Proportionate and Risk-based Approach to Quality Management for IITs

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Outline

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- Key Concepts: Proportionate & Risk-based Approach
- Risk-Based Quality Management (RBQM)
- Case Study
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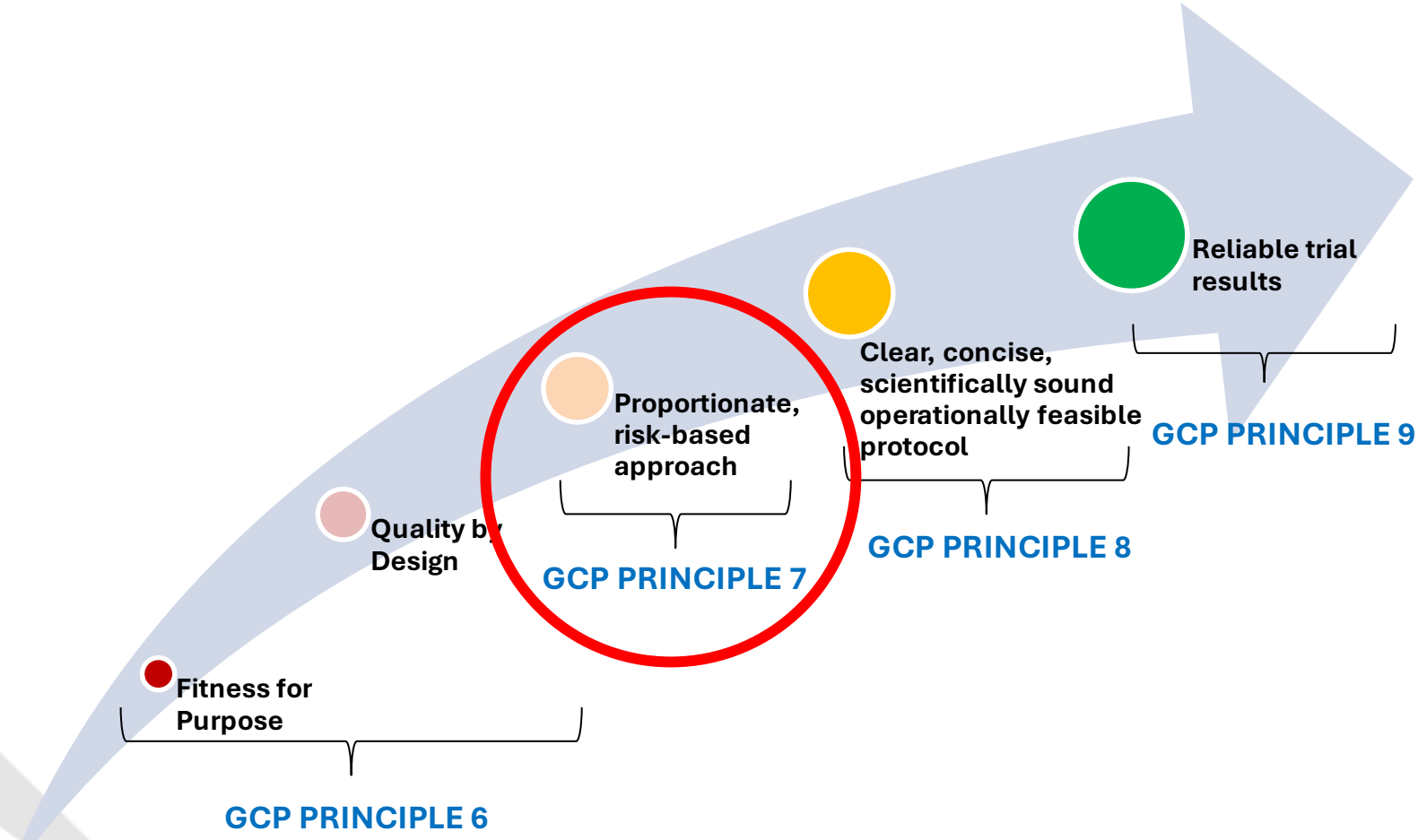
- Summary

A Quick Recap



GCP Principle 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.

