



# Overview

## ICH GCP E6(R2)

### Integrated

### Addendum



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## Introduction

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On 15 December 2016, the International Council for Harmonisation (ICH) adopted the revised E6 guideline, entitled “Integrated Addendum to Good Clinical Practice (GCP).” Now, regulatory implementation is carried out according to the same national/regional procedures that apply to other regulatory guidelines and requirements (ICH 2017).

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### Who does the new guideline affect?

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The ICH E6 addendum affects the full clinical trial cycle and research enterprise. The revisions to the guideline mainly affect sponsors, stipulating a more proactive approach to study design, as well as risk management and study monitoring. However, Contract Research Organizations (CROs), that often delegated trial-related tasks by the sponsor, need to learn about the revised practice points in the guideline. Sponsor-investigators also need to be aware of the changes and their responsibilities associated with being a sponsor. The changes associated with being a sponsor. The changes are important to investigators, Institutional Review Board/Independent Ethics Committee (IRB/IEC) members and administrators, study monitors, clinical research coordinators and professionals, and institutions/sites.

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### Why revise the guideline?

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Research has modernized in the thirty years since the original E6(R1) guideline. However, E6(R2) still has the same goal of standardization.

Standardization ensures that marketing applications to various regulatory agencies around the world can occur without redundant testing. Many pharmaceutical companies conduct multi-site international clinical trials. Repeating trials in different markets to comply with slightly different regulations is inefficient and unnecessarily delays bringing new drugs to patients.

“Lack of harmonisation may not only slow the adoption of innovative approaches to clinical trial design, management, oversight, conduct, documentation, and reporting, but may also lead to inconsistency in approaches sponsors use among the ICH regions which could add cost and time to the development of needed drug products” (ICH 2014b).

The European Medicine Agency (EMA) submitted a report in 2014 summarizing 398 GCP inspections of clinical trial sponsors, sites, and CROs from 2000-2012. The report’s critical and major findings were mostly in relation to:

Monitoring

Data management

Clinical study reports

Source documentation

This was good news, in that, most critical findings were not directly related to informed consent or human subject safety. However, the report identified concerns and areas for improvement in the design and conduct of clinical trials. It was clear that the ICH E6 guidelines that originally provided a standardized framework for harmonization needed to be modernized for the current research landscape and address these GCP inspection findings.

The ICH convened an expert working group to create an addendum to the existing E6 guideline. The expert working group was consisted of ICH members from both industry and regulatory agencies, as well as observers, to address current research topics like quality by design, quality risk management, and focus on technological tools to ensure robust conduct, oversight, and reporting.

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## Format of Revised Guideline

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The revised guideline uses an addendum-integrated format. This format embeds the revisions into the current E6(R2) guideline, identifying the change as “**ADDENDUM**” above the new text (below the old text) and using edge marks to show the changes.

include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

**1.62 Well-being (of the trial subjects)**

The physical and mental integrity of the subjects participating in a clinical trial.

**ADDENDUM**

**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.

**1.64 Monitoring Plan**

A document that describes the strategy, methods, responsibilities, and requirements for monitoring the trial.

**1.65 Validation of Computerized Systems**

A 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. The 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.

The revised guideline also includes a document history with dates and versions of the guideline, as well as a table that displays the current E6(R2) sections that were revised.

## What are the revisions?

The focus of the revisions is on increasing human subject protections and data integrity mainly through better study design and conduct. Therefore, most of the changes affect the sponsor. As seen below, the sponsor section was the most revised. No revisions were made to IRB/IEC, Investigator’s Brochure, or the clinical trial protocol and protocol amendment(s) sections.

ICH E6 Sections	Revisions Made To:
Introduction	Introduction
Glossary	1.63, 1.64, 1.65
The Principles of ICH GCP	2.10, 2.13
Institutional Review Board (IRB) / Independent Ethics Committee (IEC)	None
Investigator	4.2.5, 4.2.6, 4.9.0
Sponsor	5.0, 5.0.1, 5.0.2, 5.0.3, 5.0.4, 5.0.5, 5.0.6, 5.0.7, 5.2.2, 5.5.3 (a), 5.5.3 (b), 5.5.3 (h), 5.18.3, 5.18.6 (e), 5.18.7, 5.20.1
Clinical Trial Protocol and Protocol Amendment(s)	None
Investigator’s Brochure	None
Essential Documents for the Conduct of a Clinical Trial	8.1

The focus of the revisions includes:

- *Using a risk management approach in designing studies*
- *Promoting the use of risk-based and centralized monitoring in managing studies*
- *Addressing the reporting and follow-up of significant noncompliance (including conducting a root cause analysis, and creating a corrective and preventative action plan)*
- *Addressing technology issues (for example, specifying that electronic systems should be validated, backed-up, and safeguarded)*
- *Specifying oversight responsibilities of sponsors and investigators*
- *Improving data integrity (for example, requiring that source data are attributable, legible, contemporaneous, original, accurate, and complete)*
- *Ensuring both investigators and sponsors have access to study data and documents*

The revisions aim to balance efficiency in clinical trials while retaining human subject protections and data integrity. Analysis of progress following implementation may provide sponsors and investigators with insight into areas that require further clarification.

