ICH
harmonisation for better health

ICH E8(R1)
General Considerations for Clinical Studies

Step 4

Step 4 document – to be implemented

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

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Background

- This document has been signed off as *Step 4* document (6 October 2021) to be implemented by the ICH Regulatory Members.
- This document was developed based on a Concept Paper (14 November 2017) and Business Plan (14 November 2017).

Background for ICH E8(R1)

- Original ICH E8 adopted in 1997.
- A wider range of study designs and data sources play a role in drug development.
- Clinical study design and conduct are more complex.
- Patient-focused drug development is now a key priority.
- Quality approaches from the 20th century are not optimal for the present day.

GCP Renovation Plan from 2017

- ICH Reflection on “GCP Renovation”: Modernization of ICH E8 and Subsequent Renovation of ICH E6 January 2017.
- ICH E8 to be renovated first to introduce “quality by design” approaches and wider range of study designs and data sources.
- ICH E6 Good Clinical Practice to be renovated subsequently and refer to ICH E8 study quality principles and study designs and data sources.

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Section 1 Objectives

ICH Efficacy Guidelines

- The ICH Efficacy guidelines are an integrated set of guidance covering the planning, design, conduct, safety, analysis, and reporting of clinical studies.
- The guidelines should be considered and used in an integrated, holistic way rather than focusing on only one guideline or subsection.
- ICH E8(R1) General Considerations for Clinical Studies sets out general principles on the conduct of clinical studies.

Objectives of the Document

1. Describe internationally accepted principles and practices in the design and conduct of clinical studies that will ensure the protection of study participants and facilitate acceptance of data and results by regulatory authorities.
2. Provide guidance on the consideration of quality in the design and conduct of clinical studies across the product lifecycle.
3. Provide an overview of the types of clinical studies performed during the product lifecycle and describe study design elements.
4. Provide a guide to the ICH efficacy documents to facilitate user's access.

Section 2 General Principles

Protection of Clinical Study Participants

- Important principles of ethical conduct of clinical studies and the protection of participants, including special populations, have their origins in the Declaration of Helsinki.
- ICH E6 - Good Clinical Practice describes these principles.
- Before initiating a clinical study, sufficient information should be available to ensure that the drug is acceptably safe for the planned study in humans.

Protection of Clinical Study Participants (continued)

- Emerging non-clinical, clinical, and pharmaceutical quality data should be reviewed and evaluated.
- Care should be taken to ensure all study procedures and assessments are necessary from a scientific viewpoint and do not place undue burden on study participants.

Scientific Approach to Clinical Studies

- The purpose of a clinical study is to generate reliable information to answer the research questions and support decision making.
- The primary objectives of any study should reflect the research questions and be clear and explicitly stated.
- Clinical studies should be designed, planned, conducted, analysed, and reported according to sound scientific principles to achieve their objectives.

Patient Input into Drug Development

- Consulting with patients and/or patient organisations during drug development can help to ensure that patients' perspectives are captured.
- The views of patients (or of their caregivers/parents) can be valuable throughout all phases of drug development.
- Involving patients early in the design of a study is likely to increase trust in the study, facilitate recruitment, and promote adherence.
- Patient input ultimately supports the development of drugs that are better tailored to patients' needs.

Section 3 Designing Quality into Clinical Studies

Quality by Design of Clinical Studies

- Quality by design in clinical research sets out to ensure that the quality of a study is driven proactively by designing quality into the study protocol and processes.
- Quality by design involves the use of a prospective, multidisciplinary approach to promote the quality in a manner proportionate to the risks involved, and clear communication of how this will be achieved.
- Good planning and implementation of a clinical study also derive from attention to the design elements of clinical studies as described in Section 5.

Critical to Quality Factors

- Critical to quality factors are attributes of a study whose integrity is fundamental to the protection of study participants, the reliability and interpretability of the study results, and the decisions made based on the study results.
- The sponsor and other responsible parties of a clinical study should identify the critical to quality factors.
- It is important to determine the risks that threaten the critical to quality factors and decide whether the risks can be accepted or should be mitigated.

Critical to Quality Factors (continued)

- Proactive communication of the critical to quality factors and risk mitigation activities will support understanding of priorities and resource allocation by the sponsor and investigator sites.

Identifying the Critical to Quality Factors

- Create a culture that values critical thinking and open, proactive dialogue about what is critical to quality.
- Focus on activities that are essential to the reliability and meaningfulness of study outcomes and the safe, ethical conduct of the study.
- Seek input from a broad range of stakeholders, including patients and healthcare providers. Early engagement with regulatory authorities is encouraged, particularly when a study has novel elements considered critical to quality.

