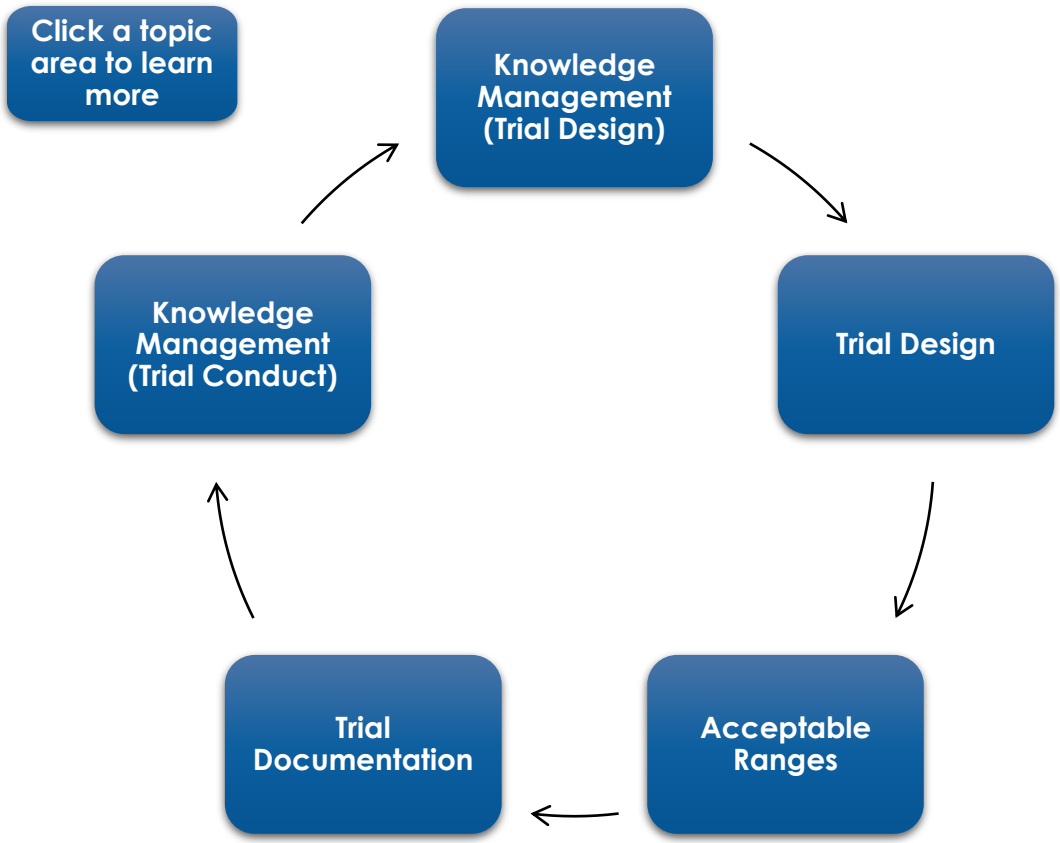
Control Strategies and Good Clinical Practice (ICH E6 (R3))



- **What are Control Strategies?** Predetermined actions/plans that are intended to manage the occurrence, impact, and/or detectability of risks associated with Critical to Quality Factors (CtQs) that are deemed to be important to participant safety and/or data reliability.
- **What does ICH E6 (R3) say about Control Strategies?** Mechanisms used to control predefined risks should be proportionate to the importance of the risk to participant's rights, safety, and well-being and reliability of study results.
- **What are the benefits of implementing control strategies?**
  - Avoid the possibility that a risk could occur
  - Reduce the likelihood that a risk could occur
  - Reduce the impact of a risk if it does occur
  - Increase the likelihood of detecting a risk quickly if it does occur

Knowledge Management

Trial Design

- **What ICH E6(R3) states:** "The design of the trial, to ensure appropriate quality and meaningful trial outcomes, may be supported by the perspectives of stakeholders; for example, patients and/or healthcare providers. Their input can increase the likelihood of meaningful trial outcomes, which are relevant to both trial participants and future patients. This input will also guide decisions on the feasibility of data collection and assure that participation in the trial does not become unduly burdensome for those involved." (Section II, ICH E6 (R3) dated 19MAY2023)