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# ICH (2016) E6(R2) Revisions by Section

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## ***Introduction***

The introduction section revisions explain the purpose of the revisions to the guideline, refer to other ICH guidelines relevant to clinical trials (for example, E2A Clinical Safety Data Management and E3 Clinical Study Reporting), and clarify that the E6(R2) addendum should replace E6(R1).

## ***Section 1 - Glossary***

ICH E6 adds the following definitions to the glossary:

- *Certified copy (section 1.63)*
- *Monitoring plan (section 1.64)*
- *Validation of computerized systems (section 1.65)*

## ***Section 2 - The Principles of ICH GCP***

Reflecting modernization from paper-based documentation to electronic systems, section 2.10 includes a minor clarification to indicate that clinical trial information (irrespective of the type of media used) should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

The emphasis on data integrity is seen through a minor revision to section 2.13, which added that quality assurance systems should focus on human subject protection and reliability of trial results.

## ***Section 3 - Institutional Review Board (IRB) / Independent Ethics Committee (IEC)***

No changes were made to this section.

## ***Section 4 - Investigator***

The investigator continues to be ultimately responsible for conducting the trial. No changes were made to the “Investigator’s Qualifications” section and the investigator is still allowed to delegate trial-related responsibilities. “Adequate Resources” revisions specify that the investigator is responsible for supervision (oversight) of persons with delegated tasks. Further, the investigator should ensure research staff are capable and trained for their assigned trial-related tasks. This is aligned with the U.S. Food and Drug Administration (FDA) regulations (Investigational New Drug Application 2016) and FDA (2009) guidance.

The added text in “Records and Reports” also mirrors the FDA in specifying that “source data should be attributable, legible, contemporaneous, original, accurate, and complete” (ICH 2016). The commonly used acronym is ALCOAC. Records and reporting may be written or electronic.

<b>A</b> tributable	<i>The record identifies who created or modified the record, when the record changed, and why it changed.</i>
<b>L</b> egible	<i>The record and dates of an entry are clear and can be interpreted and understood.</i>
<b>C</b> ontemporaneous	<i>The data are recorded in real-time, the data are observed, and records are signed (or initialed) and dated accurately.</i>
<b>O</b> riginal	<i>The record is original as it is captured, collected, or is an exact facsimile of the original.</i>
<b>A</b> ccurate	<i>The record is collected and recorded honestly and completely to demonstrate transparency.</i>
<b>C</b> omplete	<i>Up-to-date and with no omissions.</i>

***Example of "Attributable"***

A study team member who performed the assessment/procedure should sign his/her name/initials when documenting the assessment/procedure that was performed. If someone else is present during the assessment/procedure and recording on behalf of the principal investigator, that person should also sign his/her name/initials.

***Example of "Contemporaneous"***

A late data entry should be noted as such. If a study team member forgets to enter data at the correct time and must go back and do it later, the study team member should note this fact and include a date and time when entering the data.

***Example of "Original"***

Study team members should not use pencil. It is important to use pen for originals. To make changes to an original entry, draw a single line through the error, then initial and date with an explanation for the correction. No correction fluid or writing over an original entry is permitted.

## ***Section 5 - Sponsor***

The most extensive changes to ICH E6 were made to the sponsor's section, beginning with a new section on quality management.

### ***Quality Management***

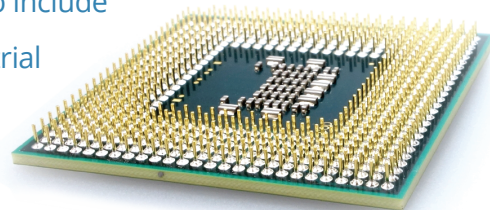
ICH E6 requires sponsors to implement a "quality management system" from trial design to trial conduct to close-out. A well-designed protocol is the most important tool for ensuring human subject protection and high-quality data (FDA 2011). The addendum adds that the sponsor should use a risk-based approach to develop the protocol and study materials. This process is outlined in section 5.0 as risk identification, risk evaluation, risk control, risk communication, risk review, and risk reporting.

### ***Active Oversight***

As stated in the previous guideline, the sponsor is still permitted to delegate trial-related responsibilities to others (for example, contractors and vendors), but the sponsor is ultimately responsible for the quality and integrity of the trial data. The revised guideline adds, in section 5.2.2, that the sponsor should ensure oversight of trial-related duties and functions carried out on its behalf, even for those responsibilities subcontracted to another party by the sponsor's contracted CRO (ICH 2016). The sponsor must plan and describe how this will be assessed. This is typically done through the sponsor's qualification/requalification audit of the CRO. This revision to ICH is a clarification of expected trial conduct to reduce misinterpretation of oversight responsibilities.

