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2025 Global Harmonization Center Clinical Trials Webinar
From Design to Execution: Quality-Driven Clinical Trials in ICH E6(R3)

Ensuring Quality in Action:

Risk-Based Monitoring and QMS in Practice

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Disclaimer

This presentation reflects the experience and opinions of the presenters and should not be attributed to IFPMA or any organization with which the presenter is employed or affiliated.

Introduction

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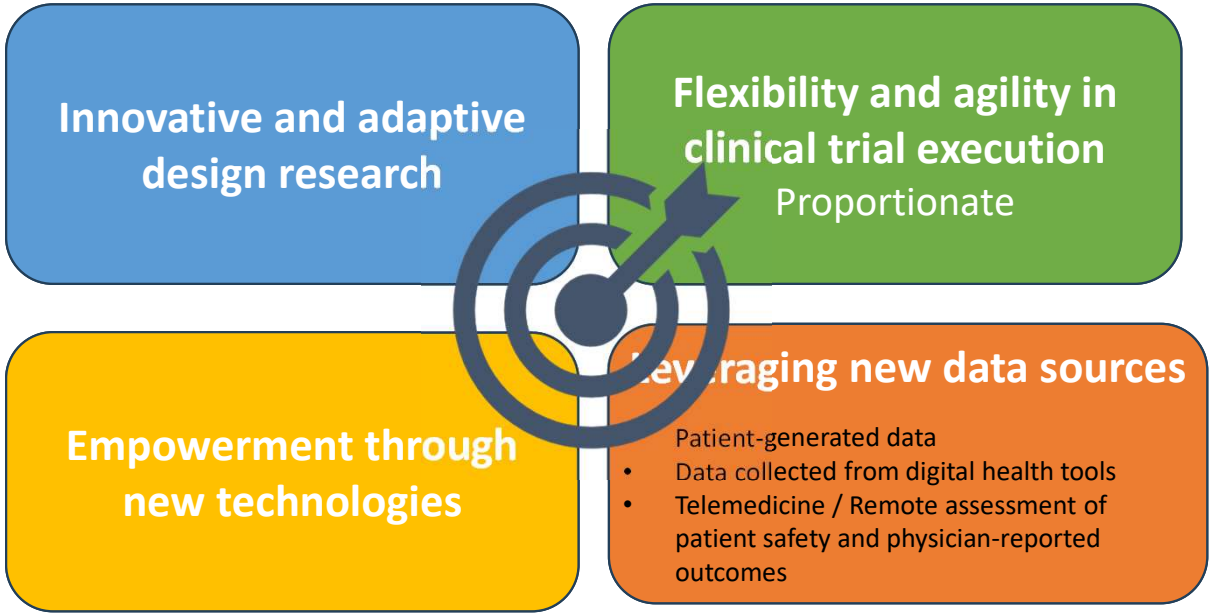
IFPMA E6(R3) Implementation Taskforce Member
18 years industry experience in Pfizer, Sanofi, Biotech
CMAC Clinical Operation and Quality Committee Member
Trainer of Study Risk Management in China Industry
China 1st DCT college strategic leader
Northwestern Kellogg University-Peking University EMBA
Peking University, Master

Agenda

- E6(R3) key changes related to risk-based monitoring and QMS
- Case sharing for risk-based monitoring
- Case sharing for QMS/cQMS

Reasons for the changes in the Transformation of ICH GCP



ICH Reflection on " GCP Renovation " (Jan 2017)

E8 Revision

- General road-map to incorporate fit-for-purpose, QBD, CTQ
- Specify comprehensive cross-references between ICH guidelines (such as ICH E5, E6, E17, E9, M3, and Series S, etc.)

E6 Revision

- Applying the foundation of E8, holistically address the planning and conduct of different types of clinical trials
- Allowing flexibility, proportionate to the risks

Background for the revision

E8 – integrating QbD into study design and conduct

↕

E6 – Applying the foundation of E8 to the conduct of clinical trials

Do not read E6(R3) in isolation

- **E6: Good Clinical Practice (GCP) – finalised in 1996**
  - Described the responsibilities of investigators and sponsors and expectations of interested parties in the conduct of clinical trials;
  - Covered aspects of monitoring, reporting, and archiving of clinical trials; and
  - Included sections for essential documents and investigator brochures
- **E6(R2) – finalised in 2016**
  - Included integrated addendum to encourage implementation of improved and more efficient approaches to GCP, while continuing to ensure human subject protection; and
  - Updated standards for electronic records.
- **E6(R3) – finalised in 2025**
  - Grounded in the foundational principle of Quality by Design (QbD)
  - Involves critical thinking
  - Utilises proportionate, risk-based approaches
  - Recognises that a one size does not fit all.