- **What are good practices:**
  Summary: A well-designed trial minimizes unnecessary complexity, integrates quality into the design, and ensures the trial design is appropriate to meet the intended goals. Multiple inputs from available stakeholders should be used to enable the trial design.
  - Use of prior knowledge/experience on the therapeutic area and investigational medicinal product when designing the trial
  - Involve external stakeholders (e.g., investigators, patients, patient advocacy groups) in helping design the trial
  - Use the experience from previous trials and real-world data to drive improvements or mitigations on the trial design
  - Develop strong communication channels during set up, which allows for improved trial design

- **What are important outputs:**
  - Protocol, or trial outline
  - Data acquisition tools
  - Operational documents, such as feasibility assessment
  - Training materials

Trial Design

- **What ICH E6(R3) states:** Risk control strategies can be built into the design of the clinical trial, reducing the need for additional resources or plans to be implemented. In Annex 1 the guideline is emphasizing the incorporation of Quality by Design, and CtQs linked to risks with Quality Measures (3.1.2). In Appendix B, the guideline asks for a description of monitoring approaches to be added in the protocol, as part of the quality control process (B.12.2). (ICH E6 (R3) dated 19MAY2023)

- **What are good practices:**
  Summary: Understanding the risks to the critical to quality factors during trial design means that strategies to control, mitigate or remove the risk can be built into the protocol. Ensuring that the trial is prospectively designed to protect what matters most.
  - Consideration of ICH E8(R1) regarding Quality by Design and a "Fit for purpose" protocol
  - Focus Areas for consideration in design of a trial are:
    - Risk Management/Risk Proportionality with CTQs/Quality Measures
    - Operational Feasibility
  - Establish a data governance framework, which includes a data flow diagram that aids identifying areas of risk

- **What are important trial elements:**
  - Study Population (e.g., diversity, vulnerability)
  - Treatment Description (e.g., dosage/regimens)
  - Choice of Control Group (internal/external control group, limitations, etc.)
  - Response Variable (e.g., patients view, duration of study))
  - Methods to reduce Bias (e.g., randomization, blinding, interim results)
  - Study Data (e.g., data integrity, patient safety, primary/secondary data collection)
  - Statistical Analysis (design adaptation, justification of sample size)
  - Improved Investigator and patient engagement

Acceptable Ranges

- **What ICH E6(R3) states:** "Risk control should be proportionate to the importance of the risk to participants' rights, safety and well-being and the reliability of trial results... The sponsor should set acceptable ranges to support this process within which variation can be accepted. Where deviation beyond these ranges is detected, an evaluation should be performed to determine if there is a possible systemic issue and if action is needed." Section 3.10.1.3. (a) & (b), ICH E6 (R3) dated 19MAY2023. "The sponsor should summarize and report the risks and the remedial actions taken in relation to important deviations from the acceptable ranges as detailed in section 3.10.1.3(b) and document them in the clinical trial report (ICH E3)". (Section 3.10.1.6, ICH E6 (R3) dated 19MAY2023)

- **What are good practices:**
  Summary: Acceptable ranges, e.g., quality tolerance limits, should be proactively set by study teams to regularly monitor risks associated with CtQs. Actions to investigate and improve performance should be taken when trends and/or deviation from preset thresholds occur.
  - Utilize Risk Based Quality Management concepts to identify and track known or anticipated risks to participant safety and data reliability
  - Define key risks to quantitative endpoint data, identify owner and mitigation strategies
    - Protocol design can include acceptable ranges for specific protocol provisions
    - Set upper and lower tolerance values (thresholds) based on trial design, therapeutic area, drug class and statistical significance
    - Setting an alert (warning) range that is tighter than the threshold values allows for early risk detection and mitigation
  - If predefined thresholds are breached, the risk owner reviews and consults key stakeholders to assess the impact to the trial
  - Implement additional mitigation strategies and reassess on an ongoing basis throughout the trial
  - Important deviations from the acceptable ranges, or predefined thresholds, must be reported in the clinical trial report

