ICH
harmonisation for better health

Module 1.1 Transcript

Interpretation and Application of ICH E6(R3):

GOOD CLINICAL PRACTICE (GCP)

Welcome to the Interpretation and Application of ICH E6(R3): Good Clinical Practice.

For instructions on how to navigate the system, please select the type of device you're using to view this module.

ICH stands for the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. The ICH GCP Guideline sets out a unified standard to facilitate the mutual acceptance of clinical trial data for ICH member countries and regions by applicable regulatory authorities.

This training is intended for anyone involved in the conduct of an interventional clinical trial. Trial conduct includes processes in relation to planning, initiating, performing, recording, oversight, evaluation, analysis, and reporting activities.

This includes sponsors and sponsor staff, investigators and investigator site staff, service providers, Institutional Review Boards (IRBs), or Independent Ethics Committees (IECs), and regulators.

The new E6(R3) Guideline defines a service provider as a person or organisation, whether commercial, academic, or other, who provides a service used by either the sponsor or the investigator to fulfil trial-related activities.

This training includes 5 separate modules that will provide an introduction to the E6(R3) Guideline and an overview of the foundational concepts described in the guideline and describe responsibilities and oversight of key parties involved in trials, data governance, informed consent of trial participants, and essential records for the conduct of a clinical trial.

This training is not a complete guide and does not substitute for reading the E6(R3) GCP Guideline. Instead, it intends to address important topics outlined in the guideline.

You may access the guideline at any time using the “Resources” button in the top right corner of the module.

Module 1 of this training is made up of three submodules.

Module 1.1 provides an overview of the guideline, highlights the relationships between the GCP Guideline and other ICH efficacy guidelines, and introduces the learner to important terms and concepts found in the guideline. Module 1.2 reviews the principles of ICH GCP, and Module 1.3 provides the learner with an in-depth understanding of the foundational concepts of designing and conducting clinical trials.

Let's get started.

Key questions you should be able to answer by the end of this module include:

- What is good clinical practice or GCP?
- What is the structure of the GCP Guideline?
- And what are the underlying concepts behind the E6(R3) revision?

[Video: Khair ElZarrad]

Hello, my name is Khair ElZarrad.

I'm the director of the Office of the Medical Policy at the Center for Drugs at the FDA and I'm also fortunate enough to be the rapporteur of ICH E6(R3), the topic of the training today. Thank you for joining us as we explore this revision, Revision 3 or "R3" of the ICH Guideline for Good Clinical Practice, or GCP.

This revision represents a significant cultural shift in the approach to designing and conducting high quality clinical trials. E6(R3) integrates the concepts of fitness for purpose, critical to quality factors, proportionality, and overall quality by design.

These concepts pervade the entire guideline across all clinical trial conduct elements. They are intended to improve the quality of clinical trials, reduce unnecessary burden, and guide appropriate allocation of resources on what matters most: the safety of the participants and the reliability of the results. You will hear about these concepts in depth in later training modules.

We want to extend our thanks to you for your time and attention in attending this training.

[Video: Peter Toomey]

Hello, my name is Peter Toomey. I'm the head of inspections at the European Medicines Agency, and I had the privilege of being the regulatory chair for the principles and Annex 1 of ICH E6(R3).

Trials with inadequate design or those conducted poorly may place participant rights, safety and well-being at risk, and yield unreliable trial results.

As technology continues to rapidly evolve and novel trial designs emerge, it is more important than ever for the good clinical practice guideline to be flexible and responsive to the developing clinical trials landscape.

The revision of the GCP Guideline is intended to be adaptable to various trial designs and new technologies. Annex 2 specifically complements the principles and Annex 1 and addresses the GCP considerations that arise from the increased use of a wider range of design elements and data sources, such as decentralised elements, pragmatic elements, and real-world data in clinical trials.

> As you will see in this training, regardless of the specific elements of trial designs utilised in individual clinical trials, a quality by design approach and the focus on critical to quality factors should be used to ensure all clinical trials produce reliable results while protecting the rights, safety and well-being of trial participants.

Good clinical practice is a standard for the planning, initiating, performing, recording, oversight, evaluation, analysis, and reporting of clinical trials that provides assurance that the data and reported results are reliable and that the rights, safety and well-being of trial participants are protected.

In this module, when we say participants are protected, we are referring to protecting their rights, safety and well-being.

The ICH E6(R3) GCP Guideline is one of ICH's efficacy guidelines. Nearly 20 efficacy guidelines have been developed and published by ICH. The E6(R3) Guideline references a number of these efficacy guidelines, which should be considered together as an integrated whole rather than in isolation. For a full list, please look at the ICH website. Where relevant, this training includes a reference to other appropriate ICH guidelines.

What is new about the ICH E6(R3) GCP Guideline structure?

For those familiar with the previous GCP versions, ICH E6(R3) has a revised structure that includes the principles of ICH GCP, annexes, and appendices.

The GCP Guideline continues to aim to provide harmonised principles and an approach to conducting clinical trials. If any unique regulatory requirements exist in the region where the trial will be conducted, it is important to recognise and comply with these requirements.

