ICH
harmonisation for better health

Module 1.2 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.

Module 1.1 provided an overview of the guideline, highlighted the relationships between the GCP Guideline and other ICH efficacy guidelines, and introduced the learner to important terms and concepts found in the guideline.

In Module 1.2, we will explore the principles of the ICH GCP Guideline, highlighting selected points from each principle.

Please refer to the Principles of ICH GCP section of the guideline for the full principles.

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.

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

- What are the ICH GCP principles?
- Where in the annexes are there more details to help apply these principles effectively?
- And how are the GCP principles practically applied in actual clinical trial scenarios?

Clinical trials should be designed and conducted ethically to protect the rights, safety and well-being of participants and scientifically to answer the research question and generate reliable results.

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

The GCP Guideline contains a set of 11 principles to guide the thoughtful and efficient approaches to the design and conduct of clinical trials. The 11 principles are designed to be a flexible framework for clinical trial conduct and can be found in the Principles of ICH GCP section of the guideline.

A flexible framework means that the principles are intended to apply to a broad range of clinical trials across different clinical trial designs and settings, provide guidance throughout the lifecycle of the clinical trial from planning to reporting, and apply across the use of different technologies and remain relevant as innovative designs and technology advance.

The 11 ICH GCP principles are interdependent and should be considered together as a whole.

Before we learn about the principles of ICH GCP, it is important to highlight the value of using a multidisciplinary cross-functional approach to get feedback to help design and conduct the trial.

The design and conduct of a clinical trial can be supported by obtaining the different perspectives of representatives across the organisation such as statisticians, scientists, and pharmacists and external parties such as patients, patient advocacy groups, their communities, and health care professionals, among others.

While gaining feedback is not one of the 11 ICH GCP principles, the preface to the principles recognises its importance to the successful design of the protocol, as well as operational feasibility when conducting the trial.

For example, patients and patient advocacy groups provide lived experience of a disease or condition and can suggest improvements to facilitate recruitment and improve the feasibility and reduce the unnecessary burden of operational approaches to data collection. Patient input during protocol development can promote protocol adherence and help to increase patient trust.

Healthcare professionals and investigators have firsthand knowledge of potential trial procedures and the data sources contributing to the trial data. They can address questions related to healthcare settings, the routine workflow of healthcare professionals, and the procedures that will be part of the trial. This group can also help identify unnecessary complexity and risk and can help determine where training and other support may improve protocol feasibility and adherence.

Early interaction with regulators is encouraged, particularly when a trial has various operational approaches, including complex design elements and technological tools and real-world data sources.

Let's look closer at the principles of ICH GCP. Principle 1 states, "clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and applicable regulatory requirement(s)." Clinical trials should be designed and conducted in ways that ensure the rights, safety, and well-being of participants.

This principle recognises the Declaration of Helsinki, which is a set of ethical principles for medical research involving humans. Simply put, a trial participant's rights, safety, and well-being should prevail over the interests of science and society.

This broad principle applies throughout the ICH GCP Guideline.

Principle 2 states, "informed consent is an integral feature of the ethical conduct of a trial. Clinical trial participation should be voluntary and based on a consent process that ensures participants (or their legally acceptable representatives, where applicable) are well-informed."

This principle recognises the importance of each participant's freely given informed consent. The application of this principle is detailed in Annex 1, Section 2.8.

Practically speaking, how do you ensure the participant is well-informed?

Select all the statements that accurately complete the sentence.

The process of informed consent should enable each participant to understand and evaluate the potential benefits, risks, and burdens of participating in the trial before participating in the trial, and when relevant new information becomes available during the conduct of the trial.

Principle 3 states that "clinical trials should be subject to an independent review by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC)."

A trial should be conducted in compliance with the protocol that received a prior IRB/IEC approval or favourable opinion. Periodic ethical review during the trial should be conducted in accordance with applicable regulatory requirements.

Annex 1, Section 1, details the IRB/IEC responsibilities, operations, procedures and records required for initial and ongoing or periodic review of a clinical trial.

Principle 4 states, "clinical trials should be scientifically sound for their intended purpose and based on adequate and current scientific knowledge and approaches."

Practically speaking, a trial should use relevant scientific knowledge to design appropriate research questions. Current scientific knowledge of the condition or disease, the underlying biological mechanism, the intended population, as well as non-clinical and clinical evidence should support the proposed trial.

This is described in Annex 1, Section 3.1.1. Additionally, the Investigator's Brochure, which is described in Appendix A, should include the current scientific state of knowledge of the investigational product. And the clinical trial protocol and protocol amendments, which are outlined in Appendix B, should support the scientific validity of the trial.

Principle 5 states that "clinical trials should be designed and conducted by qualified individuals."

Individuals, including but not limited to physicians, trial coordinators, nurses, pharmacists, scientists, ethicists, biostatisticians, and monitors should be qualified by education, professional training, and experience.

The ICH GCP Guideline recognises and discusses the need for qualified individuals throughout Annex 1 and specifically in Sections 2.1 and 3.4.

The ICH GCP Guideline introduces and emphasises the importance of applying a quality by design approach to a clinical trial.

Principle 6 states, “Quality should be built into the scientific and operational design and conduct of clinical trials.”

Recall from Module 1.1 that the quality of a clinical trial is considered fit for purpose when it meets the trial's objectives, provides confidence in the trial's results, and supports good decision making, all while protecting trial participants.

Sponsors and investigators responsible for the trial's design and/or conduct should prospectively identify critical attributes of the trial that may affect the protection of participants or the reliability and interpretability of the trial results. These critical attributes are called critical to quality factors.

