ICH E6 Guideline –R 2

優良臨床試驗指引修改及增編附錄

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2016.11.23

Statement of the Perceived Problem

- Although ICH E6 generally can be interpreted as providing sponsors flexibility to implement innovative approaches, it has been misinterpreted and implemented in ways that impede innovation by, for example, emphasizing less important aspects of trials at the expense of critical aspects
- Modernising ICH E6 by supplementing it with additional recommendations will better facilitate broad and consistent international implementation of new methodologies.

Risk-Based Monitoring

2011.08.04

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

4 August 2011
EMA/INS/GCP/394194/2011
Compliance and Inspection

Reflection paper on risk based quality management in clinical trials
Draft

Draft Agreed by the CTFG[1] for release for consultation	31 May 2011
Draft Adopted by the GCP Inspectors Working Group for consultation	14 June 2011
End of Consultation (Deadline for Comments)	15 February 2012

Comments should be provided using this template. The completed comments form should be sent to GCP@ema.europa.eu.

Keywords	Quality Management, Risk Management, Quality Tolerance Limit, Risk Control, Clinical Trial

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2013.08

Guidance for Industry

Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Good Clinical Practice (OGCP)
Office of Regulatory Affairs (ORA)
August 2013
Procedural

OMB Control No. 0910-0733
Expiration Date: 03/31/2016
See additional PRA statement in section VII of this guidance.

Issue to be Resolved

- ICH E6 should be supplemented with additional recommendations to facilitate innovative approaches to GCP to better ensure data quality and human subject protection in an environment of highly complex multinational trials.
- FDA, EMA, and MHLW/PMDA have recently issued documents related to clinical trial quality.
  - FDA's guidance focuses on a portion of quality management, risk-based approaches to clinical trial oversight by sponsors.
  - EMA's reflection paper is broader in scope and discusses risk-based quality management in clinical trials.
  - MHLW/PMDA's document provides the fundamental ideas of risk-based monitoring in clinical trials.
  - ICH has issued guidelines on pharmaceutical quality systems and quality risk management that are critical to advancing global manufacturing standards.
- A harmonised guideline on approaches to quality management for clinical trials, including risk-based monitoring and supporting the use of new technology could have a similar impact on the protection of trial participants and there liability of trial results. Prioritised, proactive quality management approaches to clinical trials are supported by industry to ensure data quality and human subject protection.

Background to the Proposal

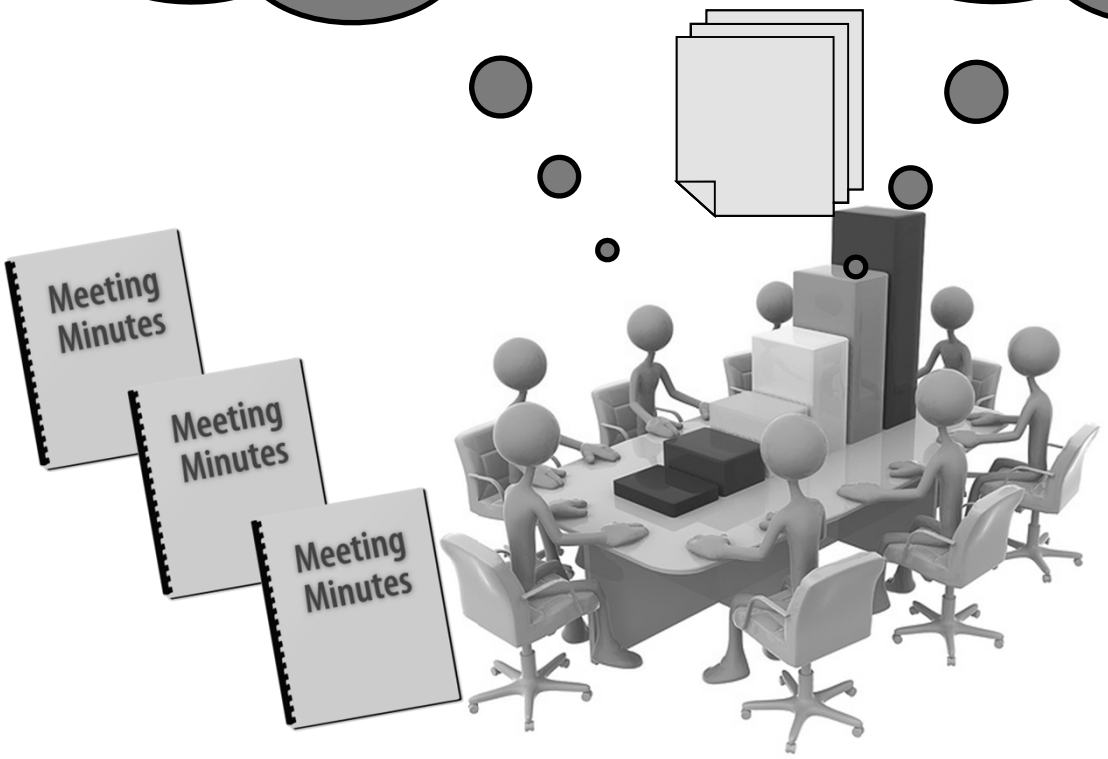
- ICH E6, Good Clinical Practice: Consolidated Guideline
- US FDA, Guidance for Industry Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring, 2012
- EMA, Reflection Paper on Risk Based Quality Management in Clinical Trials, 2013
- MHLW, Fundamental Notion on Risk Based Monitoring in Clinical Trials, 2013
- ICH Q9, Quality Risk Management
- Clinical Trials Transformation Initiative 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