Declaration of Helsinki-2024
Origins of GCP

Data source : ICH EWG training material

E6(R3) Revised Structure

E6(R3) Guideline

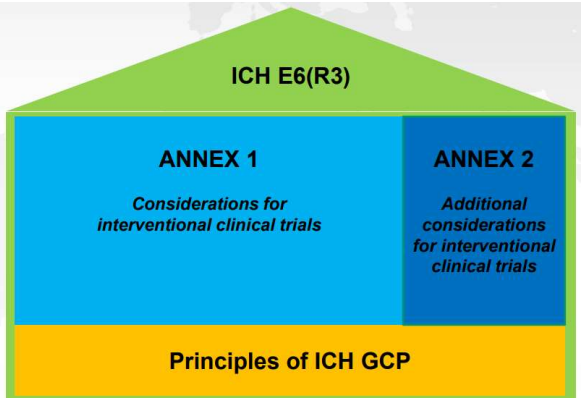
E6(R3) Principles and Annex 1 replacing E6(R2)

- **I. INTRODUCTION**
- **II. PRINCIPLES OF ICH GCP**
- **III. ANNEX 1**
  1. Institutional Review Board/Independent Ethics Committee (IRB/IEC)
  2. Investigator
  3. Sponsor
  4. Data Governance – Investigator and Sponsor
- **APPENDICES**
  - Appendix A. Investigator's Brochure
  - Appendix B. Clinical Trial Protocol and Protocol Amendment(s)
  - Appendix C. Essential Records for the Conduct of a Clinical Trial
- **GLOSSARY**

ANNEX 2 – *under public consultation from November 2024 to March 2025*

Data source : ICH EWG

What's new for E6(R3) regarding RBM&QMS



- Included language to facilitate innovations in clinical trial design, technology and operational approaches
- Set a foundation for practical/feasible expectation (through adoption of QbD and proportionate risk-based approaches) for responsibilities of sponsor and investigators in evolving clinical trial ecosystem
- Encourage fit-for-purpose approaches
  - Proportionality and risk-based approaches with a focus on the clinical tri al's critical to quality factors
  - Thoughtfulness in the design and conduct
- Avoidance of unnecessary burden on participants and investigators
- Proportionality

Quality-by-Design

- **This concept is based on ICH E8 (R1) 'General Principles for Clinical Studies', subsection 3.1**

Quality is a primary consideration […] The likelihood that a clinical study will answer the research questions while preventing important errors can be dramatically improved through **prospective attention to the design of all components of the study protocol, procedures, associated operational plans and training**. Activities such as document and data review and monitoring, where conducted retrospectively, are an important part of a quality assurance process; but, even when combined with audits, they are not sufficient to ensure quality of a clinical study.[…]

- **New Principle 6, aligning ICH E8 (R1) with ICH E6 (R3)**

6. **Quality should be built into the scientific and operational design and conduct of clinical trials.**
6.1 **Quality** of a clinical trial is **considered** in this guideline **as fitness for purpose**.
6.2 Factors critical to the quality of the trial should be identified prospectively. These factors are attributes of a trial that are fundamental to the protection of participants, the reliability and interpretability of the trial results and the decisions made based on those trial results. **Quality by design involves focusing on critical to quality factors of the trial in order to maximise the likelihood of the trial meeting its objectives.**
6.3 […]

Fitness For Purpose – Examples From the Guideline

- **Annex 1, Chapter 3: Sponsor, section 3.1 Trial Design**

3.1.4 The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures and data collection. Protocols, data acquisition tools and other operational documents should be fit for purpose, clear, concise and consistent. The sponsor should not place unnecessary burden on participants and investigators.

- Annex 1, 3.9.5. **The range and extent of oversight** measures should be fit for purpose and tailored to the complexity of and risks associated with the trial. […]

- Annex 1, 3.16.1(d) The sponsor should ensure that **data acquisition tools** are fit for purpose and designed to capture the information required by the protocol. They should be validated and ready for use prior to their required use in the trial.

