

Final Concept Paper

ICH E6 (R3) Guideline for Good Clinical Practice Annex-2

30 March 2023

Endorsed by the Management Committee on 28 April 2023

Type of Harmonisation Action Proposed

The action proposed is the development of the new Annex 2 of ICH E6(R3) Guideline entitled *Good Clinical Practice (GCP)*. When complete, E6(R3) will be composed of an overarching principles document, Annex 1 (considerations for interventional clinical trials), and Annex 2 (additional considerations for interventional clinical trials).¹ This document complies with the ICH MC request to review and approve Annex 2 Concept Paper once the updated ICH E6(R3) Principles and Annex 1 are on the verge of entering *Step 1* of the ICH development process. The original Concept Paper stated that before the drafting of Annex 2, its scope would be further clarified, to define the nature of trials involved, in an update to the concept paper. Although the initial perspective was to update the original Concept Paper with Annex 2 details, the EWG determined that a separate Concept Paper (this document) is preferred for Annex 2.

Statement of the Perceived Problem

In the two decades since ICH E6 was first drafted, clinical trials have become more complex with respect to trial design, use of technology, quantity of data collected, and involvement of central testing facilities or other service providers. ICH E6(R2) was developed with multiple addenda to address the emerging use of electronic data sources and risk management processes. Nonetheless, since the development of E6(R2), clinical trials have continued to evolve with new designs and technological innovations. It was also noted that while E6(R2) provided a great deal of details, it did not address many aspects of modern clinical trials. Advances in technologies used in clinical practice provide opportunities to integrate clinical research and clinical care. The trend of growing interoperability of technology across the data life cycle serves as a new vehicle for data exchange among multiple stakeholders in the clinical trial enterprise, including patients, researchers, and caregivers. The richness of these multiple data sources and the growing exploration and use of artificial intelligence offers the potential to significantly enhance evidence generation in clinical trials. Annex 2 provides additional consideration that are based on the foundation established in Annex 1. Annex 2 should be read and implemented with E6(R3) principles and Annex 1.

Issues to be Resolved

Thoughtful design of clinical trials is critical and it should consider available design elements and data sources that may make a trial more efficient and more accessible, while helping to ensure participants' safety and the reliability of the trial results.

¹ In the original concept paper, E6(R3) Annex 1 was described as providing considerations for traditional interventional clinical trials, while Annex 2 was described as providing considerations for non-traditional interventional clinical trials.

The proposed development of Annex 2 will include additional considerations on how GCP principles may be applied across a variety of trial designs and data sources, where applicable. This will include:

- 1- Decentralised elements, where some or all trial-related activities occur at locations other than traditional clinical trial sites, such as patient homes, mobile trial units, or local clinics, and data collection may occur remotely.
- 2- Pragmatic elements, reflecting trials that closely resemble routine clinical practice.
- 3- Real-world data (RWD) sources², for example, the use of registries, electronic health records (EHR), hospital data, pharmacy and medical claims data or wearables.

As the work on Annex 2 proceeds, this concept paper will be updated as necessary to incorporate new learning and ideas that are not described above.

Background to the Proposal

- ICH Reflection on “GCP Renovation:” Modernization of ICH E8 and Subsequent Renovation of ICH E6, 2017.
- Draft version ICH E6(R3) Principles – Published on the ICH website on 19 April 2021
- ICH E6(R2) Good Clinical Practice
- ICH E8(R1) General Considerations for Clinical Studies

Type of Working Group and Resources

The working group (WG) that will be tasked with developing Annex 2 will include certain members from the E6(R3) EWG with specific overarching expertise relevant to the scope of this Annex. New members will also be considered to ensure the scope of expertise is represented. The Annex 2 WG may include experts from various disciplines including clinical, statistical, data science, clinical outcomes assessment, regulatory compliance, ethics and potentially others. The Annex 2 WG will involve engagement with stakeholders including academia throughout the development process.

To ensure efficiency membership will be designed to be representative, but limited in size to be efficient. This will help ensure concurrent development of Annex 2 while the full EWG continues to work on addressing the development of Annex 1. Direct and frequent interactions, as well as continuity of leadership between the groups will help ensure that Annex 1 and Annex 2 are well connected and synergistic while avoiding redundancies.

Timing

We expect approximately 12-18 months are needed to develop a draft that will be subject to public consultation.

² This does not include observational studies.