Key Concepts: Proportionate & Risk-based Approach

- **Proportionate:** Tailoring level of oversight, resources, and controls to **risks inherent in the trial** and the **importance of information collected**
- **Risk-based Approach:** Proactively identifying, evaluating and managing **risks** that could **affect the rights, safety and well-being of trial participants** and **reliability of trial results**

- ✓ Prioritises critical areas
- ✓ Ensures that efforts are focused where they matter most – participant protection and ensuring reliable trial results
- ✓ Flexible and adaptable for different trials

Risk-Based Quality Management

- **Responsibility of the sponsor**
  - Further elaborated in ICH E6(R3) GCP Guideline Annex 1, S3.10
- **Design and implement efficient trial protocols**, including tools and procedures for trial conduct, to ensure
  - Rights, safety and well-being of participants
  - Reliability of trial results
- **Proactively identify, evaluate and control risks** to effectively manage risks to Critical to Quality factors
  - Prioritise and target efforts on critical / high-risk areas
- **Manage risks prior to the initiation and throughout the clinical trial**
  - From planning and design, through conduct and monitoring, to reporting and archiving
- **Communicate risks, document issues and actions taken**

Risk-Based Quality Management

Before Trial

CRITICAL TO QUALITY FACTORS

Before & During Trial

After Trial

RISK REPORTING

Critical to Quality Factors

(What could make or break the trial?)

- **Identify attributes of a clinical trial that are fundamental to:**
  - Protection of rights, safety and well-being of participants;
  - Reliability and interpretability of the trial results; and
  - Decisions made based on those results
- **May be data, processes or systems**
  - Focus on important critical data, processes and systems!
- **Identified for each clinical trial**

Risk Identification

(What could go wrong?)

- **Identify risks that may have a meaningful impact on CtQ factors**
  - Prior to trial initiation and throughout trial conduct
- **Consider risks across data, processes and systems, including computerised systems, e.g.,**
  - Trial design
  - Participant selection
  - Informed consent process
  - Randomisation
  - Blinding
  - IP administration
  - Data handling
  - Service provider activities

Risk Evaluation

(How significant is the risk?)

- **Evaluate identified risks and existing controls in place by considering:**
  - Probability: The likelihood of harm/hazard occurring

    (Will it happen?)
  - Detectability: The extent to which such harm/hazard would be detectable

    (Will it be obvious?)
  - Impact: The impact of such harm/hazard on participant protection and the reliability of trial results

    (How bad will it be?)

Risk Control

(Could something be done?)

- **Proportionate to the importance of risk to participant protection and reliability of trial results**
- **May be incorporated in, for e.g.,**
  - protocol design and implementation
  - monitoring plans
  - agreements defining roles and responsibilities
  - training
- **Pre-specified acceptable ranges could be set to support control of risks, where relevant**
  - E.g., Quality Tolerance Limits
- **To eliminate, mitigate or accept risk**

Risk Communication

(Who needs to know?)

- **Document risks and controls**
  - E.g., Protocol, monitoring plan, risk management plan, data management plan
- **Communicate risks and controls to those who will perform such actions or are affected, e.g.,**
  - Investigator site staff
  - Sponsor staff (e.g., Project Manager, Monitor, Statistician, etc)
- **Facilitates risk review and continual improvement during trial conduct**
  - E.g., Monitor to alert project manager when discrepancies in data are noted

Risk Review

(What if something else went wrong?)

- **Periodically review risk controls**
  - When there is significant impact on the goals of GCP due to
    - Substantial amendments
    - Non-compliances (including serious breaches)
  - When there is significant impact on risks identified
  - Frequency should be described in SOPs or trial-related documents (e.g., risk management plans)
- **Ascertain that risk controls remain effective and relevant, taking into account emerging knowledge and experience**
  - i.e., On-the-Job Training

Risk Reporting

- **Summarise and report important quality issues and remedial actions taken**

  (What went wrong? What actions were taken?)