- **What are important outputs:**
  - Trial risk management plan (Risk Assessment and Categorization Tool (RACT), Risk Assessment and Management tool for manual handling Proactively (RAMP)
  - Centralized Monitoring Plan (Data Visualization Dashboards)
  - Monitoring Plan
  - Statistical Analysis Plan (SAP)
  - Clinical Trial Report

Trial Documentation

- **What ICH E6(R3) states:** "Risk mitigation activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to SOPs, and training in processes and procedures." (Section 3.10.1.3 a, ICH E6 (R3) dated 19MAY2023). Reference Appendix C for further information.

- **What are good practices:**
  Summary: Plans with clear delineation of roles and responsibilities as well as evidence showing what was done, when, by whom and what the resulting actions were is important documentation to demonstrate compliance with control strategies.
  - Perform a Critical To Quality assessment at the Trial Design Phase and document risks (Using a RACT)
    - Which data/processes are critical to the quality of the trial?
    - What are the protocol execution risks to the critical data/process?
    - Which risks will be mitigated via protocol design adjustments?
    - Which risks will be mitigated/monitored via operational process/oversight/metrics (i.e., Monitoring processes or KRIs) and which functions are responsible?
    - Which risks can be accepted?
  - Perform a Cross-Functional risk assessment of critical data/process upon finalization of the protocol and document new/residual risk mitigations/monitoring/oversight strategies in risk log and in functional plans (Using a RACT and Functional Plans)
    - Who assesses and reviews what, when, and how?
  - Document evidence of those agreed functional mitigations, monitoring and oversight via Monitoring Visit Reports, Central Monitoring Reports, Risk Review Meeting Minutes/Action Logs

- **What are important outputs:**
  - RACT
  - Data Review Plan (cross functional plan)
  - Functional Plans (Data Validation Manual, Clinical Monitoring Plan, Central Monitoring Plan)
  - Monitoring Visit Reports
  - Central Monitoring reports
  - Risk Review Meeting Minutes/RAID log (Risks, Actions, Issues and Decisions)

Knowledge Management

Trial Conduct

- **What ICH E6(R3) states:** "The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience." (Section 3.10.1.5, ICH E6 (R3) dated 19MAY2023)

- **What are good practices:**
  Summary: It is critical that implemented quality management activities remain effective and relevant throughout the clinical trial. To enable this, emerging knowledge and experiences should provide a continuous feedback loop to improve efficiency and quality of the conduct of the clinical trial.
  - Use the experience in one trial to drive improvements or mitigations on other ongoing or future trials
  - Develop opportunities to share learnings across trials and key stakeholders
  - Establish a data governance framework
  - Assess trends across trials (can be achieved using dashboards and metrics) and make improvements as needed
  - Ensure ongoing review of critical to quality factors and risks associated in a trial to assess if changes are needed.
  - Ensure ongoing review of issues and protocol deviations for the trials to assess if additional risks and mitigations are evident

- **What are important outputs:**
  - Protocol
  - Trial risk management plan (RACT, RAMP)
  - Trial issue/protocol deviation management plan
  - Data visualization dashboards
  - Audit program

Further Considerations for Implementing Control Strategies

Indirect Benefits

By proactively implementing control strategies, the possibility and impact of risks occurring is reduced and early detection of risks is enhanced. Additionally, the following benefits may be realized:

- Improved site and patient engagement
- Improved participant recruitment and trial diversity
- Reduced protocol deviations
- Reduced protocol amendments
- Improved transparency and efficiency of trial operations and data collection
- Improved data trend analysis and mitigation
- Improved trial timelines equals therapies to patients quicker
- Improved data integrity and patient safety
- Improved audit and regulatory inspection readiness

Application of ICH E6(R3), specifically control strategies in clinical trials, ensure protection of the rights, safety, and well-being of participants and enhance the reliability of study results.