The concept of quality by design is embedded throughout the ICH GCP Guideline and specifically in sections 3.10: Quality Management and 3.11: Quality Assurance and Quality Control. Quality by design is described in detail in Module 1.3 of this training.

Principle 7 states, “clinical trial processes, measures, and approaches should be implemented in a way that is proportionate to the risks to participants and to the importance of the data collected and that avoids unnecessary burden on participants and investigators.”

Trial processes should support key trial objectives. In addition to being essential, clinical trial processes, measures, and approaches should be implemented and monitored in a way that is proportionate to the level of risk to the participant or the importance of the data. Simply put, the greater the risk to the protection of participants or data reliability, greater attention to the corresponding controls is needed.

Identification and management of risks to critical to quality factors should occur proactively and be adjusted when new or unanticipated issues arise.

Principle 7 is reflected throughout Annex 1, for example in Section 3.10: Quality Risk Management and Section 3.11: Quality Assurance and Quality Control.

Let's look at an example where close attention is needed. A double-blinded trial involves a clinical outcome assessment (COA) to support the efficacy of an investigational product.

COA data represent the data to be used as the primary basis for approval or the primary efficacy endpoint data. Careful attention to the collection of primary endpoint data is critical.

COAs can be inherently subjective and, therefore, susceptible to variability in their performance.

In this case, the sponsor and investigators should take a rigorous approach to monitoring the COA data and to training individuals who conduct the COA. This

might include enhanced oversight and tailored processes to identify and mitigate opportunities for error in the collection, monitoring, and management of the COA data.

A tailored approach is needed to train trial staff conducting the assessment. For example, sponsors and investigators can develop standardised procedures to perform and document COAs consistently, conduct inter-rater reliability exercises to ensure consistency in subjective assessments, and periodically retrain staff to maintain quality throughout the trial.

Compare that with a trial involving an investigational product, studying a new indication. The product under study is already approved for a different indication.

The protocol indicates that the investigational product be administered in the same way as the approved indication.

In this case, because the product is to be administered in a manner consistent with the approved product label and usual clinical practice, rather than according to a different trial-specific procedure, there is less risk involved and therefore less instruction, control, and oversight is necessary. The investigator should follow the administration procedures of usual clinical practice for the approved product.

These examples highlight risk-based proportionality. When there is a greater risk to the protection of participants or data reliability, greater attention to the corresponding controls is needed. We saw in these examples how two different trials may require responses of different proportions.

Principle 8 states that “clinical trials should be described in a clear, concise, scientifically sound, and operationally feasible protocol.”

A well-designed protocol is fundamental to protecting participants and ensuring the reliability of trial results.

Annex 1, Section 3.1 discusses the sponsor's role in trial design. Additionally, topics that generally should be included in the protocol can be found in Appendix B, Clinical Trial Protocol, and Protocol Amendments.

Together, Principles 6, 7, 8, and 9 are examples of principles that support quality by design and risk proportionality, key concepts of the ICH E6(R3) Guideline.

Module 1.3 will further introduce these concepts and how to design and conduct trials with a proactive risk-based approach.

Principle 9 states, “Clinical trials should generate reliable results.”

While this is a short statement, generating reliable results is a complex task. The quality and amount of information generated should be fit for purpose.

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.

Systems and processes, including computerised systems should also be fit for purpose for use in the trial. As described in Principle 9.4 of the ICH GCP Guideline, the trial should incorporate efficient and robust processes for managing records and data to help ensure that record integrity and traceability are maintained and a person's information is protected.

This allows accurate reporting, interpretation and verification of the relevant clinical trial-related information. Essential records should be retained securely by sponsors and investigators for the required period in accordance with applicable regulatory requirements. Clinical trials should be registered in a timely manner on a publicly accessible and recognised database, and their results should be posted publicly.

The principle of generating reliable results is embedded throughout Annex I, specifically in Sections 2.12, 3.16.1, and Section 4, and Appendix C: Essential Records for the Conduct of a Clinical Trial. We'll learn more about generating and maintaining reliable data later in this training.

Principle 10 states, "Roles and responsibilities in clinical trials should be clear and documented appropriately."

It states that the sponsor may transfer or the investigator may delegate activities, but they retain overall responsibility for their respective activities.

Agreements should clearly define roles, activities, and responsibilities that the sponsor or investigator transfers or delegates.

The sponsor or investigator should maintain appropriate oversight of the aforementioned activities.

Annex 1, Sections 2.3, 3.6, and 3.9 discuss sponsor and investigator responsibilities, as well as approaches to sponsor and investigator oversight.

Principle 11 states, "Investigational products used in a clinical trial should be manufactured in accordance with applicable Good Manufacturing Practice (GMP) standards and be managed in accordance with the product specifications and the trial protocol."

Last, but certainly not least, this principle is about the quality of the investigational product being used in the trial. Importantly, GMP standards ensure the quality of the manufactured product. Measures should ensure that the investigational product provided to trial participants retains its quality. The product should be used in accordance with the protocol and the Investigator's Brochure. Appropriate processes

should be implemented for the handling, shipping, storage, dispensing, returning, and destroying, or alternatively disposing of the investigational product.

Annex 1, Sections 2.10 and 3.15 provide detailed information.

In Module 1.2, we answered: What are the ICH GCP Principles? Where in the Annexes are more details to help apply these principles effectively? And, how are the ICH GCP Principles practically applied in actual clinical trial scenarios?

Thank you for completing this module.

Module 1.3 will share an in-depth understanding of the foundational concepts of designing and conducting clinical trials.