ICH E6 (R2) Addendum
Impact and Action Planning for Site and Sponsor Teams

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Session Objectives for You

• Describe the key updates to the ICH E6 GCP Guideline impacting running clinical trials for sites and sponsors

• Identify how the finalized ICH guideline affects oversight for clinical trials for sponsors and sites

• Recognize the essential elements to include in implementing the new requirements to ensure quality across studies no matter the size of the site or sponsor
Where were you in 1996?
ICH E6 (R2) Finalized

• 1997 – 2016

• Purpose:
  • Provides unified standard for: European Union, Japan, United States, Canada, and Switzerland
  • Facilitate mutual acceptance by the regulatory authorities of data from clinical trials.

• Step 5: Implementation period
  • To Notify: EC, MHLW/PMDA, FDA, Health Canada, Swissmedic
  • EMA June 14th, 2017
  • FDA in FR March 1st, 2018
ICH E6 (R2) Finalized

• Response to:
  • Increase in scale, complexity, and cost of clinical trials
  • Global Audit Findings

• Focus:
  • Updating and clarifying standards for electronic records and essential documents
  • Encourage sponsors to implement improved oversight and management of clinical trials
  • Facilitate innovative approaches (QRM, QbD, technology) to clinical trials
ICH Topics

ICH Guidelines / Work Products / 

The ICH topics are divided into four categories and ICH topic codes are assigned according to these categories.

Quality Guidelines
Harmonisation achievements in the Quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.

Safety Guidelines
ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity. A recent breakthrough has been a non-clinical testing strategy for assessing the QT interval prolongation liability: the single most important cause of drug withdrawals in recent years.

Efficacy Guidelines
The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/genomics techniques to produce better targeted medicines.

Multidisciplinary Guidelines
Those are the cross-cutting topics which do not fit uniquely into one of the Quality, Safety and Efficacy categories. It includes the ICH medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI).
ICH “E” Topics

1997 → 2016

- E1 Clinical Safety for Drugs used in Long-Term Treatment
- E2A - E2F Pharmacovigilance
- E3 Clinical Study Reports
- E4 Dose-Response Studies
- E5 Ethnic Factors
- E6 Good Clinical Practice
- E7 Clinical Trials in Geriatric Population
- E8 General Considerations for Clinical Trials
- E9 Statistical Principles for Clinical Trials
- E10 Choice of Control Group in Clinical Trials
- E11 Clinical Trials in Pediatric Population
- E12 Clinical Evaluation by Therapeutic Category
- E13 Clinical Evaluation
- E15 Definitions in Pharmacogenetics / Pharmacogenomics
- E16 Qualification of Genomic Biomarkers
- E17 Multi-Regional Clinical Trials
- E18 Genomic Sampling
- Cross-cutting Topics
More Background

• ICH E6, Good Clinical Practice: Consolidated Guideline
• EMA, Reflection Paper on Risk Based Quality Management in Clinical Trials, 2013
• MHLW, Fundamental Notion on Risk Based Monitoring in Clinical Trials, 2013
• ICH Q9, Quality Risk Management
• Clinical Trials Transformation Initiative (CTTI) workshops on quality by design and quality risk management
• TransCelerate Biopharma, Inc. risk-based monitoring resources
• Sensible Guidelines for the Conduct of Clinical Trials meetings, 2007-2012
More Background cont.

- Other relevant ICH Guidelines:
  - E2A (clinical safety data management), E3 (clinical study reporting), E7 (geriatric populations), E8 (general considerations for clinical trials), E9 (statistical principles), and E11 (pediatric populations)

- New questions: how to best manage the operations and strategy of a trial
  - Action Plan
    - System
    - Project

- An additional update to ICH E6 and ICH E8 in the near future
Gap Analysis & Action Plan

- Procedures & Validated Methods
- Documentation Systems
- Training
- Validation of Computerized Systems
- Quality Control
- Quality Assurance

System Level Impact to Support Study Level
Key Updates ICH E6 R2 Addendum
Poll

• Do you require a certification process for providing copies of source documents for monitoring?
  A. Yes
  B. No
  C. I do not know
What Do The New Definitions Mean to Me? Section 1 Glossary

1.38 Monitoring

• The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

• Adden 1.64 Monitoring Plan:
  • A document that describes the strategy, methods, responsibilities, and requirements for monitoring the trial.