- Annex 1, 3.16.1(v) For **systems used or deployed by the investigator/institution**, assess whether such systems, if identified as **containing source records** in the trial […] are fit for purpose or whether the risks from a known issue(s) can be appropriately mitigated.

Avoidance of Unnecessary Burden
- Examples From the Guideline

- **Annex 1, 3.11.4 Monitoring**

Some of these monitoring activities (e.g., centralised monitoring) may be conducted by different methods. […] The monitoring approach should consider the activities and services involved, including decentralized settings,

- Annex 1, 3.11.4.1 Investigator site monitoring

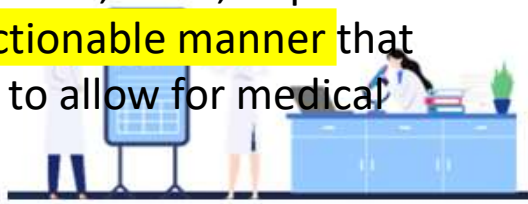
[…] The frequency of monitoring activities should also be determined based on identified risks. Monitoring activities and their frequency should be modified as appropriate using knowledge gained.
. […] Monitoring may include remote and secure, direct read-only access to source records, other data acquisition tools and essential record retention systems.

- **Annex 1, 3.11.4.3 Monitoring Plan**

[…] The monitoring strategy should ensure appropriate oversight of trial conduct and **consider site capabilities and the potential burden.**

- **Draft Annex 2, section 3.9 Safety Assessment and Reporting**

3.9.1 Safety information in clinical trials **with decentralised and/or pragmatic elements** may [...] come from multiple sources. For example, some trials may capture information via remote visits, DHTS, EHRs, in-person visits or a combination thereof. [...] The safety information should be provided in an actionable manner that provides the investigator with an overview on the health status of the trial participant to allow for medical decision marking.



ICH E6(R2) 'Risk-based Quality Management' Concept

- **ICH E6(R2), coming into effect in the EU 14 June 2017, initiated the implementation of risk-based considerations to the processes used to manage a clinical trial.**

- **E6(R3) deep dive the reason why RBQM is needed, further advanced this concept**
  5.0 Quality Management
  The sponsor should implement a system to **manage quality throughout all stages of the trial process.** Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the **design of efficient clinical trial protocols and tools and procedures** for data collection and processing, as well as the collection of **information that is essential to decision making.**The methods used to assure and control the quality of the trial should be **proportionate to the risks** inherent in the **trial and the importance of the information collected.**

Linking 'Risk-based Quality Management' with 'Quality By Design'

- **ICH E8(R1), coming into effect in the EU 14 April 2022, complemented the E6(R2) requirement in relation to the 'design of efficient clinical trial protocols' by implementing critical-to-quality factors for study design**

Engagement of stakeholders (including patients)
Benefit/risk of the investigational product and trial interventions
Study objectives & meaningful clinical study design, e.g. relevant eligibility criteria, feasibility
Protection of participants' rights and safety (Informed Consent, IRB/IEC approval ...)
Qualification/training needs
Data collection needed to meet the study objectives
Minimization of bias (randomization, blinding)

Risk-based Approaches to Trial Management

- **Continuation of the E6(R2) RBQM concept**
  Annex 1, section 3. Sponsor, introduction

The responsibility of the sponsor entails the implementation of **risk-proportionate approaches** to ensure the rights, safety and well-being of the trial participants and the reliability of the trial results throughout the clinical trial life cycle.

- **chapter 7** [...] Clinical trial processes, measures and approaches should be implemented in a way that is **proportionate to the risks** to participants and to the importance of the data collected and that avoids unnecessary burden on participants and investigators.

7.1 Trial processes should be **proportionate to the risks inherent** in the trial and the importance of the information collected.

7.2 The focus should be on the **risks associated with trial participation**. For clinical trials involving patients, the focus should be on risks that go beyond those associated with usual medical care. The risks relating to investigational products that have a marketing authorization when used in the clinical trial context may differ from the usual care of patients and should be taken into consideration.

7.3 **Risks to critical to quality factors** should be managed proactively and adjusted when new or unanticipated issues arise once the trial has begun.

Risk-based Approaches to Quality Management

3.11.1 Quality assurance [...] includes implementing risk-based strategies to identify potential or actual causes of serious non-compliance with the protocol, GCP and/or applicable regulatory requirements to enable their corrective and preventive actions.
3.11.3 Quality control should be applied using a risk-based approach to each stage of the data handling to ensure that data are reliable and have been processed correctly. [...]