### ***Electronic Systems***

ICH E6 recognizes that sponsors routinely use electronic systems for trial data. Further changes were added in section 5.5, "Trial Management, Data Handling, and Record Keeping," to include that the sponsor should use a risk assessment in validating electronic trial data handling and/or remote trial data systems. As before, the guideline requires the sponsor to maintain standard operating procedures (SOPs) for using these electronic data systems. The addendum adds specific requirements that the SOPs must include system setup, installation, use, validation and functionality testing, data backup, recovery, and training for users. The addendum also clearly puts the responsibility for reliable data on the sponsor, requiring in section 5.5.3(h) that the sponsor ensure the integrity of the data, even when making changes to the computerized systems (such as, software upgrades or migration of data) (ICH 2016).



## Monitoring

Effective monitoring is critical to ensuring both subject protections and high quality trial data. Monitoring continues to be the sponsor's responsibility. By far, the most substantial changes to ICH E6 are related to study monitoring. The addendum incorporates elements from the FDA's (2013) risk-based monitoring guidance, which supports alternative approaches (specifically, risk-based and combination activities) to monitoring. The revised ICH E6 requires that the sponsor 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. The sponsor may choose on-site monitoring, a combination of on-site and centralized (off-site) monitoring, or, where justified, centralized monitoring (only). The sponsor should document the rationale for the chosen monitoring strategy (e.g., in the monitoring plan).

The ICH E6 addendum defines centralized monitoring and distinguishes it from on-site monitoring. Centralized monitoring allows the real-time review of accumulating trial data, which helps to identify missing or inconsistent data, examine trends, identify data errors, analyze sites/investigators, and/or select sites for targeted on-site monitoring.

Note: If the sponsor is planning to perform off-site reviews of source documents (centralized monitoring), this should be established and agreed to by the site, well before study initiation. Centralized monitoring may be more time-consuming for sites than typical on-site visits.

Per section 5.18.6(e), "monitoring reports," including both centralized reports and on-site monitoring visit reports, are now required to be provided to the sponsor (including appropriate sponsor management and CRO staff) by the monitor in a timely manner and with sufficient detail to allow sponsors to follow up, if needed. This allows and requires the sponsor to follow-up on identified serious noncompliance. In section 5.20, the addendum adds the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions (for example, a corrective and preventative action plan) if noncompliance is or may be serious.



Finally, each study now requires a study-specific monitoring plan. The plan should take into consideration potential risks of harm to human subjects and data integrity. The monitoring plan should not only include how the study will be monitored, but a rationale. Additionally, the monitoring plan should also emphasize the monitoring of critical data and processes, especially those that are not routine clinical practice and require extra training (ICH 2016).



## Section 6 - Clinical Trial Protocol and Protocol Amendment(s)

No changes were made to this section.

## Section 7 - Investigator's Brochure

No changes were made to this section.

## Section 8 - Essential Documents for the Conduct of a Clinical Trial

ICH E6(R2) adds in the introduction section a requirement to specify that both the sponsor and investigator/institution (site) conducting the trial should maintain their respective essential documents in a system that provides processes for locating the document, as well as providing for document identification, version history, search, and retrieval.

ICH E6(R2) adds more about document control, specifying that the sponsor should not have exclusive control of case report form (CRF) data submitted by the investigator, and that the investigator/institution should have control of all their own essential documents before, during, and after the trial. ICH E6(R2) clarifies that the sponsor should ensure that the investigator has continuous access to the CRF data reported to the sponsor (ICH 2016). Also, ICH E6(R2) states that copies used to replace original documents must meet the definition of certified copies.



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## Law or guidance?

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The FDA adopted ICH E6(R1) and subsequently ICH E6(R2) as guidance. Therefore, the ICH E6 guidelines do not have the force of law in the U.S. and are not regulations. In the Federal Register Notice, FDA stated that the ICH E6 guideline "does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both" (FDA 2018, 8882-3).

Health Canada implemented ICH E6(R1) in 1997. The revised ICH E6(R2) has not yet been implemented by Health Canada. Health Canada did advise of its intent to implement with a target date of 1 April 2019.

The European Commission adopted ICH E6(R2) on 15 December 2016 and has set an effective date of 14 June 2017.

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## Summary

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The ICH E6(R2) guideline continues to provide practical standardization for the conduct of clinical trials. The revisions reflect a modernizing and evolving research landscape and do not change the core of the guideline. Sponsors, investigators, and others in the research enterprise should be aware of the integrated addendum and new procedures in order to continue to design and conduct clinical trials that protect human subjects and ensure data integrity.



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## References

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- International Council for Harmonisation (ICH). 2014. "Final Business Plan Addendum for ICH E6: Guideline for Good Clinical Practice." Accessed June 6, 2017.
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- U.S. Food and Drug Administration (FDA). 2018. "E6(R2) Good Clinical Practice: Integrated Addendum to E6(R1); International Council for Harmonisation; Guidance for Industry." Federal Register 41(83):8882-3.

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## Additional Resources

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- International Council for Harmonisation (ICH). 2014. "Final Concept Paper Addendum for ICH E6: Guideline for Good Clinical Practice." Accessed June 6, 2017.
- International Council for Harmonisation (ICH). 2015. "Addendum to ICH E6 (R2) presentation." Accessed January 20, 2017.