to support or refute hypotheses and informing future research directions.

Critical pathway activities in clinical trial ?

These include:

- Protocol Development
- Ethical/Regulatory Review and Approval
- Site Selection and Preparation
- Participant Recruitment and Enrollment
- Data Collection and Management
- Data Analysis and Interpretation
- Reporting and Dissemination
- Next step of clinical development(if any)

It could be more… depending on the ultimate purpose of the clinical trial.

Critical Pathway Should be.

- A series of interconnected steps that must be completed in a logical sequence to avoid delays and ensure the trial's success.

- By appropriately managing the critical pathway activities, clinical trial design can optimize the research process, minimize risks, and ultimately contribute to the development of new and effective treatments(drug, device, new treatment methods) for diseases.

Key aspects of clinical trial design under ICH E6(R3):

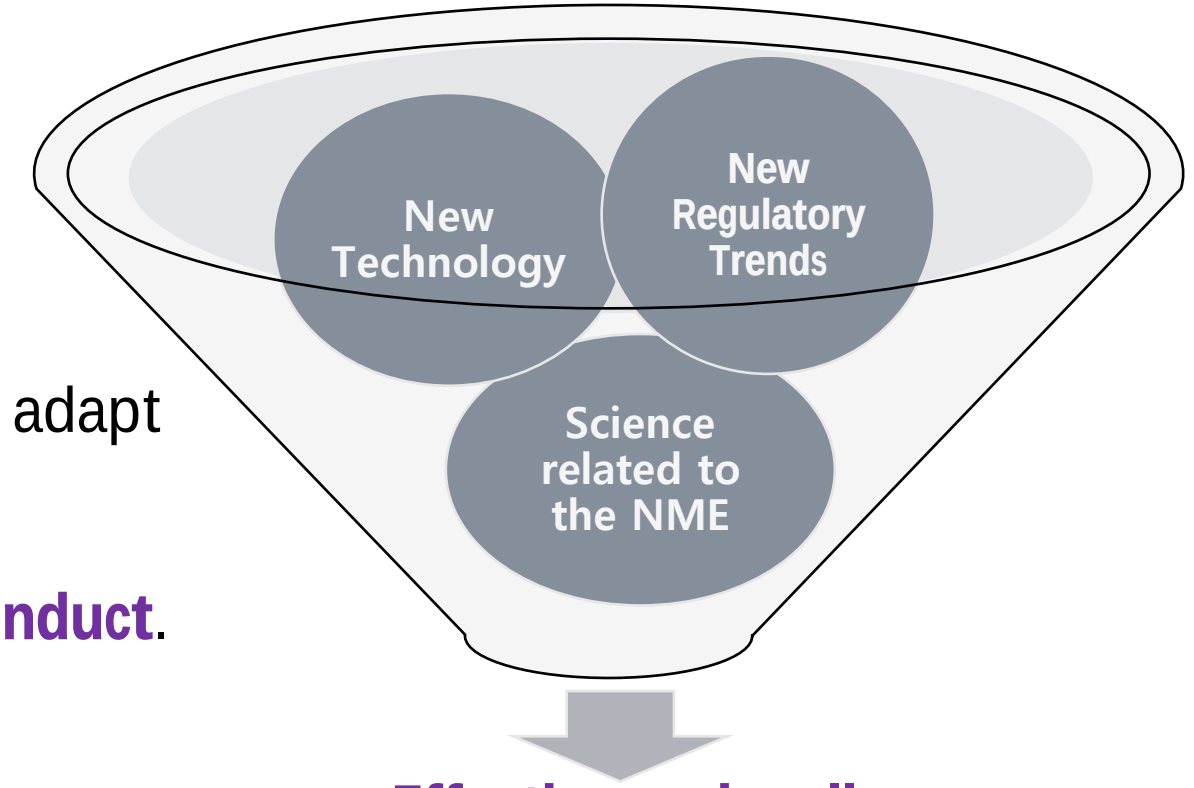
- **Quality by Design (QbD):**
  - Sponsors should integrate quality considerations throughout the trial lifecycle, from planning to execution, rather than relying on retrospective checks.
- **Risk-Based Approach:**
  - Sponsors need to identify and manage risks associated with the trial, tailoring oversight and monitoring strategies accordingly.
- **Flexible Designs:**
  - ICH E6(R3) encourages the use of flexible trial designs, including decentralized and pragmatic trials, to adapt to specific patient populations and therapeutic areas.
- **Transparency and Communication:**
  - Sponsors are expected to foster open communication and transparency among all stakeholders, including participants.

Key aspects of clinical trial design under ICH E6(R3):

- **Patient-Centricity:**
  - ICH E6(R3) emphasizes the importance of patient involvement and engagement in trial design and conduct.
- **Sponsor Oversight:**
  - While sponsors can delegate tasks, they remain ultimately accountable for trial conduct, data quality, and participant safety.
- **Data Governance:**
  - Sponsors should establish robust data governance practices to ensure data integrity and reliability.
- **Stakeholder Collaboration:**
  - Effective communication and collaboration among sponsors, investigators, CROs, and other stakeholders are crucial for successful trial conduct.

Flexibility, Flexible Trial Design

Flexible trial design refers to the ability to adapt the trial protocol and conduct **based on evolving needs and circumstances,** while maintaining **scientific rigor and ethical conduct**.



Options(examples) for Flexible Trial Design

- Flexible trial design refers to the ability to adapt the trial protocol and conduct based on evolving needs and circumstances, while maintaining scientific rigor and ethical conduct.

  •Adaptive Designs:

  Adjusting trial parameters (e.g., sample size, treatment arms) based on accumulating data.

