
ICH E6 - QMS
Risk-based Quality Management
in Clinical trials
2018
ICH Guideline Training
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2018 KRPIA
ICH Guideline Training

주 최 : Ministry of Food and Drug Safety
National Institute
of Food and Drug Safety Evaluation

주 관 : KRPIA
Korean Research-based Pharma
Industry Association

Risk-Based Quality Management in Clinical Trials

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Agenda

- Risk-based Clinical QMS
- Non-Compliance Management
  - Root Cause Analysis (RCA)
  - Corrective Action and Preventive Action (CAPA)
- CRO Oversight
- Conclusion

Risk-based Clinical QMS

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ICH GCP (R2): Introduction

"to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting, while continuing to ensure human subject protection and reliability of trial results"

- Risk Based Quality Management to increase Efficiency and Quality (Subject Protection & Data Reliability)
- Substantial evolution of clinical trials with increases in scale, complexity, cost, and technology capabilities requires modernization of approach to GCP
- Adoption of Quality-by-Design (QbD) and Quality Risk Management (QRM) principles and methodologies in clinical development (ICH Q9 & Q10 adapted)

Time-consuming, expensive, not proportionate to risk (One size fits all)

More systematic, prioritized, risk-based approach (Fit for purpose)

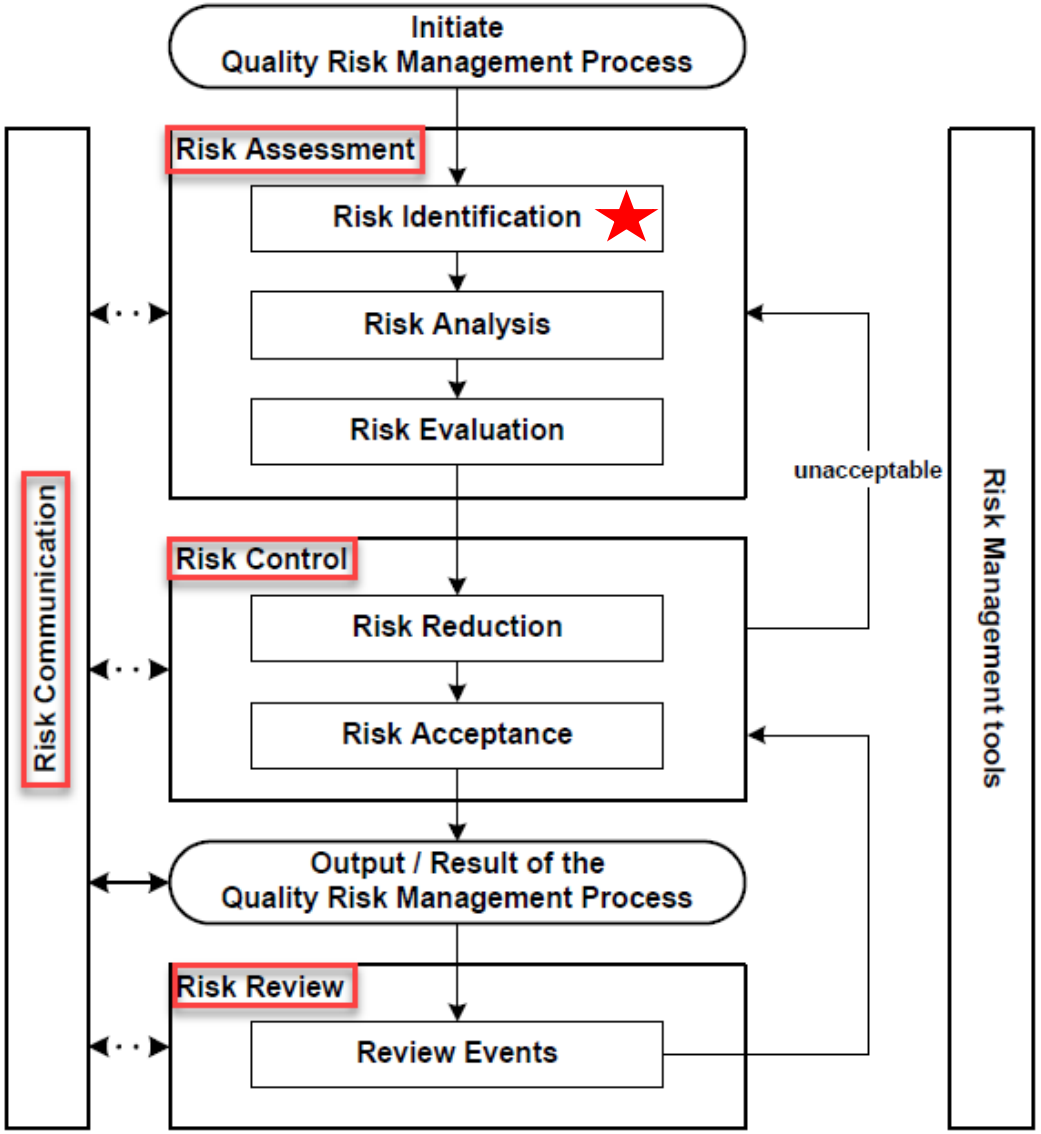
ICH GCP (R2): Sponsor Responsibilities

- **Quality Management (5.0)**
  - Implement a system to manage quality throughout all stages of the trial process
  - Focus on essential trial activities to ensuring human subject protection and the reliability of trial results
  - Methods for quality assurance and quality control should be proportionate to the risks
  - Avoid unnecessary complexity, procedures, and data collection

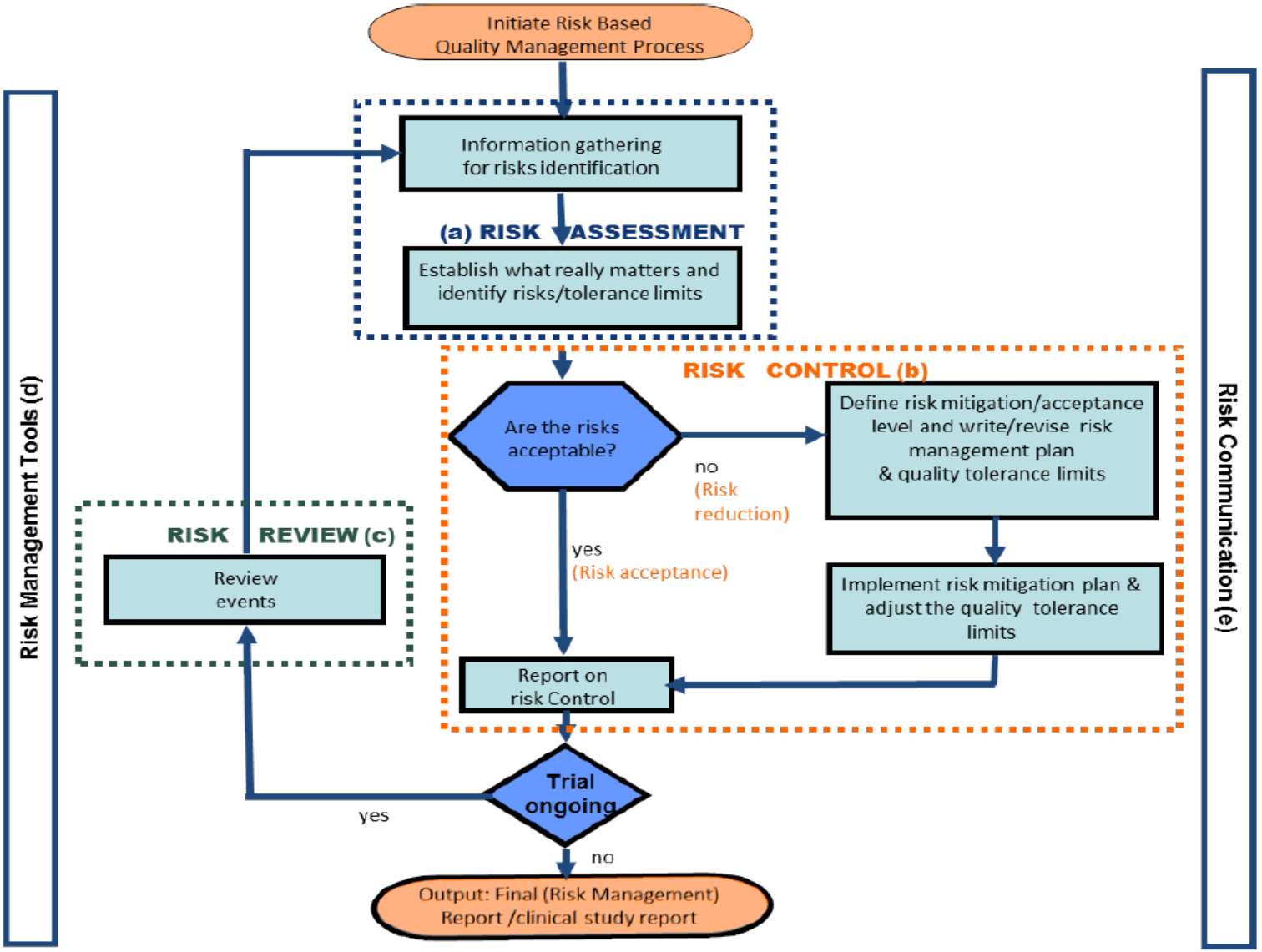
Effective risk-based quality management system