1.39 Monitoring Report:

• A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor’s SOPs.

• [add R2 draft] Outcomes of any centralized monitoring should also be reported.”
What Do The New Definitions Mean to Me?  
Section 1 Glossary

• Adden 1.63 Certified Copy:

  • A copy *(irrespective of the type of media used)* of the original record that has been verified  
    • i.e., by a dated signature  
    OR  
    • by generation through a validated process  

  • to have the same information, including data that describe the context, content, and structure, as the original.

• Adden 1.65 Validation of Computerized Systems:

  • Process of establishing and documenting  
    • that the specified requirements of a computerized system can be consistently fulfilled  
    • from design until decommissioning of the system or transition to a new system.

  • Approach to validation should be based on a risk assessment that takes into consideration  
    • the intended use of the system and  
    • the potential of the system to affect human subject protection and reliability of trial results.
Updates to the 13 Principles of GCP

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

• Adden 2.10: This principle applies to all records referenced in this guideline, irrespective of the type of media used.

2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

• Adden 2.13: Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.
Key Implications / Actions Needed

- **System and Project Level Impact**
  - Process, Documentation, Training, QC, QA (Governance), Study Level
  - **Certified Copy** (1.63)
  - **Monitoring Plan** (1.64)
  - **Validation of Computerized Systems** (1.65)
  - **GCP Principles** (2.10 & 2.13)

  Process, Documentation, Training, QC, QA (Governance), Study Level
New Changes for Investigators / Sites

• No Additions or Changes for Section 3 IRB/IEC

• Investigator: Adden 4.2.5
  • Investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.

• Investigator: Adden 4.2.6
  • If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions,
    • the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and
    • should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
New Changes for Investigators / Sites cont.

Section 4.9 Records and Reports

- Adden 4.9.0 The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site’s trial subjects.

  - Source data should be **attributable, legible, contemporaneous, original, accurate, and complete.**  
    
    [ALCOA-C]

  - Changes to source data should be **traceable, should not obscure the original entry, and should be explained if necessary** (e.g., via an audit trail).

Handwritten/ Electronic documentation and changes to documentation must have these attributes and answer the associated questions:

- **Attributable** - Is it obvious who wrote it? Who is it about?
- **Legible** - Can it be read?
- **Contemporaneous** - Was the documentation created when the data were observed?
- **Original** - Is it a copy; has it been altered?
- **Accurate** - Are conflicting data recorded elsewhere? Is it complete?
- **Complete** - Are changes to source data traceable through proper error correction? Are changes to electronic records include an audit trail? Are all fields complete?
Key Implications / Actions Needed

- **Process, Documentation, Training, QC, QA (Governance), Study Level**
  - Task Delegation (4.2.5)
  - GCP Principles (2.10 & 2.13)

- **System and Project Level Impact**

- **Process, Documentation, Training, QC, QA (Governance), Study Level**
  - Third Party Providers (4.2.6)
  - GCP Principles (2.10 & 2.13)

- **ALCOA (4.90.0)**
  - Certified Copy (1.63)
  - GCP Principles (2.10)

- **Electronic Systems (1.65)**
  - GCP Principles (2.10 & 2.13)

Process, Documentation, Training, QC, QA (Governance), Study Level
Poll

• Have you implemented any Quality Risk Management (QRM) within your Clinical Trial Program?
  A. Yes
  B. No
  C. I do not know
New Changes for Sponsors: Quality Management Systems

Adden 5.0 **Quality Management:**

- **Implement a system to manage quality throughout all stages of the clinical trial** (e.g., design, conduct, recording, evaluation, reporting and archiving)

- **Focus on trial activities essential** to ensuring human subject protection and the reliability of trial results.