3.11.2 Audit
When performed, audits should be conducted in a manner that is proportionate to the risks associated with the c onduct of the trial (see section 3.10.1.1).
The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality contro l functions, is to evaluate whether the processes put in place to manage and conduct the trial are appropriate to e nsure compliance with the protocol, GCP and the applicable regulatory requirements.

4.2.3 Data Life Cycle Elements Procedures for review of trial-specific data, audit trails and other relevant metada ta […] should be risk-based, adapted to the individual trial and adjusted based on experience during the trial.

Proportionality

Re-emphasis of the E6(R2) proportionality concept

5.0.4. Risk control: The sponsor should decide which risks to reduce and/or which risks to accept. The approach used to reduce risk to an acceptable level should be **proportionate** to the significance of the risk.

ICH E6(R3), introduction

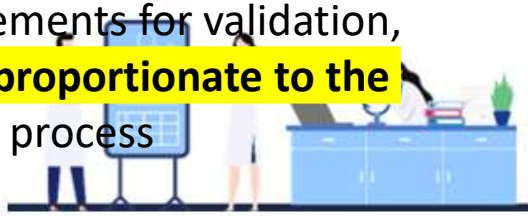
[…] **Clinical trial processes and risk mitigation strategies** implemented to support the conduct of the trial should be **proportionate** to the **importance of the data** being collected and the **risks to trial participant safety** and **data reliability**. […]

Annex 1, subsection 2.3.1 **The level of investigator oversight** of the delegated activities should depend on the nature of the delegated activities and be **proportionate** to the importance of the data being collected and the risks to trial participant safety and data reliability.

Annex 1, subsection 3.11.4.5.1 (d) **Actions taken in relation to the deviations, errors or omissions** should be **proportionate to their importance.**

Annex 1, subsection 3.12.1 **Noncompliance** with the protocol, SOPs, GCP and/or applicable regulatory requirements) […] **should lead to appropriate and proportionate action** by the sponsor to secure compliance.

Annex 1, subsection 3.16.1 (ii) […] **requirements for computerised systems** (e.g., requirements for validation, audit trails, user management, backup, disaster recovery and IT security) [...] should be **proportionate to the importance of the computerised system and the data or activities** they are expected to process



Risk-based Monitoring Progression

Traditional Monitoring:

- Onsite
- 100%SDV
- Manual review
- High cost

Risk-based Monitoring 1.0:

- Centralized, onsite, and remote monitoring
- "Targeted“ SDV/SDR
- Reduced costs
- One-size-fits-all approach

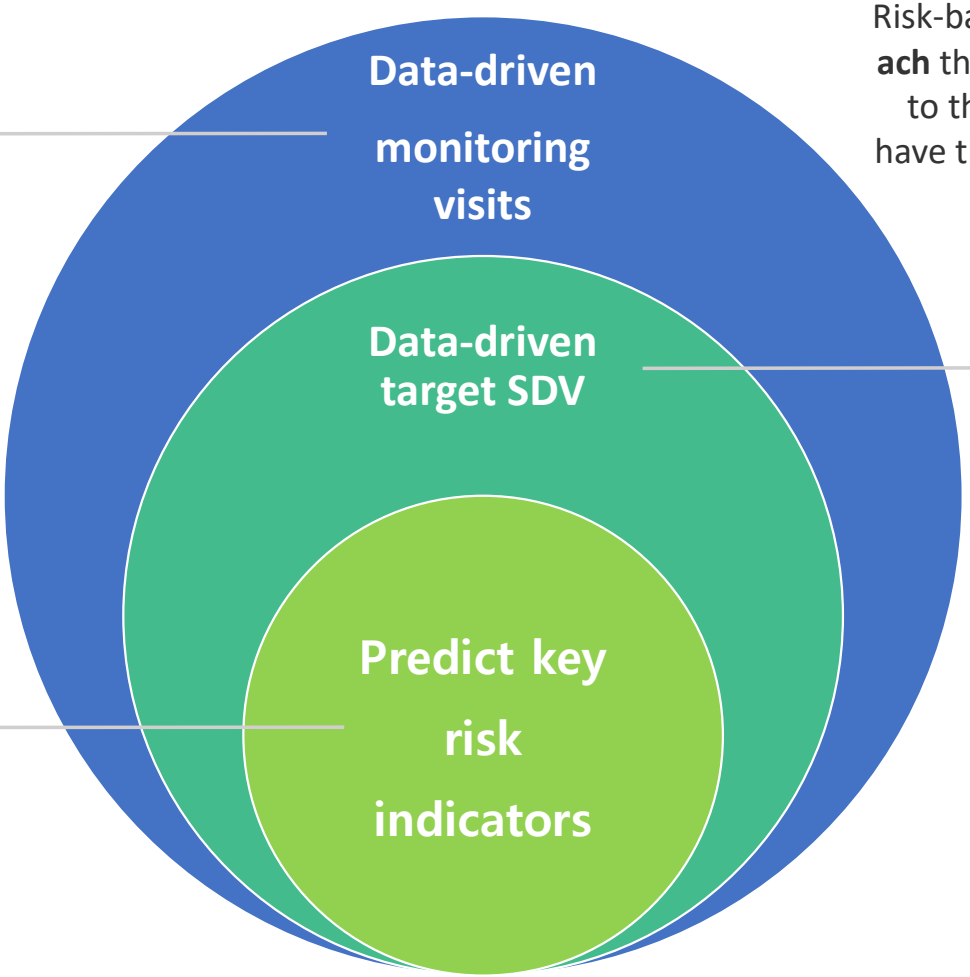
Data-Driven Monitoring (Risk-Based Monitoring 2.0):