- Identification of the risks on a continuous basis for risk-bearing activities throughout the design, conduct, evaluation and reporting of clinical trials
- The process should start at the time of protocol design so mitigation can be built into the protocol and other trial related documents (e. g. monitoring plan)
- A systematic process to identify, assess, control, communicate and review the risks associated with the clinical trial during its lifecycle (ICH Q9)

Overview of a typical quality risk management process
(ICH Q9: Quality Risk Management)



Risk based QMS for clinical trials
(EMA Reflection Paper)



(a) Risk Assessment

- Knowledge and understanding of 'what really matters' for establishment of priorities and identification of risks
  - What may go wrong?
  - What is the probability (chance/likelihood) of a negative outcome?
  - What would be the impact on subject protection/data reliability?
- With the priorities in perspective, risk assessment consists of the identification of the negative outcomes, their impact and their chance/probability of occurrence.
- Usually conducted by interdisciplinary teams
- Begin with a well-defined problem description or risk question
- Useful risk management tools
  - e.g. Fishbone diagrams, Failure Mode Effects Analysis (FMEA)
- Output:
  - 'risk score' (quantitative) or
  - 'risk rating (High/Medium/Low)' (qualitative)

(a) Risk Assessment
1. Information gathering for risk identification

System Level: indirectly affect a trial	
Organization/responsibilities	• Organograms, communication plans, contractual partners
Quality systems and processes	• SOPs
Facilities and computerized systems	• IT infrastructure, document management system, data management system, IVRS, eCRF system
Human resources (incl. training and qualifications of personnel)	• JDs, training plans, performance management
Compliance metrics, performance measurements	• KPIs, KQIs, audit and inspection outcomes
Regulatory framework	• Knowledge of HA requirements

Project Level (a trial or clinical program): directly linked with the trial	
IMP related risk area	• Physico-chemical properties, manufacturing process, PK/PD/toxicological properties, labelling and packaging requirements
Trial design related risk area	• Complexity of design, trial population, therapeutic area, sample size calculation, eligibility criteria, non-medicinal protocol related activities (e.g. biopsies)
Operational risk area	• Study budget, development deadlines, staff resource level and study specific training (e.g. GCP experience at site), study management team and responsibilities, site selection and management, CRO involvement, trial supply processes and management, site set up and infrastructure, lab setup, setup of databases (e.g. IVRS, eCRF), site monitoring and central monitoring, clinical data management, safety reporting, trial reporting and communications

