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SCIENCE MEDICINES HEALTH

ICH E8(R1)– General Considerations for Clinical Studies – Finalised

PCWP/HCPWP – 24 November 2021

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GCP Renovation

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ICH Reflection on "GCP Renovation": Modernization of ICH E8 and Subsequent Renovation of ICH E6

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12 January 2017

ICH is inviting public review and comment on a reflection paper on Good Clinical Practice (GCP) "Renovation", which contains the ICH proposal for further modernization of the ICH Guidelines related to clinical trial design, planning, management, and conduct. The scope of the proposed renovation includes the current E8 General Considerations for Clinical Trials and further revision to the E6 Guideline for Good Clinical Practice, which is already undergoing modernization with the recent production of ICH E6(R2).

The reflection paper is available for download via the following link:

- Reflection paper on GCP Renovation

The goal of the potential renovation is to provide updated guidance that is both appropriate and flexible enough to address the increasing diversity of study types and data sources that are being employed to support regulatory and other health policy decisions, as appropriate. The underlying principles of human subject protection and data quality would remain. ICH's decision to invite stakeholder comment on the

E8 clinical trial design principles

E6 GCP clinical trial conduct principles

Problem statement – GCP Renovation

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ICH Reflection Paper on GCP Renovation, January 2017

*"…recognizing that the **most important tool** for ensuring human subject protection and high-quality data is **a well-designed and well-articulated protocol,** the renovated E6 would also refer to the proposed-to-be-revised E8 guideline for a more comprehensive discussion of study quality considerations and relevant discussion and guidance in other ICH E guidelines…"*

→ ICH E8 **(R1)**

→ ICH E6 **(R3)**

Involving Stakeholders in GCP Renovation

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Two-fold approach:

Stakeholder engagement during the **drafting process**:

- Global Workshop on ICH E8 – Oct 2019, Washington, D.C.
- ICH E6 GCP stakeholder engagement plan
- Regional Workshops on ICH E6 revision in June 2020
- Regional Representatives of academic research engage with the ICH E6 GCP Expert Working Group – ongoing since August 2020

Stakeholder engagement is **built into** the revised ICH E8 **guideline**:

- Foresees involvement of patients in study planning, anchored among E8 principles
- Stipulates including stakeholders across disciplines in study planning & design for identifying what is critical to study quality

Document Structure

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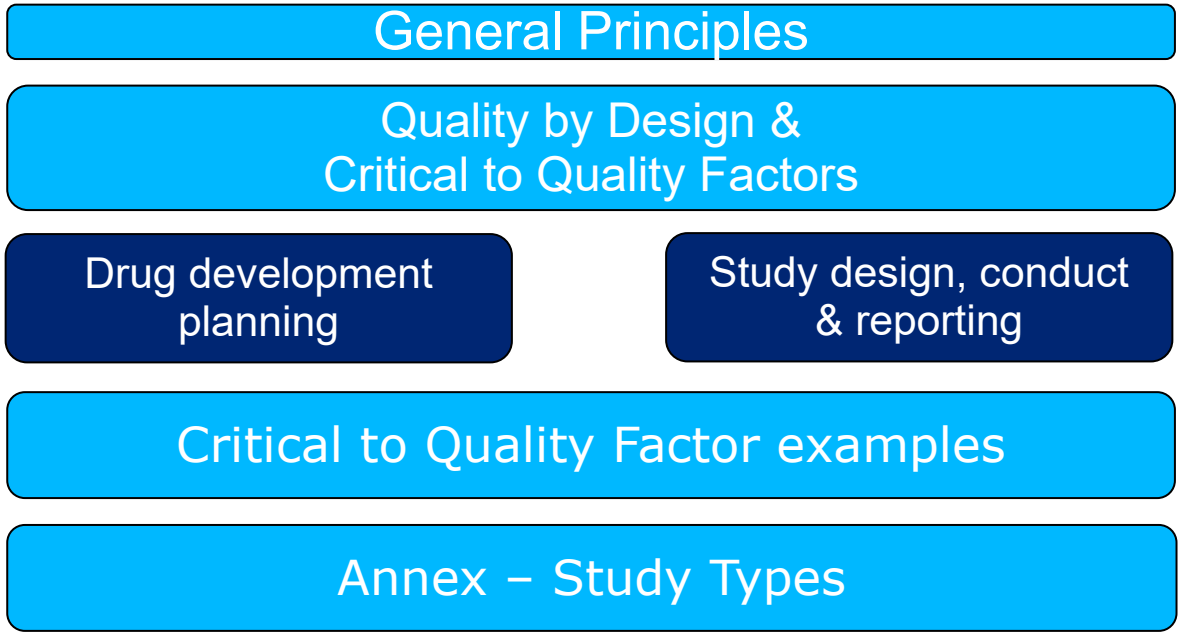
E8 (R1) - Integrative Overview



