

Final Concept Paper

ICH E8(R1): Revision of General Considerations for Clinical Trials dated 14 November 2017

Endorsed by the Management Committee on 14 November 2017

Type of Harmonisation Action Proposed: Revision of existing ICH Guideline (code: E8(R1))

Statement of the Perceived Problem:

ICH E8 *General Considerations for Clinical Trials*, which sets out general principles on the conduct of clinical trials, was adopted in 1997 and has not undergone revision. Since its adoption, clinical trial design and conduct have become more complex, impacting the time and cost required to develop drugs. A wide range of both trial designs and data sources play a role in drug development and are not adequately addressed in the original E8 guideline. Approaches for optimizing trial quality, which promote the reliability, efficiency, and patient focus of clinical trials are needed. This involves identifying the factors that are critical to the quality of a clinical trial at the design stage and planning the trial conduct proportionate to the risks to these quality factors, thereby protecting human subjects and ensuring the reliability of trial results.

Issues to be Resolved:

The E8 Guideline has high level descriptions of trial objectives and design, but does not address how design or planning considerations can optimize trial and data quality. The set of trial designs described in E8 is limited and does not reflect the range of designs in use today.

To resolve these issues, E8(R1) will:

- 1) identify a basic set of critical-to-quality factors (e.g. eligibility criteria, masking, types of controls, outcome ascertainment, site feasibility, safety monitoring, statistical analysis, and investigational product handling and administration) that can be adapted to different types of trials to support the meaningfulness and reliability of trial results and to protect human subjects.
- 2) address a broader range of trial designs and data sources.
- 3) provide an updated comprehensive guide to, or cross-referencing of, all other relevant ICH guidelines that inform the design, planning and conduct of clinical research, without reproducing the detailed material found in those guidelines.

Background to the Proposal

The plan for E8(R1) is an outcome of the ICH Reflection Paper “*GCP Renovation*”: *Modernization of ICH E8 and Subsequent Renovation of ICH E6* which outlined an approach to renovate and modernize ICH Guidelines related to clinical trial design, planning, management, conduct, and reporting. E8(R1) is intended to address the concern about the principles of trial design and planning that are needed to ensure an appropriate level of data quality through revision to the current ICH E8 *General Considerations for Clinical Trials*. The proposed revision will include a review of the issues and questions that are most critical to clinical trial quality and the ability for a trial to achieve meaningful and reliable results. Additionally, E8(R1) will incorporate the most current guidelines for achieving fit-for-purpose data quality as one of the essential considerations for all clinical trials, including the broad range of trial designs and data sources currently in use. Following the E8(R1), the ICH Reflections Paper proposed to update ICH E6(R2) *Good Clinical Practice* to address the increasing diversity of trial designs and data sources.

The revision of ICH E8 is expected to:

- Enhance the reliability of trial results through attention to trial quality
- Better integrate overall design and planning with subject protection and data reliability considerations that are the focus of ICH E6, statistical considerations that are the focus of ICH E9, and other considerations addressed in other ICH Efficacy guidelines.
- Enhance the utility of the ICH Efficacy guidelines by including critical-to-quality factors as a key consideration in planning and design of clinical trials
- Promote the quality of trial design and conduct for a broad range of trial types and data sources with critical-to-quality factors aligned to the objectives of the trial

Strategic Importance of the Topic

This work will support improved trial design and conduct for a broad range of trial types and data sources and will promote the availability of high quality evidence. The overall goal is to promote trials that lead to efficient and timely decision making, and ultimately to improved access to safe and effective drugs with meaningful impact on patients.

Feasibility:

Some of the expertise needed for this EWG may currently be allocated to ongoing ICH E9 guideline work, but it is considered that E8 work is critical and can and should proceed while the ICH E9 work is being completed.

Type of Expert Working Group and Resources

This EWG will include experts from relevant disciplines including clinical, statistical, data science, patient-reported outcome/clinical outcome assessment experts, and potentially others. The group will work closely with E9 and E6 experts.

Timing

The guideline work is estimated to require 36 months to complete. Work should be conducted primarily by email and teleconferences. Four to six face to face meetings may be necessary to address difficult topics.