(a) Risk Assessment
2. Establishing priorities for risk evaluation

- To identify the 'risks that really matter' and establish priorities
- Prioritization oriented to meet GCP objectives and study objectives
- Priorities first to be established at the time of planning and preparation (design) of a trial including the corresponding documents, trial specific plan, data collection tools and all processes of the trial
- Can use qualitative or quantitative process methodologies based on risk categories considering likelihood of occurrence, impact, and detectability of risks
- Priorities to be continuously reviewed and adapted as deemed necessary during trial conduct

(b) Risk Control

- Decision making to accept risks (with limited impact) or define mitigation measures for identified risks and for a risk management plan
- The amount of effort for risk control should be proportional to significance of the risk and importance of the process/outcome
- **Risk mitigation actions:**

System related	Project related
• Documented procedures • Contracts between parties with clearly defined R&R • Measures of oversight of delegated/contracted tasks • Determination of communication plans • Tailored training • Use existing data in different DBs for risk assessment/mitigation, e.g. develop IT-tools and automatic data interfaces • Quality performance measurement for internal/external service providers	• Protocol design process with collaboration of expert functions • Designing of training material, trial specific monitoring plans, audit, data management etc. considering identified priorities and risks • Safety monitoring procedure adapted to each project and stage of the project e.g. post-approval trials (safety profile is known) • Trial specific adaptation of extent and nature of monitoring, e.g. adaptation of on-site monitoring visits, SDV focused on particular data, central monitoring, data handling, and evaluation, reporting

(b) Risk Control

- Predefined quality tolerance limits:
  - Detect deviations from the tolerance range to rectify or modify the processes to improve the conduct of study
  - Oversight and monitoring on the parameters 'that matter' help to design with more risk based strategies
  - Can be set for a specific trial or general limits applied to all trials
  - Examples:

Trial Data	• Occasional omission of measurements • Early or late performance of study visits • Can be tracked in EDC)
Trial Protocol procedures	• Tolerance limits of protocol deviation to trigger monitoring (additional visits or training)
Trial Management procedures	• Defined metrics for oversight/management/monitoring • Targeted audit/monitoring • e.g. excessive delays in data entry or SAE reporting, lack of data variability

(c) Risk Review

- Ongoing reassessment of the risks by review of;
  - New information emerging during conduct of the trial

    e.g. new pre-clinical data, new safety data, updated IB, Protocol Amendment
  - Outputs of trial management activities

    e.g. Monitoring output, Data management, Data Monitoring Committee Meeting Output, Audit Reports
- Assess impact on risk management plan and tolerance limits

ICH GCP (R2): Sponsor Responsibilities

- **Risk-based approach to QMS (5.0)**
  - Critical processes and data identification
  - Risk identification
    - System level, Trial level
  - Risk evaluation
    - Against existing risk controls considering likelihood, impact, detectability
  - Risk control
    - Decision making whether to reduce or accept
    - Mitigation action (proportionate to risk, incorporated in protocol design, monitoring plan, trainings, etc)
    - Predefined quality tolerance limits
  - Risk communication
  - Risk review
    - Periodic review of risk control measures for effectiveness
  - Risk reporting
    - CSR to include quality management approach and summary of important deviations from predefined quality tolerance limits and remedial actions taken

Non-Compliance Management

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ICH GCP (R2): Sponsor Responsibilities