- Methods used should be **proportionate to the risks**

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**Quality management includes:**

- Design of efficient clinical trial protocols,

- Tools and procedures for data collection and processing

- Collection of information that is essential to decision making

Ensure that all aspects of the trial are:

- **operationally feasible** and

- should avoid **unnecessary complexity, procedures and data collection**

Operational documents: clear, concise and consistent
5.0 Quality Management

- (5.0.1) Critical Process and Data Identification
- (5.0.2) Risk Identification
- (5.0.3) Risk Evaluation
- (5.0.4) Risk Control
- (5.0.5) Risk Communication
- (5.0.6) Risk Review
- (5.0.7) Risk Reporting
Flow of QRM in GCP

Initiate Risk Based Quality Management Process:

- Information gathering for risks identification

(a) RISK ASSESSMENT:
- Establish what really matters and identify risks/tolerance limits

(b) RISK CONTROL:
- Are the risks acceptable?
  - yes (Risk acceptance)
    - Implement risk mitigation plan & adjust the quality tolerance limits
  - no (Risk reduction)
    - Define risk mitigation/acceptance level and write/revise risk management plan & quality tolerance limits

Risk Management Tools:
- Risk Review (c):
  - Review events
- Risk Communication (e)
- Trial ongoing:
  - yes
  - Output: Final (Risk Management) Report / clinical study report
  - no

Act

Plan

Check

Do
Integrating Quality Risk Management Process with Flow of GCP Sponsor Oversight

**Institution Level QRM**
- Cross-functional team
- Risk Management Leader(s)
- Risk Tool / Platform
- Risk Assessment (Compliance, Financial, etc.)
- Link to historical data from metrics / audit findings

**Develop Study Risk Management Plan (MP, DMP, SMP, etc.)**
- List of potential threats
- Risk assessment
  - Product
  - Disease
  - Patient
  - Self
  - Sponsor
  - IRB

**Pre-study**

**During the Trial**

**Plan(s) Management**
- Timeliness of data completion
  - Enrollment
  - AE
  - Deviation
  - Audit results
  - Noncompliance
  - Staff turn-over
  - Risk mitigation adjustment

**Study Closure**
- Enrollment outcomes
- Deviations outcomes
- Audit readiness
- Metric adjustment from Risk Management Plan statistics

**IMPACT ANALYSIS**

**Re-Assess & Adjust**
5.18 Extent and Nature of Monitoring

• Adden 5.18.3
  • Develop a **systematic, prioritized, risk-based approach to monitoring** clinical trials.

• **Flexibility** in the **extent and nature** of monitoring described is intended to permit varied approaches that improve the **effectiveness and efficiency** of monitoring.

• May choose **on-site** monitoring, a **combination** of on-site and centralized monitoring, or, where justified, **centralized** monitoring.

• Sponsor should document the **rationale** for the chosen monitoring strategy (e.g., in the monitoring plan).
  • **On-site monitoring** is performed at the sites at which the clinical trial is being conducted.
  • **Centralized monitoring** is a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g., data managers, biostatisticians).
5.18 Extent and Nature of Monitoring cont.

- **Centralized monitoring processes:**
  - provide **additional** monitoring capabilities,
  - can complement and reduce the extent and/or frequency of on-site monitoring, and
  - help **distinguish** between reliable data and potentially unreliable data.

- Review, that may include statistical analyses, of accumulating **data from centralized monitoring** can be used to:
  - (a) identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations.
  - (b) examine data trends such as the range, consistency, and variability of data within and across sites.
  - (c) evaluate for systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems.
  - (d) analyze site characteristics and performance metrics.
  - (e) select sites and/or processes for targeted on-site monitoring.
• Adden 5.18.6 (e)
  • Reports of on-site and/or centralized monitoring should be provided to the sponsor,
    • including appropriate management and staff responsible for trial and site oversight) in a timely manner for review and follow up.
  • Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan.
  • Reporting of centralized monitoring activities should be regular and may be independent from site visits.
New Changes for Sponsor Monitoring

Monitoring Plan (5.18.7)

- Monitoring responsibilities of each party involved
- Monitoring strategy
- Reference applicable monitoring policies and procedures
- Monitoring of critical data and processes