  - Including instances in which acceptable ranges are exceeded
- **Document in clinical trial report**
  - ICH E3: Structure and Content of Clinical Study Reports
  - Inform on issues and mitigation actions to decide if reliability of trial results was affected

Risk-Based Quality Management

Before Trial

Identify **CtQ factors**

CRITICAL TO QUALITY FACTORS

Before & During Trial

Identify and prioritise risks to CtQ factors

Evaluate probability, detectability and impact of risk

Review risk control measures

Implement **control**, using proportionality approach

Document and **communicate** risks and controls

After Trial

Summarise and **report** in clinical trial report

RISK REPORTING

CASE STUDY

Case Study 1

Objective: A delicious sunny-side up for breakfast.

Protocol:

Recipe: How to Fry an Egg

You need:

- 1 large egg
- 1 teaspoon olive oil
- Pinch of sea salt and black pepper
- Cast iron skillet, stove

Chef's Instructions:

1. Crack the egg into a small bowl.
2. Heat olive oil over medium heat in a pan.
3. Carefully pour in the egg.
4. Cover and cook for 2-3 minutes.
5. Transfer to a plate and serve.
6. Reinstate the kitchen workspace.

Factors Affecting Quality

- **Egg**
- **Olive oil**
- Sea salt
- Black pepper
- Small bowl
- **Cast iron skillet**
- **Stove**
- ***Pan lid***
- *Spatula*

Which factors are Critical to Quality?

Case Study 1 - Example

Proportionate & Risk-Based Approach

Identify CtQ Factors		Identify Risk	Evaluate Risk				Control Risk
Category	**Items**	**What could go wrong?**	**Probability**	**Detectability**	**Impact**	**Risk Score (P x D x I)**	**Could something be done?**
Ingredients	Egg	Egg is too small – recipe calls for large egg.	Low	High	High	3	Cannot be mitigated. Accept.
		Only refrigerated eggs available, hence egg may not be fresh.	High	Low	High	27	Buy fresh eggs from supermarket the day before.
	Olive oil	Oil is not hot enough – egg may stick to the pan and yolk will break.	Low	Low	High	9	Buy cooking olive oil from supermarket the day before.
Tools	Cast iron skillet	Pan is not hot enough – egg may stick to the pan and yolk will break.	High	Low	High	27	Heat the pan at medium heat for at least 5-6 mins → Update recipe.
	Pan lid	Lid is too small to cover pan - egg white may not cook properly.	Low	High	High	3	Cannot be mitigated. Accept.
	Stove	No gas while cooking egg.	Low	High	High	3	Cannot be mitigated. Accept.

- Probability: Low (1), Medium (2), High (3)
- Detectability: High (1), Medium (2), Low (3)
- Impact: Low (1), Medium (2), High (3)
- **Risk Score = Probability x Detectability x Impact**

Risk Score Matrix
1-3: Low risk
4-17: Medium risk
18-27: High risk

Case Study 2

Title	A randomised, double-blinded, placebo-controlled clinical trial to assess the efficacy and safety of XYZ in dengue patients	
Primary Objective	To determine the efficacy of the IP compared to placebo with respect to reduction in viral load at 48 hours post-treatment start	
Secondary Objective	To assess fever clearance time, safety and tolerability, changes in laboratory markers, clinical evolution, and time to clinical recovery	
Trial Design	5 days of treatment duration (inpatient or self-administered) and ~30 days of outpatient visits.	
Inclusion / Exclusion Criteria	Inclusion criteria • **Age 18–60 years** • Fever ≥38°C with clinical suspicion of dengue • **Onset of fever ≤48 hours before first dose** • Positive rapid antigen or PCR test	Exclusion criteria • Severe disease at screening • Abnormal laboratory parameters (e.g., low hemoglobin, abnormal liver/renal function) • Use of prohibited medications (anticoagulants, PPIs, NSAIDs) • Significant comorbidities (cardiac, respiratory, renal, hepatic, immunocompromised, etc.)
Data Collected	• Demographics and medical history • Physical examinations, **vital signs, daily body temperature, ECG** • Laboratory tests: Hematology, Biochemistry, Coagulation, including Hepatitis/HIV screening • Virology: **viral load by PCR**, antigenemia, antibody levels • **Clinical signs and symptoms (daily)** • Imaging: chest X-ray, abdominal ultrasound (for plasma leakage) • **Adverse events and serious adverse events**	
Trial Processes	• Informed consent → **Screening** → **Eligibility assessment** • Randomisation • Blinding and emergency code breaking • **IP administration (inpatient or self-administered at home)** • Safety monitoring (stopping rules) • Laboratory sample collection, processing, and shipment. • **Off-site procedures**	
Computerised Systems	• **Interactive Response Technology (IRT) for randomisation and emergency code break** • **Electronic Data Capture (EDC) system for eCRF and AE reporting**	