- **Non-compliance (5.20)**

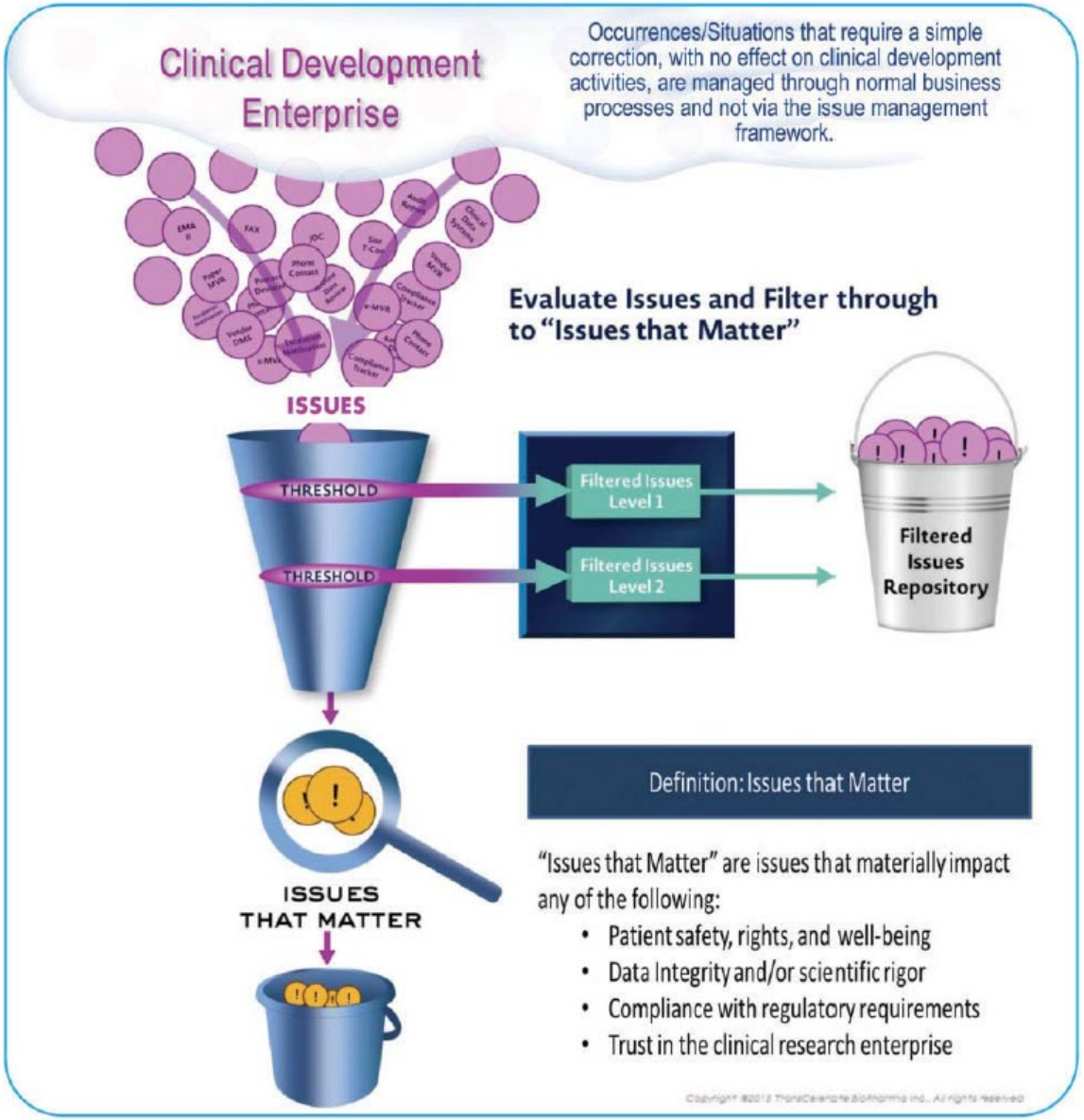
  Prompt action to non-compliance by sponsor to secure compliance

  - Follow-up of non-compliance that has or may significantly affect human subject protection or reliability of trial results
  - By performing a root cause analysis (RCA) and implementing corrective and preventive actions (CAPA)

Issue Management Process (TransCelerate)

- What to manage?
  - Non-compliance (Deviation) with impact on subject protection/data reliability
  - Risks that matter = Issues that matter
- Establish a centralized, cross-functional process for issue management
- Elements of end-to-end process
  - Establishing thresholds (e.g. predefined tolerance limits)
  - Documentation requirements consistent with the level of impact
  - Communication plan (including notification and escalation to drive actions and accountability for appropriate levels of management)
  - Corrective and preventive action (CAPA) management: Investigation and CAPA implementation
  - Trending and analytics requirements (including identification of stakeholders)