Background for ICH E6 meeting

- Many practices in clinical trial design, conduct, recording, and oversight are not informed by **risk-based approaches** for assuring quality.
- ICH E6 does not adequately address use of **technology** in clinical trial oversight and management
  A. Electronic systems and electronic data capture
  B. Electronic trial master file

Revision of ICH E6

Addendum to ICH E6



Monthly Telephone conference

ADDENDUM E6 (R2)

Addendum E6 (R2)

Step 2 version, dated 11Jun 2015

E6	**ADDENDUM to R1 document** **Additions to Sections: Introduction** **1.11.1, 1.38.1, 1.39, 1.60.1, 2.10, 4.2.5, 4.2.6, 4.9.0, 5.0, 5.0.1, 5.0.2, 5.0.3, 5.0.4, 5.0.5, 5.0.6, 5.0.7, 5.2.1, 5.2.2, 5.5.3 (b), 5.5.3 (h), 5.18.3, 5.18.6 (e), 5.18.7, 5.20.1, 8.1**

Introduction (addendum portion)

- Since the development of the ICH GCP Guideline, the scale, complexity, and cost of clinical trials have increased. Evolutions in technology and risk management processes offer new opportunities to increase efficiency and focus on relevant activities. This guideline has been amended 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 data integrity. Standards regarding electronic records and essential documents intended to increase clinical trial quality and efficiency have also been updated.
- This ICH GCP Guideline addendum provides a unified standard for the European Union (EU), Japan, the United States, Canada and Switzerland to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

1. GLOSSARY

- 1.11.1 Certified Copy
  - A paper or electronic copy of the original record that has been verified (e.g., by a dated signature) or has been generated through a validated process to produce an exact copy having all of the same attributes and information as the original.
- 1.38.1 Monitoring Plan
  - A description of the methods, responsibilities, and requirements for monitoring the trial
- 1.39 Monitoring Report, add…..
  - Outcomes of any centralized monitoring should also be reported.

1. Glossary (cont.)

- 1.60.1 Validation of computerized systems
  - A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled. Validation should ensure accuracy, reliability, and consistent intended performance, from design until decommissioning of the system or transition to a new system.

4. INVESTIGATOR

- 4.2.5
  - The investigator is responsible for supervising any individual or party to whom the investigator delegates study tasks conducted at the trial site.
- 4.2.6
  - If the investigator/institution retains the services of any party to perform study tasks they should ensure this party is qualified to perform those study tasks and should implement procedures to ensure the integrity of the study tasks performed and any data generated.