- ICH E8/E6 revision+technology advance
- AI-enabled data-driven decision-making
- Proportionate, risk-based SDV/SDR
- Improved efficiency
- Precise monitoring

Before 2016	2016-2022	2023 and Beyond
100%SDV	50%SDV-25%SDV	Gradually follow global approach

Elements for Efficient Monitoring

Transform from fixed frequency to data-driven dynamic frequency



Risk-based monitoring (RBM), an **adaptive appro ach** that **directs monitoring focus and activities** to the evolving areas of greatest need which have the most potential to impact **patient safety and data quality--- *TransCelerate***

Transform from random SDV to risk-proportionate SDV

Proactively predict key risk indicators

SDV- proportionate to risks

Data transcription risk model

Define indicators

- Design KRIs
- Including incremental & cumulative analysis

Assess Risk level

- Assess the risk level of each patient and each indicator

Patient risk stratification

- Unsupervised machine learning model
- Consider the different stage

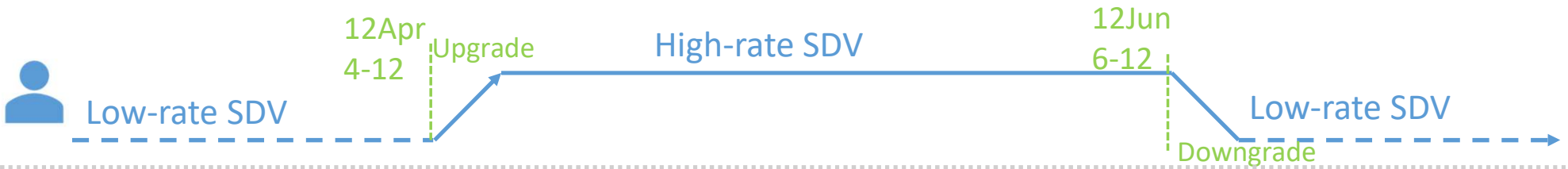
High risk - high rate of SDV
Low risk - low rate of SDV

Determine the site's SDV plan based on the site's his torical data → Dynamically adjust the SDV level based on the patient's real-time risk level → CRAs perform SDV based on RBM guide