Issue Identification and Triage



Notification and escalation pathway based on the nature, extent, and impact of the issue (e.g. minor/major/critical, Category I/II/III)

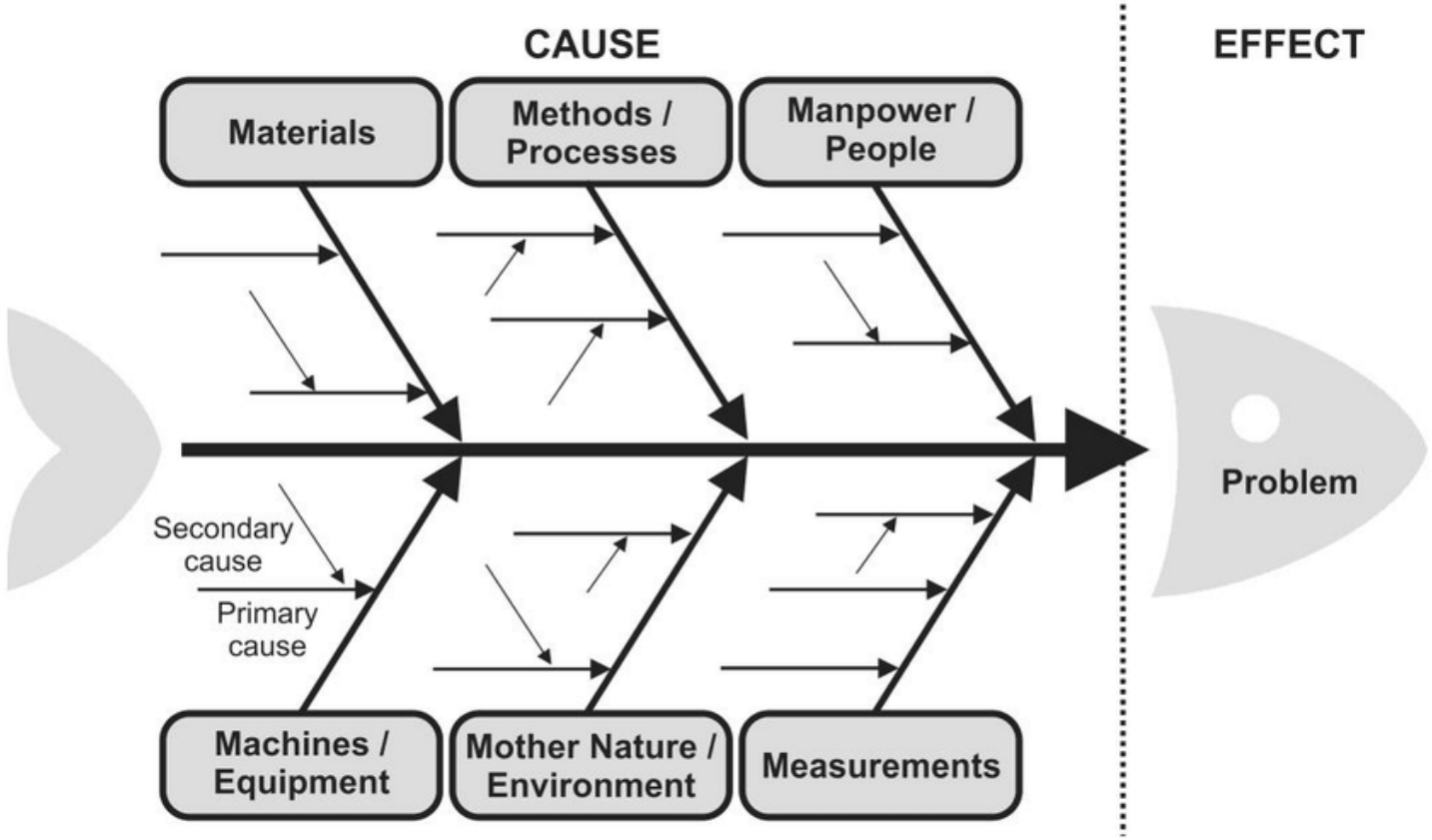
CAPA Process:
Investigation and CAPA implementation