- 4.9 Records and Reports
- 4.9.0 The investigator 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. 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)

5.0 Quality Management

- The quality management system should use a risk based approach as described below.
  - 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

- 5.0.1 Critical Process and Data Identification
  - During protocol development, the sponsor should identify those processes and data that are critical to assure human subject protection and the reliability of study results.
- 5.0.2 Risk Identification
  - Risks to critical study processes and data should be identified. Risks should be considered at both the system level (e.g. facilities, standard operating procedures, computerized systems, personnel, vendors) and clinical trial level (e.g. investigational product, trial design, data collection and recording).
- 5.0.3 Risk Evaluation
  - The identified risks should be evaluated by considering:

    a) The likelihood of errors occurring, given existing risk controls.

    b) The impact of such errors on human subject protection and data integrity.

    c) The extent to which such errors would be detectable.

- 5.0.4 Risk Control
  - The sponsor should identify those risks that should be reduced (through mitigating actions) and/or can be accepted. 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 standard operating procedures, and training in processes and procedures.
  - Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or data integrity. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.
- 5.0.5 Risk Communication
  - The quality management activities should be documented and communicated to stakeholders to facilitate risk review and continual improvement during clinical trial execution.
- 5.0.6 Risk Review
  - 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.
- 5.0.7 Risk Reporting
  - The sponsor should describe the quality management approach implemented in the trial (ICH E3, Section 9.6 Data Quality Assurance) and summarize important deviations from the predefined quality tolerance limits in the clinical study report.

5.2 Contract Research Organization (CRO)

- 5.2.1 …….The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf.
- 5.2.2 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

Addendum…

- The sponsor should document approval of any subcontracting of trial-related duties and functions by a CRO.

5.5.3When 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).

(b) Maintains SOPs for using these systems.

- The SOPs should cover system setup, installation, and use. The SOPs should describe system validation and functionality testing, data collection and handling, system maintenance, system security measures, change control, and data backup, recovery, contingency planning and decommissioning. The responsibilities of the sponsor, investigator, and other parties with respect to the use of these computerized systems, should be clear and the users should be provided with training in the use of the systems.

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

5.18.3 Extent and Nature of Monitoring

- The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials. The flexibility in the extent and nature of monitoring described in this section is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring. A combination of onsite and centralized monitoring activities may be appropriate. The 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 ongoing and/or cumulative data collected from all trial sites in a timely manner. Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring by such methods as:
  a) Routine review of submitted data.
  b) Identification of missing data, inconsistent data, data outliers or unexpected lack of variability and protocol deviations that may be indicative of systematic or significant errors in data collection and reporting at a site or across sites, or may be indicative of potential data manipulation or data integrity problems.
  c) Using statistical analyses to identify data trends such as the range and consistency of data within and across sites.
  d) Analyzing site characteristics and performance metrics.
  e) Selection of sites and/or processes for targeted on-site monitoring.

5.18.6 Monitoring Report

Addendum

(e) Monitoring results 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 as indicated. Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan.

5.18.7 Monitoring Plan

The sponsor should develop a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. The plan should describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used and the rationale for their use. The plan should also emphasize the monitoring of critical data and processes. Particular attention should be given to those aspects that are not routine clinical practice and that require additional training. The monitoring plan should reference the applicable policies and procedures.

5.20 Noncompliance

- When significant noncompliance is discovered the sponsor should identify the cause and ensure that appropriate corrective and preventive actions are implemented, effective and documented. If required by applicable law or regulation the sponsor should inform the regulatory authority(ies) when the non-compliance is a serious breach of the trial protocol or GCP.

8.ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

The sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents. The storage system (irrespective of the media used) should provide for document identification, search, and retrieval.

Depending on the activities being carried out, individual trials may require additional documents not specifically mentioned in the essential document list. The sponsor should include these as part of the trial master file.

The 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 the copy should fulfill the requirements for **certified copies**.

The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during and after the trial.

THANKS FOR YOUR ATTENTION

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