  •Decentralized Trials (DCTs):

  Utilizing remote monitoring, digital technologies, and virtual visits to reduce the burden on participants.

  •Pragmatic Trials:

  Conducting trials in real-world settings to assess the effectiveness of interventions in routine clinical practice.

Another relevant guideline for clinical trial designing, ICH E8

- ICH E8 **GENERAL CONSIDERATIONS FOR CLINICAL STUDIES.**

  - ICH E8 provides an overall introduction to clinical development, designing quality into clinical studies and focusing on those factors critical to the quality of the studies.

  - The guidelines should be considered and used in an integrated, holistic way rather than focusing on only one guideline or subsection.

It emphasizes related to clinical trial design and plan

- ✓ ***Scientific Approach in Clinical Study Design, Planning, Conduct, Analysis, and Reporting***
- ✓ ***Patient Input into Drug Development***

Another relevant guideline for clinical trial designing, ICH E8

- ICH E8(general consideration for clinical studies) provides more practical consideration of CtQ factors from the beginning of clinical development plan, through designing clinical study

Major relevant topics in E8

- **Drug Development Planning**
- **Designing Quality into Clinical Studies : QbD, Critical to Quality Factor, Consideration in identifying CtQ factors**
- **Design elements and data sources for clinical studies**

Another relevant guideline for clinical trial designing, ICH E8

- E8 explains about ‘Good planning and implementation of a clinical study’ ; also derive from attention to the design elements of clinical studies as described in Section 5, such as:

  - the need for clear pre-defined study objectives that address the primary scientific question(s);
  - selection of appropriate participants that have the disease, condition, or molecular/genetic profile that is being studied;
  - use of approaches to minimize bias, such as randomization, blinding or masking, and/or control of confounding;
  - endpoints that are well-defined, measurable, clinically meaningful, and relevant to patients.

Implementing the QbD concept in clinical trial design

; Sponsor’s perspective

Sponsor's Considerations for QbD implementation

- ICH E6(R3)'s principles include the need for a shift in mindset **from compliance-focused monitoring** to **proactive risk management** including the potential need for significant investments in new technologies and infrastructure.

- **Additionally, sponsors may face challenges in adapting to new oversight expectations, updating SOPs, and ensuring vendor systems support data traceability and risk-based data monitoring**

Potential obstacles

- **Mindset Shift and Integration of QbD:**

  - **From Compliance to Risk:**

ICH E6(R3) emphasizes a risk-based approach, requiring a shift in focus from solely ensuring compliance to proactively identifying and mitigating risks throughout the trial. This requires a change in how sponsors approach trial planning, execution, and oversight.

  - **Integrating QbD:**

Sponsors need to embed QbD principles into the very fabric of their trials, from design and planning to execution and closeout. This demands a more integrated and proactive approach, rather than viewing QbD as a separate add-on.

Potential obstacles

- **Oversight and Vendor Management:**

  - **Strengthened Oversight:**

  ICH E6(R3) increases expectations for sponsor oversight, even when tasks are delegated to vendors. Sponsors need to ensure robust oversight mechanisms are in place for all outsourced activities.

  - **Vendor System Integration:**

  Many vendors' systems may not be readily compatible with the data traceability and risk-based monitoring requirements of ICH E6(R3). Sponsors need to carefully assess vendor systems and ensure they can meet the new requirements.

Potential obstacles

- **Data Management and Technology:**

  - **Data Traceability:**

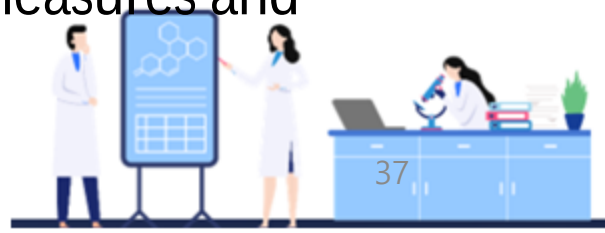
Ensuring data traceability throughout the trial, especially with increasing reliance on vendors and technology, is a major challenge. Sponsors need to ensure data collected and managed by vendors is easily traceable and auditable.

  - **System Inventory and Validation:**

Sponsors need to maintain a comprehensive inventory of all computerized systems used in the trial, detailing their purpose, validation status, and security measures.

  - **Cybersecurity and Data Security:**

The increased reliance on technology necessitates robust cybersecurity measures and data security protocols to protect sensitive trial data.



Potential obstacles

- **Training and Resources:**

  - **Training Gaps:**

  Implementing ICH E6(R3) requires specialized training for sponsor personnel on new regulatory expectations, risk-based approaches, and QbD principles.

  - **Resource Allocation:**

  The increased demands on sponsors, including more rigorous oversight, risk management, and technology investments, may require additional resources and personnel.

Potential obstacles

- **Adapting Processes and SOPs:**

  - **Updating SOPs:**

  Sponsors need to review and update their standard operating procedures (SOPs) to align with the risk-based and proactive approach mandated by ICH E6(R3).

  - **Process Redesign:**

  Implementing QbD principles may require redesigning existing processes to ensure they are efficient, effective, and aligned with the new guidelines.

Conclusion

In essence, implementing ICH E6(R3) requires a fundamental shift in how sponsors approach clinical trials, moving from a reactive, compliance-focused approach to a proactive, risk-based approach that leverages QbD principles throughout the trial lifecycle.

This shift will necessitate investments in training, technology, and process redesign to ensure compliance and achieve the intended benefits of the new guideline.

Thank you for listening.

If any question about ICH E6(R3) and clinical trial planning, please email me.

- ***Bang Seong Yun(Sally Bang), bangsy0@gmail.com***