Sponsors should document the rationale for the chosen strategy. (5.18.3)
Monitor should provide monitoring results in a timely manner (5.18.6.e)
% of onsite vs centralized monitoring

MONITORING is NOT just the MONITOR. APPLY Cross-functionally.
Key Implications / Actions Needed

5.0 Quality Management

5.18 Monitoring

System and Project Level Impact

Process, Documentation, Training, QC, QA (Governance) Study Level
Poll

- Does your vendor management include oversight of the vendors sub-contractors?
  - A. Yes
  - B. No
  - C. I do not know
Poll

• Does your core training for your staff include Root Cause Analysis training?
  A. Yes
  B. No
  C. I do not know
New Changes for Sponsors: Vendor Oversight

5.2 Contract Research Organization (CRO)

• 5.2.2 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

• Adden 5.2.2
  • Sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf,
    • including trial-related duties and functions that are subcontracted to another party by the sponsor’s contracted CRO(s).
Documenting Oversight Activities

Reports vs. other approaches for central activities

• Traditional elements
• Description of any noncompliance, potential noncompliance, data irregularities, or other deficiencies identified
• Description of any actions taken, to be taken, or recommended, including the person responsible for completing actions and the anticipated date of completion
• Documentation with sufficient detail to allow verification that the monitoring plan was followed
• Management timely review and follow-up

FDA: RBM Guideline
5.5 Trial Management, Data Handling, and Record Keeping

5.5.3 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

- (a) Ensure and document that the electronic data processing system(s) conforms to the sponsor’s established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation).

- Adden 5.5.3 (a): The sponsor should base their approach to validation of such systems on a risk assessment.

- Taking into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.
5.5 Trial Management, Data Handling, and Record Keeping cont.

5.5.3 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:
• (b) Maintains SOPs for using these systems.

• Adden 5.5.3.(b) Electronic records SOPs should:
  • cover system setup, installation, and use.
  • describe system validation and functionality testing, data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning, and decommissioning.

• Responsibilities of the sponsor, investigator, and other parties should be clear to the use of these computerized systems, and the users should be provided with training in their use.
5.5 Trial Management, Data Handling, and Record Keeping cont.

5.5.3 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

• Adden 5.5.3.(h)
  • Ensure the integrity of the data including any data that describe the context, content, and structure.
    • This is particularly important when making changes to the computerized systems, such as software upgrades or migration of data.
5.20 Noncompliance

5.20.1 Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

- Adden
  - If noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions.
8.1 Adden
Essential Documents

• Sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents including source documents.

• Storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

• Essential documents for the trial should be supplemented or may be reduced where justified (in advance of trial initiation) based on the importance and relevance of the specific documents to the trial.
8.1 Adden
Essential Documents cont.

• Sponsor should ensure that the investigator has control of and continuous access to the CRF data reported to the sponsor. The sponsor should not have exclusive control of those data.

• When a copy is used to replace an original document (e.g., source documents, CRF), the copy should fulfill the requirements for certified copies.

• Investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during, and after the trial.
Key Implications / Actions Needed

- Process, Documentation, Training, QC, QA (Governance), Study Level
- Electronic Records SOP and Integrity (5.5.3 (b) (h))
- CRO Oversight (5.2)
- RCA & CAPA (5.20.1)
- Essential Documents (8.1) Certified Copies (1.63)

System and Project Level Impact

Process, Documentation, Training, QC, QA (Governance), Study Level
Gap Analysis & Action Plan

- Procedures & Validated Methods
- Documentation Systems
- Training
- Validation of Computerized Systems
- Quality Control
- Quality Assurance

System Level Impact to Support Study Level
Summary and Additional Questions

• Describe the key updates to the ICH E6 GCP Guideline impacting running clinical trials for sites and sponsors

• Identify how the finalized ICH guideline affects oversight for clinical trials for sponsors and sites

• Recognize the essential elements to include in implementing the new requirements to ensure quality across studies no matter the size of the site
For questions after the course, contact:

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