Site selection and risk level preliminary assess

Case: Data-driven SDV

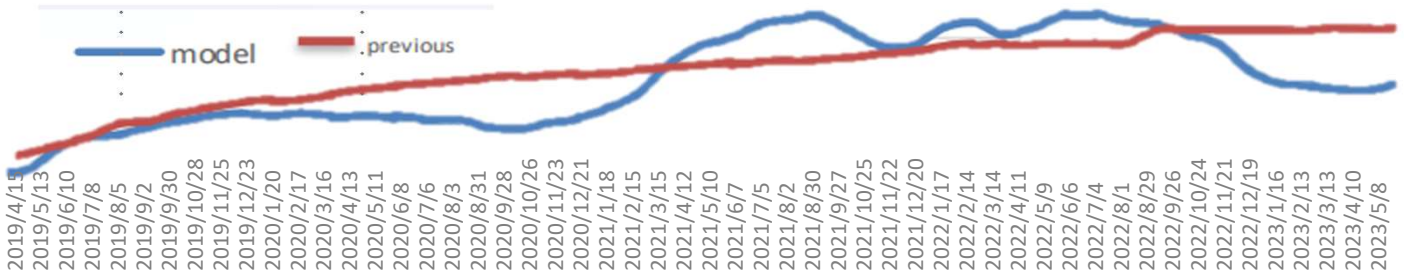
Targeted Source Data Verification (Patient Perspective)



SDV results

The CRA conducted SDV, identified critical missing data, requested the site to improve data entry, and ultimately resolved potential risks

Targeted Source Data Verification (Study Perspective)



Data source： coming from Sanofi sharing in CMAC

- A high rate of SDV is conducted on sites with risks to improve data quality.
- Compared with previous processes, non-essential SDV is reduced by 20%.

Case： Data-driven monitoring visit

Preparation

Critical processes
Critical data

- DMP, DVP, CMP
- Monitoring Plan (MP)
- RBM signal detect for site level over sight (Setup Instructions)

Implementation

Continuous risk assessment

- Predict the monitoring activities based on workload and risk factors
- Adopt a risk - based approach supported by RBM signal to focus efforts on the sites that are in the greatest need of monitoring/oversight

Site A

Onsite monitoring visit

Offsite monitoring visit

Onsite monitoring visit

Offsite monitoring visit

Predictive monitoring work

Evaluation Risk

Ad hoc monitoring visit

Site B

Onsite monitoring visit

Offsite monitoring visit

Onsite monitoring visit

Data source： coming from Sanofi sharing in CMAC

Risk–Based Quality Management

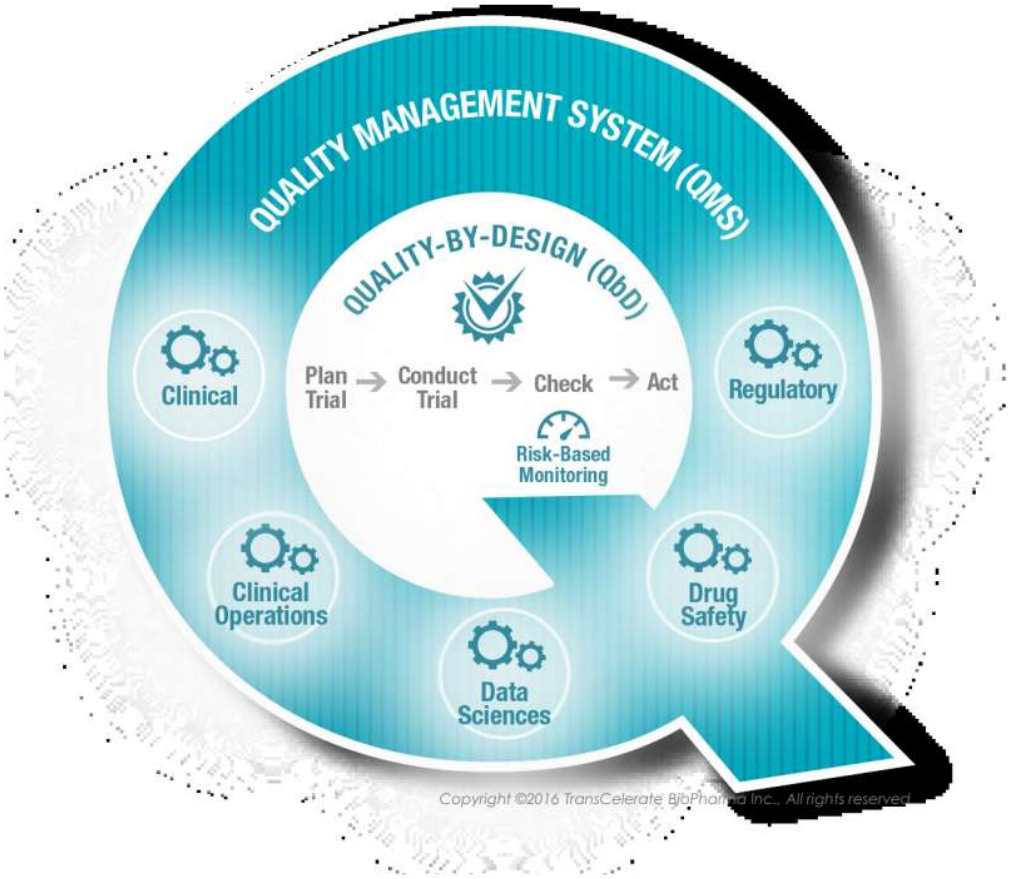
- Summarize and report important quality issues (including instances in which acceptable ranges are exceeded) and the remedial actions taken and document them in the clinical trial report.