- Execution of concurrent activities to address the issue:
  - Immediate actions to correct and/or contain
  - Robust thorough investigation to determine the root cause(s)
  - Holistic assessment of the scope and impact
- Development and implementation of a comprehensive action plan:
  - CAPAs to address the identified root cause(s)
  - Robust effectiveness checks to evaluate the collective CAPAs to ensure absence of future occurrences of the issue

Root Cause Analysis (RCA)

- Identification of data and documentation relevant to the issue to determine the scope and potential for occurrences elsewhere
- Application of appropriate root cause investigation tools or techniques, e.g.
  - Brainstorming
  - Five Whys
  - Fishbone Diagram
- Identification of risk factors that can be leveraged to develop preventive actions
- Confidence to the true root cause(s) identified
- Trained personnel conducting the investigations

Fishbone (Ishikawa) Diagram
- Cause and Effect Diagram



Five Whys: *Example*

I am constantly late for work *(Problem statement)*

1. **Why? –** I get up too late.
2. **Why? –** I don't get up when the alarm first goes off.
3. **Why? –** I am still tired.
4. **Why? –** I go to bed very late.
5. **Why? –** I like to watch late night TV. ***(→ Root Cause)***

Five Whys

PI did not get IRB approvals for PI change and provided remote oversight *(Problem statement)*

1. **Why did the PI try to provide oversight remotely?**
   - Because the PI and investigational site staff were not aware that a PI cannot provide oversight remotely and that IRB approvals for a new PI have to be in place before the transition.
2. **Why did was the PI not aware?**
   - Because the PI was not very experienced with GCP.
3. **Why was PI not experienced with GCP?**
   - Because the PI had never attended a GCP training.
4. **Why had the PI never attended a GCP Training?**
   - Because this was not properly checked during site feasibility.
5. **Why was this not properly checked during site feasibility?**
   - Because the site feasibility questionnaire did not contain such a question. ***(→ Root Cause)***

Corrective Action and Preventive Action (CAPA)

- **Correction:**
  - Action to eliminate a detected non-conformity
  - A correction addresses the event itself, not the root cause
- **Corrective Action:**
  - Action to eliminate the cause of a detected non-conformity or other undesirable situation (preventing recurrence)
- **Preventive Action:**
  - Action to eliminate the cause of a potential non-conformity or other undesirable potential situation (preventing occurrence)

CRO Oversight

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ICH GCP (R2): Sponsor Responsibilities

- **Quality Management (5.2)**
  - Oversight of any trial-related duties and functions carried out on its behalf, including those that are subcontracted to another party by CROs

- The same requirements of Quality Management apply to CROs, vendors or other service providers delegated by the sponsor
- No guidance on minimum standard for CRO oversight
- Develop CRO oversight strategy, e.g.
  - Risk-based vendor qualification process
  - Assess vendor's QMS including subcontractor qualification process
  - Contract with clear R&R (which procedures to be followed)
  - Key performance/quality metrics
  - Communication plan on non-compliance (issue escalation)
  - Regular monitoring/quality risk assessment

Conclusion

- ICH GCP (R2) encourages risk-based quality management in clinical development to increase efficiency with more focusing on essential trial activities that impact on subject protection and data reliability
- Quality-by-Design (QbD) and Quality Risk Management (QRM) principles and methodologies adopted as an accepted standard
- Non-compliance ('Issues that matter') should be managed by effective RCA and CAPA implementation
- Risk-based CRO oversight strategy (including subcontract) needs to be developed

Reference

- *ICH E6 (R2) Good Clinical Practice*
- *ICH Q9 Quality Risk Management*
- *ICH Q10 Pharmaceutical Quality System*
- *EMA, Reflection paper on risk-based quality management in clinical trials*
- *TransCelerate's Clinical Quality Management System: Issue Management*

Thank You

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