Identifying the Critical to Quality Factors (continued)

- Periodically review critical to quality factors to determine whether adjustments to risk control mechanisms are needed.
- The foundation of a successful study is a scientifically sound and operationally feasible protocol.

Section 4 Drug Development Planning

Section 4 Introduction

- Drug development planning builds on knowledge acquired throughout the investigational process from target identification through non-clinical and clinical evaluation.

4.1 Quality of Investigational Medicinal Product

- Ensuring adequate quality and characterisation of physicochemical properties of investigational medicinal product is an important element in planning a drug development program.

4.2 Non-Clinical Studies

- Assessment of the preclinical characteristics, including physiological and toxicological effects of the drug serve to inform clinical study design and planned use in humans.
- Before proceeding to studies in humans there should be sufficient non-clinical information to support initial human doses and duration of exposure.

4.3 Clinical Studies

- Clinical drug development is defined as studying the drug in humans.
- Clinical drug development is conducted in a sequence that builds on accumulated and emerging knowledge.
- Clinical drug development includes studies with different objectives, different designs, and different dependencies.

4.3.1 Human Pharmacology

- Initial administration of a drug to humans is usually intended to determine the tolerability of the dose range and to determine the nature of adverse reactions that can be expected.
- Pharmacokinetic studies are important to assess the clearance of the drug and to anticipate possible accumulation of parent drug or metabolites, interactions with metabolic enzymes and transporters, and potential drug-drug interactions.
- Pharmacodynamic data can provide early estimates of activity and efficacy and may guide the dosage and dose regimen in later studies.

4.3.2 Exploratory and Confirmatory Safety and Efficacy Studies

- After initial clinical studies provide sufficient information on safety, clinical pharmacology and dose, exploratory and confirmatory studies are conducted to further evaluate both the safety and efficacy of the drug.
- Exploratory and confirmatory studies may use a variety of study designs.
- Exploratory studies aim to refine the effective dose(s) and regimen, refine the definition of the targeted population, provide a more robust safety profile for the drug, and include evaluation of potential study endpoints for subsequent studies.

4.3.2 Exploratory and Confirmatory Safety and Efficacy Studies (continued)

- Confirmatory studies are designed to confirm that a drug is safe and effective for use for the intended indication and recipient population.
- Study endpoints selected for confirmatory studies should be clinically relevant and reflect disease burden or be of adequate surrogacy for predicting disease burden or sequelae.
- Confirmatory studies are often intended to provide an adequate basis for marketing approval, and to support adequate instructions for use of the drug.

4.3.3 Special Populations

- Some groups in the general population require additional investigation during drug development because they have unique risk/benefit considerations, or because they can be anticipated to need modification of the dose or schedule of a drug.
- These include but not limited to pregnant, lactating, pediatric, and geriatric populations.

4.3.4 Post-Approval Studies

- Post-approval studies may be performed to provide additional information on the efficacy, safety, and use of the drug in more diverse populations.
- Post-approval studies may be conducted to address a regulatory requirement.
- Post-approval studies may explore use of the drug in the real-world setting of clinical practice and may also inform health economics and health technology assessments.

4.4 Additional Development

- After initial approval, drug development may continue with studies of new or modified indications in new patient populations, new dosage regimens, or new routes of administration.

5. Design Elements and Data Sources for Clinical Studies

Section 5 Introduction

- There is a wide range of study designs and data sources to address study objectives.
- Clear objectives will help to specify the study design. The study objectives are further refined through specification of estimands [ICH E9(R1)].
- Interventional studies, and in particular randomised studies, play a central role in drug development, as they can better control biases.
- Studies without randomisation (interventional or observational) can play a role in certain settings when randomisation is not feasible.

Section 5 Introduction (continued)

- Multiple sources of data may be employed in studies.
- Studies may use study-specific data collection processes.
- Data such as that obtained from electronic medical records or digital health technologies may be leveraged to increase the efficiency of studies or generalisability of study results.

5.1 Study Population

- The study population should be chosen to support the study objectives.
- The degree to which a study succeeds in enrolling the desired population will impact the ability of the study to meet its objectives.
- The study population may be narrowly defined to reduce the risk to study participants or to maximise the sensitivity for detecting a certain effect.
- Conversely, it may be broadly defined to more closely represent the diverse populations for which the drug is intended.

5.2 Treatment Description

- The definition of treatments should align with the objectives of the study.
- The treatment(s), including controls, under study should be described explicitly and specifically.
- These might be individual treatments (including different doses or regimens), combinations of treatments, or no treatments, and can include specification of background treatments.

5.3 Choice of Control Group

- The major purpose of a control group is to separate the effect of the treatment(s) from the effects of other factors such as natural course of the disease, other medical care received, or observer or patient expectations (See ICH E10).
- The source of control group data may be internal or external to the study.

