



GENERAL CONSIDERATIONS FOR CLINICAL STUDIES E8(R1)

Step 2 document – to be released for comments

Date: 06 June 2019

International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use



ICH E8(R1)

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Background

- Clinical studies of medical interventions are conducted to provide information that can ultimately improve access to safe and effective drugs with meaningful impact on patients, while protecting those participating in the studies.
- Since adoption of ICH E8 General Considerations for Clinical Trials in 1997, clinical study design and conduct have become more complex, impacting the time and cost required to develop drugs.

Background

- A wider range of both study designs and data sources now play a role in drug development and were not addressed in the original E8 guideline.
- Approaches for optimizing study quality which promote the reliability, efficiency, and patient focus of clinical trials are needed, these involve:
 - Identifying the factors that are critical to the quality of a clinical study at the design stage.
 - Planning the study conduct proportionate to the risks to these quality factors, thereby protecting human subjects and ensuring the reliability of study results.

Background

- ICH E8 was published in 1997 and has not been revised until now.
- ICH Reflection on “GCP Renovation”: Modernization of ICH E8 and Subsequent Renovation of ICH E6 (2017)
 - Proposed revision of E8 as 1st step towards a broader GCP renovation.
 - E8(R1) will inform the development of future guidelines.
- E8(R1) was developed based on a Concept Paper (14 Nov 2017) and a Business Plan (14 Nov 2017).
- E8(R1) has been signed off as a *Step 2* document (08 May 2019) to be issued by the ICH Regulatory Members for public consultation.
- Anticipating finalization as a *Step 4* document to be implemented in the local regional regulatory system: Jun 2020

Key Principles

- Protection of clinical study subjects is a shared responsibility (investigators, sponsors, IRB/IECs).
- Clinical studies should be designed, conducted, and analysed according to sound scientific principles and reported appropriately.
- Consulting with patients and/or patient organisations in the design, planning and conduct of clinical studies helps to ensure that all perspectives are captured.

Guideline Objectives

- Describe internationally agreed upon principles and practices to facilitate regulatory acceptance.
- Provide guidance on the consideration of quality in the design and conduct of clinical studies, including:
 - Identification of factors critical to the quality of the study.
 - Management of risks to those factors during study conduct.
- Provide an overview of the types of clinical studies performed during the product lifecycle, including:
 - Study design aspects that support the determination of quality factors critical to ensuring the protection of study subjects and ability to meet the study objectives.
- Provide a guide to all of the ICH Efficacy Guidelines.

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Summary of Guideline Content

- *Quality by Design of Clinical Studies*
 - Quality of a clinical study is fitness for purpose. The quality of the information generated should therefore be sufficient to support good decision making.
 - The quality of a study is driven proactively by designing quality into the study protocol and processes.
 - Critical to quality factors should be determined for each study.
 - Risks that threaten the integrity of the critical to quality factors should be identified and managed in a proportionate manner.

Summary of Guideline Content

- *Development Planning*
 - Across the product lifecycle, different types of studies will be conducted with different objectives and designs.
 - The design of a given clinical study should reflect the state of knowledge and experience related to the intervention and the condition to be treated or prevented.
 - The results of prior studies should inform the plan of later studies. Emerging data will frequently prompt a modification of the development strategy.
 - Knowledge of the drug at the point in development when the study is designed will therefore inform the identification of critical to quality factors and control processes used to manage them.

Summary of Guideline Content

- *Design Elements for Clinical Studies*

- Study objectives impact the choice of study design and data sources, which in turn impact the strength of a study to support regulatory decisions and clinical practice.
- Key elements of study design are described while allowing for flexibility in how they can be combined. The elements outlined are expected to be relevant to study types and data sources in use in clinical studies now, and that may be developed in the future.
- Study design encompasses multiple important elements including population, intervention, control group, response variable, methods to reduce or assess bias, and statistical analysis.
- Study data may be acquired from various sources internal or external to the study.
- The combination of study design elements and data sources impacts the identification of critical to quality factors.

Considerations

- The ICH Efficacy guidelines cover the design, conduct, analysis and reporting of clinical studies. The guidelines should be used in an integrated manner rather than one or other guideline or subsection being focussed on in isolation of the others.
- E8(R1) provides an overall introduction to clinical development, designing quality into clinical studies and focusing on those factors critical to the quality of the studies.

Considerations

ICH E family of guidelines – need to be read together

E8 General Considerations for Clinical Trials

Design and analysis:

E4 Dose-Response Studies
E9 Statistical Principles for Clinical Trials
E10 Choice of Control Group in Clinical Trials
E17 Multi-Regional Clinical Trials

Conduct and reporting:

E3 Clinical Study Reports
E6 Good Clinical Practice

Safety reporting:

E1 Clinical Safety for Drugs used in Long-Term Treatment
E2A - E2F Pharmacovigilance
E14 Clinical Evaluation of QT
E19 Safety Data Collection

Populations:

E5 Ethnic Factors
E7 Clinical Trials in Geriatric Population
E11 - E11A Clinical Trials in Pediatric Population
E12 Clinical Evaluation by Therapeutic Category

Genetics/genomics:

E15 Definitions in Pharmacogenetics / Pharmacogenomics
E16 Qualification of Genomic Biomarkers
E18 Genomic Sampling

Conclusions

- The revised guideline focuses on designing quality into clinical studies, considering the diversity of clinical study designs and data sources used to support regulatory and other health policy decisions.
- The principles and approaches set out in this guideline, including those of quality by design, should inform the approach taken to the design, conduct, and reporting of clinical studies and the proportionality of control measures employed to ensure the integrity of the critical to quality factors.

Contact

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