- Risks should be identified across processes and systems prior to trial initiation and throughout trial conduct.
- Ensure that risk control is proportionate to the importance of the risk to participants' rights, safety and well-being and the reliability of trial results.
- Where relevant, set pre-specified acceptable ranges (e.g, Quality Tolerance Limits at trial level) beyond which deviations could represent systemic issues.

- Implement additional risk control measures, as needed.

Data source : coming from ICH EWG training material

RBQM, RBM, QBD, PDCA, CTQ, KRI, QTL

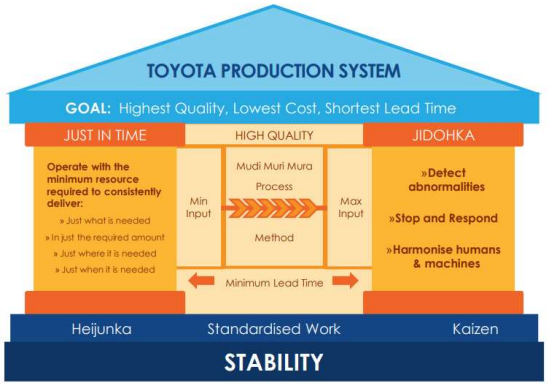


Data source : TransCelerate

QMS-cQMS

A Quality Management System (QMS) is an integrated system through which organizations can systematically plan and achieve quality objectives linked to their broader strategic goals.

QMS are increasingly and successfully being used in other industries, as well as in pharmaceutical manufacturing, to control quality, monitor, and improve performance in complex environments.

