

CRSO Regulatory Blog Post

FDA issues ICH E8 Revision

April, 2022

On April 8, 2022, the U.S. Food and Drug Administration (FDA) adopted and issued the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) [E8\(R1\) General Considerations for Clinical Studies](#). ICH E8 guidelines sets out general scientific principles for the conduct, performance, and control of clinical trials, and addresses a wide range of topics in trial design and execution. This revision is the first major revision since 1997. It marks the initial step in the [ICH's Good Clinical Practice Renovation project](#) and will continue with the revision of E6(R2) guidelines on Good Clinical Practice (GCP). A draft version of E6(R2) was made available in March of 2021.

What changes were made with the E8 revision?

- (1) E8(R1) addresses study quality to ensure the protection of study participants and the generation of reliable and meaningful results, while promoting study efficiency.
- (2) E8(R1) addresses a broad range of study designs and data sources.
- (3) E8(R1) provides updated cross-referencing to other relevant ICH guidelines that inform the design, planning, and conduct of clinical research.

How are E8 and E6 guidelines related?

The E6 Guideline on Good Clinical Practice and the E8 are both part of the E "Efficacy" family of ICH guidelines. They are complementary and should be read together with other ICH guidelines relevant to the conduct of clinical trials.

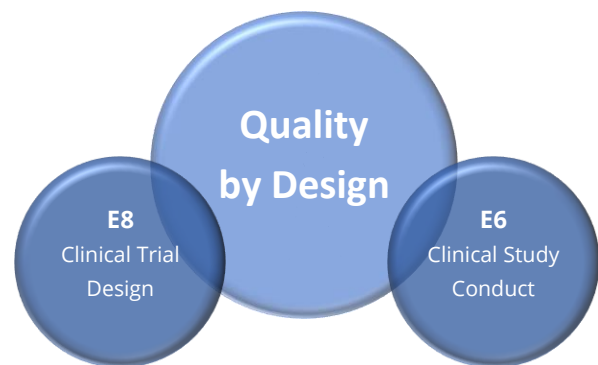
Whereas E8 primarily addresses principles and practices in design to assist sponsors and other parties in planning and designing clinical trials, E6 Good Clinical Practice (GCP) describes responsibilities and expectations for conducting clinical trials by all involved. E6 is also intended to apply to other studies impacting the safety and well-being human subjects.

ICH E8(R1) and ICH E6(R3) will interplay to provide a shift toward greater efficiency and focus on risk-based quality management.

What is a Quality by Design approach?

ICH E8(R1) offers a new emphasis on quality by design, that is, an early focus on the design of all components of the study protocol, procedures, associated operational plans and training.

The quality by design approach to clinical research involves focusing on *critical-to-quality* factors to ensure the protection of the rights, safety, and well-being of study participants; the generation of reliable and meaningful results; and the management of risks to those factors using a *risk proportionate approach*.



The approach of prospectively building quality by focusing on the design of all study components are intended to compliment current retrospective quality assurance activities, such as monitoring and auditing, that alone are not sufficient in ensuring quality of a clinical study.

What are critical-to-quality factors and how are they involved in risk management?

Critical-to-quality factors are attributes of a study whose integrity is essential to the protection of study participants, the reliability and interpretability of the study results, and the decisions made based on the study results. They are considered critical because, if they were compromised by errors of design or conduct, the reliability or ethics of decision-making based on the results of the study would also be undermined. Different factors will stand out as critical for different types of studies. The identification of critical-to-quality factors should be supported by proactive, cross-functional discussions and decision-making at the time of study planning.

Once the critical-to-quality factors are identified, it is important to determine the risks that threaten their integrity and decide whether they can be accepted or should be mitigated, based on their probability, detectability, and impact. Where it is decided that risks should be mitigated, the necessary controls should be put in place and communicated, and the necessary actions taken to mitigate the risks.

Does the ICH E8 revision provide any other new perspectives?

ICH E8(R1) places an emphasis on including a wide range of perspectives in study design, including patient (or patient organization) insights. The logic is that involving patients early in the process likely increases trust in the study, encourages recruitment, and helps with protocol adherence

Additionally, the revision addresses a wider range of study designs, beyond the traditional randomized controlled interventional trial that was the focus of the 1997 version, as these play an increasingly important role in drug development.

More Information Available

If you have questions regarding the revised guidance, please contact the CRSO at crso@med.unc.edu. Please also let us know if you have any regulatory updates that you would like us to write about.