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# ICH E6 Guideline Revision Fact Sheet

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02/02/16

## DESCRIPTION

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First update in 20 years to address changes to scale and complexity of clinical trials.

## TOPICS

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- OVERVIEW OF CHANGES
- DEFINITIONS
- PRINCIPLES
- INVESTIGATOR PROVISIONS
- SPONSOR PROVISIONS
- TRIAL AND DATA RECORDS
- NON-COMPLIANCE

# First Update in 20 Years to Address Changes to Scale and Complexity of Clinical Trials

The ICH E6, *Good Clinical Practice (GCP): Consolidated Guideline* describes the responsibilities and expectations of all participants in clinical trials, including investigators, monitors, sponsors and IRBs. The Guideline is being revised for the first time since its initial publication in 1996 with a draft Integrated Addendum published on June 11, 2015. This is the second step of a five step process for finalizing the revised Guideline with comments from Japan, the EU, FDA, and Canada (all adopters of the existing version of the Guideline) pending.<sup>1</sup>

The revisions in the Integrated Addendum are intended to address the problem of changes to the scale and complexity of clinical trials and to ensure appropriate use of technology and a modern approach to GCP. The hope is to enable implementation of innovative approaches to clinical trial design, management, oversight, conduct, documentation, and reporting that will better ensure human subject protection and data quality.<sup>2</sup>

The proposed changes in the draft Addendum are outlined below. The revisions focus on the use of electronic documents and systems, record-keeping requirements, risk-based monitoring and clarifying investigator and sponsor responsibilities.

## Overview of changes

### DEFINITIONS

The draft Addendum adds three new definitions to the ICH Guideline. As with other changes throughout the document, the definitions relate to use of electronic documents and systems and monitoring of trials. The following definitions are new:

- **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.<sup>3</sup>
- **Monitoring Plan:** A description of the methods, responsibilities and requirements for monitoring the trial.<sup>4</sup>

- **Validation of Computer 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.<sup>5</sup>

In addition, the term "**monitoring report**" is revised to add the second sentence to the existing definition: "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. Outcomes of any centralized monitoring should also be reported."<sup>6</sup>



#### PRINCIPLES OF ICH GCP

Section 2 of the Consolidated Guideline outlines the principles of ICH GCP. It is untouched with the exception of one revision to Subsection 2.10, which relates to recording, handling, and storage of clinical trial information. The draft Addendum adds the clarifying sentence: "This principle applies to all records (paper or electronic) referenced in this guideline."

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#### INVESTIGATOR PROVISIONS

There are a few changes regarding requirements for investigators. First, there are two additional investigator responsibilities introduced in new sub-sections as follows:

- 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.<sup>7</sup>

An additional requirement is outlined in another new sub-section relating to records and reports, which states:

- 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).<sup>8</sup>

## **SPONSOR PROVISIONS**

The bulk of the changes in the draft Addendum relate to the sponsor's responsibilities. The first revision is the introduction of a section regarding Quality Management, which is provided below. This section goes into detail about who the sponsor can manage quality in a trial and using methods that are proportionate to the risk in the trial and the importance of the information collected. This new Section reads as follows:

### **5.0 Quality Management**

The sponsor should implement a system to manage quality throughout the design, conduct, recording, evaluation, reporting and archiving of clinical trials. Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the efficient design of clinical trial protocols, data collection tools and procedures, and the collection of information that is essential to decision making. The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected. The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures and data collection. Protocols, case report forms, and other operational documents should be clear, concise and consistent. The quality management system should use a risk-based approach as described below.

#### **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 and summarize important deviations from the predefined quality tolerance limits in the clinical study report (ICH E3, Section 9.6 Data Quality Assurance).<sup>9</sup>

Additional changes regarding the sponsor's responsibility can be found in Section 5.1 regarding Quality Assurance and Quality Control. These changes address the sponsor responsibility to have appropriate oversight of contractors.<sup>10</sup>



### TRIAL DATA AND RECORDS

The issue of trial data management is also addressed in Section 5.5.3, which has been revised to include guidance about SOPs for data management and sponsor responsibility for the integrity of data.<sup>11</sup> Later in Section 8.1 the draft Addendum addresses essential documents for the conduct of the clinical trial that indicates the sponsor and investigator/institution “should maintain a record of the location(s) of their...essential documents.” There is an explicit requirement that the investigator/institution should have access to and control over the essential documents and that the sponsor should not have exclusive control.<sup>12</sup>

### NON-COMPLIANCE

Again, the draft Addendum clarifies the sponsor’s responsibilities in Section 5.20.1, which now indicates that a sponsor is required to perform a root cause analysis and implement appropriate corrective and preventative action when significant noncompliance is discovered.<sup>13</sup>

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### REFERENCES

1. See Website: <http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>, accessed 09/17/2015.
2. See Final Concept Paper Addendum for ICH E6: Guideline for Good Clinical Practice dated 2 June 2014, available at: [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E6/E6\\_R2\\_Concept\\_Paper\\_July\\_2014.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2_Concept_Paper_July_2014.pdf), accessed 09/17/2015.
3. Section 1.11.1, p. 3, Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2), Current Step 2 version, 11 June 2015, available at: [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E6/E6\\_R2\\_Addendum\\_Step2.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2_Addendum_Step2.pdf)
4. Id. 1.38.1, p. 6.
5. Id.1.60.1, p. 8
6. Id.
7. Id., p. 14.
8. Id., p. 19.
9. Id., p. 21-2.
10. Id., p. 21-2.
11. Id., p. 24.
12. Id., P. 47.
13. Id., p. 34.

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