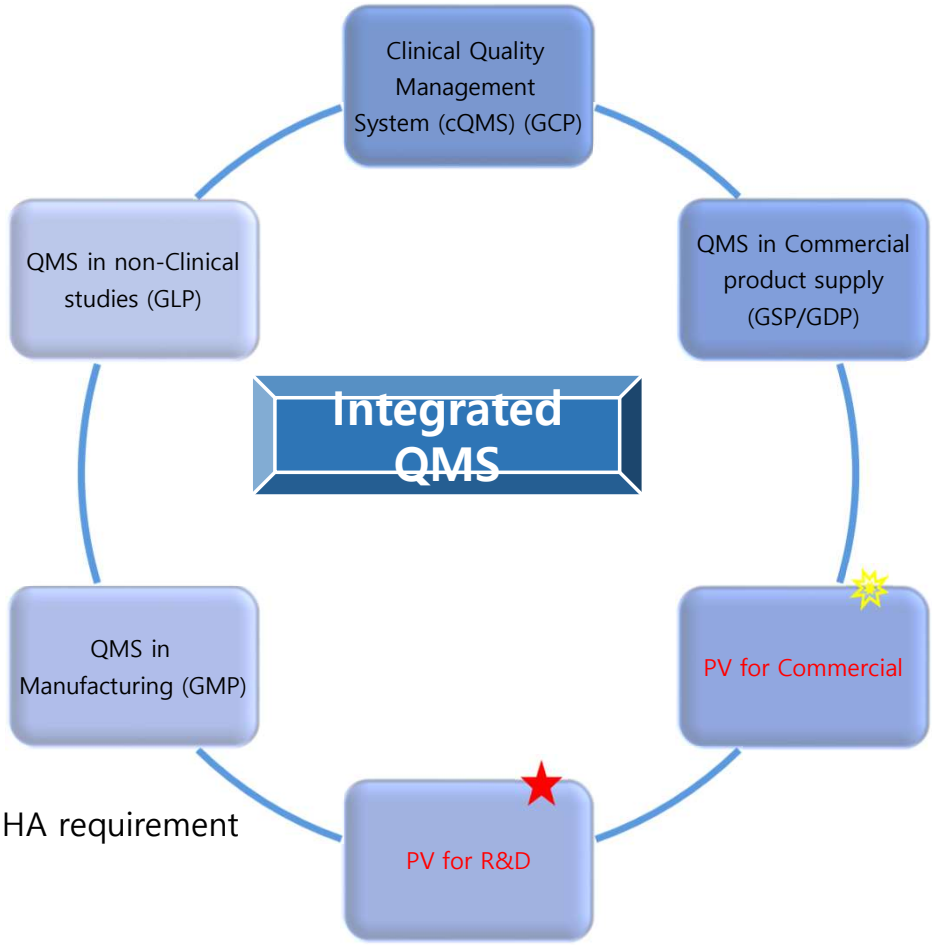


A Clinical QMS is an integrated framework through which organizations systematically define quality objectives linked to their broader strategic goals

Data source : TransCelerate

QMS planning in Start-up Companies

Potential Molecule | Candidate drug | Clinical Trial | Registration | Market Introduction, Surveillance & Expansion



★ Core business can meet the basic HA requirement

✸ Meet minimum HA requirement

cQMS at Clinical Trial Level

Phase 3 study

CPA	CRA	PM	CRM	QC	CS+DM+Stat	PV
• TMF review	• MV per MP • MV compliance rate 95%+	• CO-visits per CO-M planning • Tracking the issue identified • Work with partners	• CO-visits from people perspective to ensure the function delivery	• Independent review from both project & people perspective per QC plan • Tier 1,2 ,3 levels	• Data review per DMP • Data surveillance • PD review • Dry Run	• Safety monitoring per SMP

QA

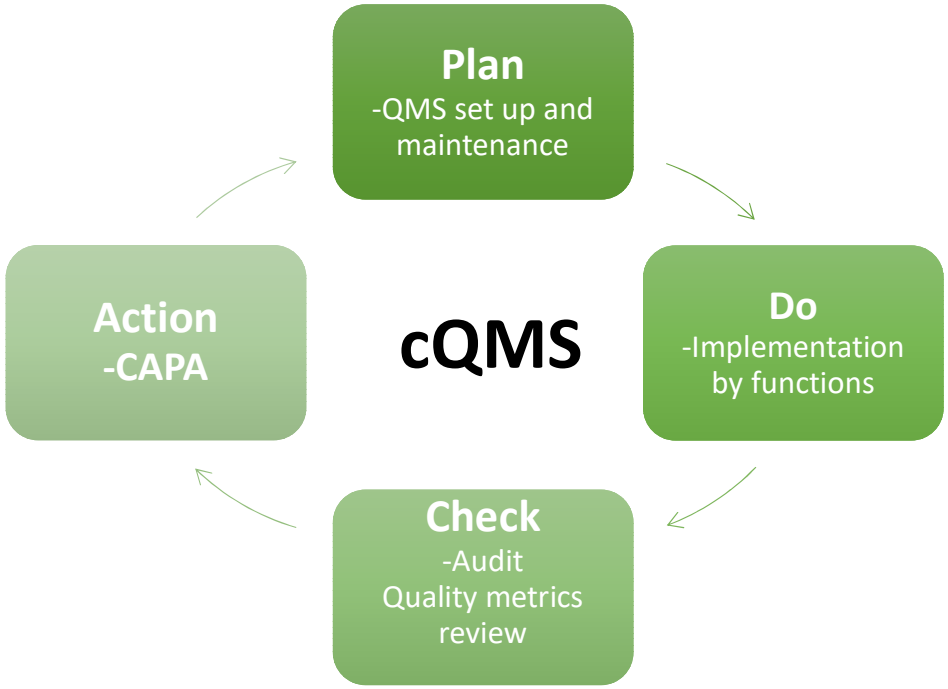
Vendor audit ; Site audit ; TMF audit

Site was selected by the assessment for risk factors, i.e., enrolment, site performance/quality, previous experience, etc.

•All CAPAs are followed and on track.

•**Individual vendor audit completed before official vendor initiation**

cQMS- systematically assures the product delivered with quality



People Qualified

Process Controlled

System Validated

Product Delivered with Quality

Summary

Those not be changed: GCP foundation
What need to be changed: mindset and capability upgrade

E6R3 calls for
Critical Thinking
Flexibility/avoid unnecessary burden

Pay attention to the HA update
Participant industry training
Enhance the capability

Thank you

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