5.3 Choice of Control Group (continued)

- An internal control group helps ensure that the only differences between treatment groups are due to the treatment and not due to differences in the selection of participants, the timing and measurement of study outcomes, or other differences.
- Important limitations of the use of external controls are discussed in ICH E10.
- The suitability of the use and choice of external control should be carefully considered and justified.

5.4 Response Variables

- A response variable is an attribute of interest that may be affected by the drug.
- Study endpoints are the response variables that are chosen to assess drug effects.
- The primary endpoint should be capable of providing clinically relevant and convincing evidence related to the primary objective of the study (ICH E9).

5.4 Response Variables (continued)

- Secondary and exploratory endpoints are used to further explain or support study findings or for generating hypotheses for later research.
- The definition of each study endpoint should be specific and include how and at what time points in a participant's treatment course of the drug and follow-up it is ascertained.

5.5 Methods to Reduce Bias

- The study design should address potential sources of bias that can undermine the reliability of results.
- In studies with internal control groups, randomisation is used to ensure comparability of treatment groups.
- Events after randomisation [intercurrent events (E9(R1)] may affect the validity and interpretation of comparisons between treatment groups.
- Concealing the treatment assignments (blinding) limits the occurrence of conscious or unconscious bias in the conduct and interpretation of the study.

5.5 Methods to Reduce Bias (continued)

- Knowledge of interim results has the potential to introduce bias or influence the conduct of the study and interpretation of study results.
- Observational studies introduce unique challenges to the assessment and control of bias.
- These include ensuring that the individuals have the condition under study and ensuring comparability between treatment groups, in prognostic factors associated with the choice of therapies, in the ascertainment of response variables, and in post-baseline concomitant patient care.

5.6 Statistical Analysis

- The statistical analysis of a study encompasses important elements necessary to achieving the study objectives.
- The specification and documentation of the statistical analysis are important for ensuring the integrity of the study findings.
- The principal features should be clearly specified in a protocol written before the study begins.
- Full details of the planned statistical analysis should be specified and documented before knowledge of the study results that may reveal the drug effects.

5.7 Study Data

- Study data comprise all information generated, collected, or used in the context of the study ranging from existing source data to study-specific assessments.
- Study data can be broadly classified into two types: (1) data generated specifically for the present study (primary data collection) and (2) data obtained from sources external to the present study (secondary data use).
- Procedures to ensure the protection of personal data of the individuals being studied should be implemented.

5.7 Study Data (continued)

- Study data should be of sufficient quality to address the objectives of the study and, in interventional studies, to monitor participant safety.
- Data quality attributes include consistency (uniformity of ascertainment over time), accuracy (correctness of collection, transmission, and processing), and completeness (lack of missing information).
- There are additional considerations with secondary data use.

6. Conduct, Safety, Monitoring, and Reporting

6.1 Study Conduct

- Risk proportionate mitigation measures should be employed to ensure the integrity of the critical to quality factors.
- Adherence to the study protocol and other relevant documents is essential.
- Individuals involved in study conduct should receive training commensurate with their role.
- The manner and timelines in which study data are collected and managed are critical.
- Inappropriate access to data during the conduct of the study may compromise study integrity.

6.2 Participant Safety during Study Conduct

- Procedures and systems for the identification, monitoring, and reporting of safety concerns during the study should be clearly specified.
- Clear criteria for stopping treatment or study procedures for a participant while remaining in the study are necessary to ensure the protection of the participants but should also minimise loss of critical data.
- An important component of safety monitoring in many clinical studies is the use of an independent data monitoring committee.

6.3 Study Reporting

- Clinical studies and their results should be adequately reported using formats appropriate for the type of study.
- Consideration should be given to providing a factual summary of the overall study results to study participants in an objective, balanced, and non-promotional manner, including relevant safety information and any limitations of the study.
- The transparency of clinical research includes the registration of clinical studies, before they start, on publicly accessible and recognised databases, and the public posting of clinical study results.

7. Considerations in Identifying Critical to Quality Factors

7. Considerations in Identifying Critical to Quality Factors

- The identification of critical to quality factors should be supported by proactive, cross-functional discussions and decision making at the time of study planning.
- Different factors will stand out as critical for different types of studies, following the concepts introduced in Sections 4 through 6.

Conclusions

- Clinical studies of medicinal products are conducted to provide information that can ultimately improve access to safe and effective products with meaningful impact on patients, while protecting those participating in the studies.
- This document provides guidance on the clinical development lifecycle, including designing quality into clinical studies, considering the broad range of clinical study designs and data sources used.

Contact

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