2 GENERAL PRINCIPLES

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2.1 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** and should be observed in the conduct of all human clinical investigations.
- **Before initiating** a clinical study, **sufficient information should be available** to ensure that the drug is **acceptably safe for the planned study in humans**.
- **Emerging** non-clinical, clinical, and pharmaceutical quality **data** should be **reviewed** and **evaluated**, as they **become available**, by qualified experts to assess the **potential implications for the safety of study participants**. Ongoing and future studies should be appropriately adjusted as needed, **to take new knowledge into consideration and to protect study participants.**

2.2 Scientific Approach in Clinical Study Design, Planning, Conduct, Analysis, and Reporting

- **Quality** of a clinical study is considered in this document as **fitness for purpose**.
- The **purpose** of a clinical study is to **generate reliable information** to **answer the research questions** and **support decision making** while **protect**ing study **participants**.
- The **quality** of the information generated should therefore be **sufficient to support good decision making.**
- **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.
- This involves the use of a **prospective, multidisciplinary approach** to promote the quality of protocol and process design, and clear communication of how this will be achieved.

2.3 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.**
- Patients also provide **their perspective of living with a condition**, which may **contribute** to the **determination**, for example, of **endpoints** that are **meaningful to patients**, selection of the **appropriate population and duration** of the study, and use of **acceptable comparators**. This ultimately **supports the development of drugs that are better tailored to patients' needs**.

ICH E8 Quality of a clinical study

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Quality of a clinical study is …. fitness for purpose.

Purpose of a clinical study is to generate reliable information to answer the research questions and support decision making while protecting study participant. The quality of the information generated should therefore be sufficient to support good decision making.

Quality by design .. to ensure that the quality of a study is driven proactively by designing quality into the study protocol and processes. ..

- use prospective, multidisciplinary approach to promote the quality of protocol and process design,
- in a manner proportionate to the risks involved,
- clear communication of how this will be achieved.

Quality by Design concept – Chapter 3

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Identifying attributes whose integrity is fundamental to study quality via:

- Open dialogue, multiple stakeholders
- Triage and focus on essential activities
- Proactive implementation and communication in protocol
- Continuous review and risk-proportionate adaptations

…to optimally align research objectives with planning, conduct and decision making by promoting flexibility instead of one-size-fits-all strategy.

→ *Reflected in 'Quality by Design' and 'Critical to Quality Factor' concepts.*

ICH E8 Section 3.1 Quality by Design of Clinical Studies

Establishing a Culture that Supports Open Dialogue:

- .. values and rewards critical thinking and open dialogue about quality ..beyond sole reliance on tools and checklists.

Focusing on Activities Essential to the Study:

- .. essential to the reliability and meaningfulness of study outcomes for patients..safe, ethical conduct .. for study participants. Consider whether nonessential activities may be eliminated...to simplify conduct…improve efficiency…target critical areas.

ICH E8 Section 3.1 Quality by Design of Clinical Studies

Engaging Stakeholders in Study Design:

- ..best informed by input from a broad range of stakeholders, including patients and treating physicians. It should be open to challenge by subject matter experts and stakeholders from outside, as well as within, the sponsor organisation.

Reviewing Critical to Quality Factors:

- Build on accumulated experience and knowledge with periodic review of critical to quality factors to determine whether adjustments to risk control mechanisms are needed, since new or unanticipated issues may arise once the study has begun

E8 (and E6) revision – goals and conclusion

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Facilitate objective-centered, yet flexible approach to clinical studies, including:

- Quality by design process & stakeholder engagement
- Enabling a broad range of study designs and different data sources
- Upfront assessment of risks specific to a study design, protocol and procedures
- Proportionate management of the risks and controls focusing on critical study elements
- Use of technology to ensure robust conduct, oversight, and reporting
- Change management will be a key to implementation of E8 (and E6) revision.

E8(R1) supports **designing quality into clinical studies**, considering the **diversity of clinical study designs** and **data sources** used to support **regulatory** and other **health policy decisions**.

Conclusion on ICH E8(R1)

- This document **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**.

Everyone involved in the conduct of clinical trials should read and understand this guideline.

Change the way we all work – don't add more to the status quo.

Change Management is the greatest challenge

– adjusting behaviors, attitudes – away from preconceived ideas and interests – and on to a new, better, way of working.

E8 (R1) finalisation

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Procedural aspects:

- ICH E8 Step 4 reached on 6 October 2021 and published on ICH website
- ICH E8 Step 5 in progress in regions (EU adopted in 14 October 2021 with 6 months to come into application (14 APRIL 2022)

Thank you!

Any questions?