Which factors are Critical to Quality?

Case Study 2 - Example

Identify Critical to Quality Factors

- **Data**
  - Primary Endpoint: Viral load by PCR
  - Secondary Endpoint: Vital signs (including daily body temperature), ECG, Labs (Hematology, Chemistry, Coagulation), clinical signs and symptoms
  - Safety: Adverse Events
  - Protocol deviations
- **Processes**
  - Informed consent (Involvement of minors ≤ 21 yo)
  - Screening & eligibility (Fever onset ≤ 48 hours before first dose)
  - IP Administration (Self-administered at home)
  - Off-site procedures
- **Systems** → **Ensure validation is performed**
  - Interactive Response Technology (IRT) system
  - Electronic Data Capture (EDC) system

Case Study 2 - Example

Proportionate & Risk-Based Approach

Identify CtQ Factors	Identify Risk	Evaluate Risk				Control Risk
CtQ Factor Impacted	**What could go wrong?**	**Probability**	**Detectability**	**Impact**	**Risk Score (P x D x I)**	**Could something be done?**
Data Collection (Secondary Endpoint)	Daily body temperature not collected by participants during outpatient visit period.	High	Low	High	27	• Create participant diary to record body temperature. • CRC to train patient and remind patient for the first few days and every 2-3 days to ensure compliance. • Monitor to verify that data is present.
	Problems with data or sample collection during off-site visits may lead to protocol deviations, or incomplete or missing data.	High	Medium	High	18	• Create manual and checklist for off-site visits and train the responsible staff. • Home visit staff should report to site on completion status of visit before leaving.
Enrollment (Screening & Eligibility, IP Administration)	Protocol deviations due to delayed IP administration, or high screen failure rate as IP needs to be dosed within 48 hours of fever onset.	High	High	Low	3	Plan time for screening.
IP Administration	Participants forgot to take IP during self-administration of IP.	Medium	Low	Medium	4	CRC to remind participants daily.
Informed Consent	Unable to obtain consent from legal representative for participants who are minor, due to time constraints.	Low	High	High	3	Train investigator site staff.

- Probability: Low (1), Medium (2), High (3)
- Detectability: High (1), Medium (2), Low (3)
- Impact: Low (1), Medium (2), High (3)
- **Risk Score = Probability x Detectability x Impact**

Risk Score Matrix
1-3: Low risk
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Alternative Approach for RBQM for IITs

- **ICH E6(R3) GCP Guideline** applies to **interventional clinical trials of investigational products that are intended to be submitted to regulatory authorities** (i.e., for product registration)
- **The Principles of GCP** may be applicable to **other interventional clinical trials of investigational products** that are **not intended to support marketing authorisation applications** in accordance with local requirements

→ In other words, **investigator-initiated clinical trials (IITs) that are intended to transform clinical care only need to comply with the Principles of GCP.**

A Recap: GCP Principle 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.

- Trial processes should be proportionate to the risks inherent in the trial and the importance of the information collected.
- The focus should be on the risks associated with trial participation.
- Risks to critical to quality factors should be managed proactively and adjusted when new or unanticipated issues arise once the trial has begun.
- Trial processes should be operationally feasible and avoid unnecessary complexity, procedures and data collection.