The GCP Guideline sets out 11 foundational principles about clinical trial conduct. They are intended to apply across various clinical trial types and settings and to remain relevant as technological and methodological advances occur. Module 1.2 describes the principles in detail.

The guideline includes 2 annexes. The annexes provide the basis for the appropriate interpretation and application of principles. Various approaches to the provisions in the annexes can be considered, provided they are justified and achieve the intended purpose of the application of the principles.

The annexes highlight the roles and responsibilities of sponsors, investigators and IRBs or IECs.

Annex 1 covers considerations for interventional clinical trials. It includes sections related to the responsibilities of the IRB or IEC, investigator, and sponsor.

Annex 1 also includes a new section related to data governance.

Annex 2 provides additional considerations for sponsors, investigators, and IRBs or IECs, focusing on examples of interventional clinical trials that incorporate decentralised elements, pragmatic elements, or real-world data. While the clinical trial ecosystem is likely to continue evolving, the considerations outlined in Annex 2 may still apply to the operational approaches and data sources utilised. The application should also align with local regulatory requirements.

The GCP Guideline has 3 appendices which outline 2 foundational documents for interventional clinical trials of investigational products and the essential records required for their conduct.

Appendix A, The Investigator's Brochure or IB: The IB includes information on the physical, chemical, and pharmaceutical properties of the investigational product. It has a compilation of the current clinical and non-clinical data on the investigational product. Appendix A provides an overview of the development of the IB and outlines the minimum information that should be included in this document.

Appendix B provides an overview of topics that should generally be included when developing and/or updating a clinical trial protocol.

Appendix C, Essential Records for the Conduct of a Clinical Trial, provides guidance on the maintenance and retention of essential records. This section has been significantly revised from the E6(R2) version. Rather than providing a list of documents to maintain, the E6(R3) version recognises that the nature and extent of records produced and subsequently maintained are dependent on the trial design. This appendix provides guidance on determining the essentiality of trial records, management of essential records, and a list of records that, depending on your trial, may be considered essential records. More training on essential records is provided in a later module.

The ICH E6(R3) GCP Guideline ends with a glossary of terms used in the guideline.

What are the underlying concepts behind the ICH E6(R3) GCP Revision?

The ICH E6(R3) GCP Guideline emphasizes the importance of proactively building quality into clinical trials. This concept may look familiar as it is also described in the ICH E8(R1) Guideline for general considerations for clinical studies, another of the ICH efficacy Guidelines.

How do you proactively build quality into the scientific and operational design and conduct of clinical trials?

Here in Module 1.1, we'll introduce quality by design, quality management, and other key concepts related to building quality into clinical trials. These concepts will be described in detail in Module 1.3.

Quality by Design in clinical trials is a prospective and multidisciplinary approach that focuses on gathering input on the trial design from interested parties, identifying critical trial attributes and identifying, prioritising, and controlling the important risks to trial attributes. These attributes are called critical to quality factors.

This approach can proactively prevent errors that could impact the protection of participants, or undermine the reliability of the data or decision-making based on the trial results.

Quality management includes the design and implementation of efficient clinical trial protocols, including tools and procedures for trial conduct to ensure the protection of participants and the reliability of trial results.

In more general terms, quality by design and quality management involve proactive activities to identify and manage risks associated with critical aspects of a clinical trial.

Broadly speaking, fit for purpose refers to something that is adequate, suitable, or appropriate for its intended use. The term fit for purpose appears 14 times in the E6(R3) Guideline; It's important to understand how this concept should be considered when planning and conducting clinical trials.

The GCP Guideline applies the term fit for purpose in multiple different contexts. The term is interpreted differently depending on the context in which it is being used. For example, fit for purpose is stated in the context of the quality of the clinical trial, computerised system, data acquisition tools, and oversight measures, all of which appear in the GCP Guideline. Different actions and strategies will need to be taken to ensure trial elements are fit for purpose in each context.

The quality of the clinical trial is considered fit for purpose if it meets the trial's objectives, provides confidence in the trial's results, and supports good decision making, all while protecting trial participants.

Critical to quality factors are attributes of a clinical trial whose integrity, if compromised due to inadequate design and or poor conduct, could jeopardise participant protection or the reliability of decision making based on the trial's results.

Critical to quality factors can be data, processes or systems, and will be identified for each individual clinical trial.

While many factors can affect the quality of a trial, not all of them will be critical to the protection of participants or the overall reliability of the trial's results.

Simply put, critical to quality factors are the most important data, processes and systems in a clinical trial that should be collected, conducted and managed correctly,

safely, consistently and reliably. These factors help ensure participants are protected and trial results are reliable.

Risk proportionality is a core element of both quality by design and quality management. It involves tailoring the level of effort and oversight to the risks that matter most, those impacting the critical to quality factors.

The concepts of quality by design, quality management, fit for purpose, critical to quality factors, and proportionality are important concepts in the ICH E6(R3) Guideline. They will be described in detail in Module 1.3.

This brings us to the end of Module 1.1, Overview of ICH E6(R3).

In this module, you learned what is good clinical practice, what is the structure of the GCP Guideline, and what are the underlying concepts behind the ICH E6(R3) revision.

Thank you for completing this module. Module 1.2 will explore the Principles of the ICH GCP Guideline, highlighting selected points from each principle.