Case Study 2 - Example

Alternative Approach for RBQM for IITs

Aspects of a Clinical Trial	Factor for Consideration	Risk	Affects	Probability	Impact	Risk Score (P x I)	Controls
Trial Design							
Phase of Clinical Trial							
Trial Population							
PI's Experience							
Resources							
Facilities							
Informed Consent Requirements							
Registration Status of IP							
Randomisation							
Blinding							
Data Collection and Handling							
Trial Monitoring							

- Probability: Low (1), Medium (2), High (3)
- Impact: Low (1), Medium (2), High (3)

Risk Score Matrix (P x I)
1: Low risk / 2-4: Medium risk / 6-9: High risk

Case Study 2 - Example

Alternative Approach for RBQM for IITs

Aspects of a Clinical Trial	Factor for Consideration	Risk	Affects	Probability	Impact	Risk Score (P x I)	Controls
Trial Design	Blinding	Possible unblinding due to lack of segregation between blinded and unblinded teams for IP management	Reliability of trial results	NA	High	NA, IP is supplied in blinded bottles	NA
	Complex trial process	Protocol deviations due to delayed IP administration, as IP needs to be dosed within 48 hours of fever onset	Reliability of trial results	High	Low	3	• Plan time for screening.
Trial Population	Vulnerable Population	Non-compliance of informed consent requirements for vulnerable population (e.g., adults lacking mental capacity, minors)	Participant protection	Medium	Medium	4	• Train investigator site staff.
PI's Experience	Inexperienced PI	PI does not have sufficient experience to conduct a clinical trial, which is usually more complex	Both	NA	High	NA, PI had conducted more than 10 clinical trials	NA
Resources	No Clinical Research Coordinator	Non-compliances may arise for clinical trials with complex operations, due to the lack of dedicated CRC	Both	NA	High	NA, dedicated CRC is available	• Ensure that backup CRC is available when main CRC is on leave.
	Inadequate no. of investigator site staff	Inadequate medical care due to insufficient number of investigator site staff	Participant protection	NA	High	NA, there is sufficient investigator site staff	NA

- Probability: Low (1), Medium (2), High (3)
- Impact: Low (1), Medium (2), High (3)

Trial-specific risks

Risk Score Matrix (P x I)
1: Low risk / 2-4: Medium risk / 6-9: High risk

Case Study 2 - Example

Alternative Approach for RBQM for IITs

Aspects of a Clinical Trial	Factor for Consideration	Risk	Affects	Probability	Impact	Risk Score (P x I)	Controls
Data Collection and Handling	Incomplete or missing data	Daily body temperature (secondary endpoint) not collected by participants during outpatient period	Reliability of trial results	High	High	9	• Create participant diary to record body temperature. • CRC to train patient and remind patient for the first few days and every 2-3 days to ensure compliance. • Monitor to verify that data is present.
		Problems with data or sample collection during off-site visits may lead to protocol deviations	Reliability of trial results	High	High	9	• Create manual and checklist for off-site visits and train the responsible staff. • Home visit staff should report to site on completion status of visit before leaving.

- Probability: Low (1), Medium (2), High (3)
- Impact: Low (1), Medium (2), High (3)

Trial-specific risks

Risk Score Matrix (P x I)
1: Low risk / 2-4: Medium risk / 6-9: High risk

Summary

- A proportionate and risk-based approach to quality management allows
  - Critical areas to be prioritised
  - Efforts to be focused on participant protection and reliability of trial results
  - Flexibility and the adaptation for different trials
- As per ICH E6(R3) GCP Guideline Annex 1, risk-based quality management requires
  - Identification of CtQ factors
  - Risk identification > evaluation > control (eliminate, mitigate or accept risk)
  - Risk communication
  - Risk review
  - Risk reporting
- Alternative proportionate and risk-based approach could be used for interventional clinical trials of investigational products that are not intended to support marketing authorisation applications

References

- ICH E6 (R3) Guideline for Good Clinical Practice, 6 Jan 2025
- ICH E3 Structure and Content of Clinical Study Reports, 30 Nov 1995

Thank You!

We welcome your queries!

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