REMARQUE SYSTEMS℠

ICH E6 (R3) Revision Overview

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- When technology changes everything: The new goals of ICH E6 (R3)

ICH E6 (R3): The Foundation for modern clinical research

Three decades ago, an international committee came together to create a revolutionary document designed to improve the efficiency of new drug development. Dubbed ICH E6, it has provided consistent guidance for clinical trials around the world. Today, plans are underway to update it for the second time in four years. Why?

The industry is embracing a vast array of emerging technologies: an avalanche of diverse electronic data sources that harness new modes of collection and support innovative trial designs. These technologies bring new opportunities for speed, efficiency, and collection of real world data to support patient-centric operations. They also demand new risk-based strategies and supporting ecosystem platforms to protect patients, data integrity, and even the broader public health. Yet, the industry is concerned that researchers may not be taking full advantage of these advances because, under ICH E6 (R2) guidelines, they require too much additional paperwork.

In an effort to remove such burdens, the working group is introducing, ICH E6 (R3). Its goal remains consistent with the original version: to maximize efficiencies and facilitate innovations in clinical trials. To succeed, this draft will be flexible enough to adapt to designs and technologies that have not yet been conceived. Focusing more broadly on principles and objectives, including further advancing the concept of risk-based approaches. A major focus will be on Non-Traditional Intervention Clinical Trials.

Universal guidelines help streamline the development path

Since 1990, the International Council for Harmonisation Of Technical Requirements For Pharmaceuticals for Human Use (ICH) has undertaken a global effort to improve the efficiency of new drug development, prevent duplication of clinical trials in humans, and minimize the use of animal testing, all without compromising safety and effectiveness. The guidelines are developed through a five-phase, consensus-driven process, bringing together the concerns and insights of both regulators and industry. There are advantages to both.

With clinical trials happening globally, having the same standards across regulatory bodies not only ensures the integrity of results but the harmonization of the process. Standard requirements for trial design, protocols, data collection, and monitoring mean trials can be conducted multi-regionally. Sponsors can concurrently submit complete applications in multiple regions. Regulators can provide a more rapid, efficient, and consistent review. Most importantly, there is a far higher potential for first-cycle approval, providing universally earlier access to new medicines and immediate benefit to the patients.

The updates will be phased in through two parts

The initial guidelines focused on monitoring, reporting, and archiving. The second iteration encouraged more efficient approaches to these activities, including updating standards for electronic records. Driven by the evolving paradigms of evidence generation, an increasingly digital world, and innovative clinical trial designs, the ICH E6 (R3) will be a full rewrite of the guidelines, to be implemented across all regulatory agencies.

These new guidelines will come out in two parts.

Annex 1

- Available for public view in fall 2021, will be specific to interventional trials.
- Refining the concepts found in ICH E6 (R2), it will consider the principles as they relate to the use of unapproved or approved drugs in a controlled setting with the prospective allocation of treatment to participants and collection of trial data.

Annex 2

- Expected within a further 12-18 months
- Will expand guidelines to encompass diverse trial types, including pragmatic clinical trials and decentralized clinical trials, as well as those trials that incorporate real-world data sources. Will also will delve into novel areas that were not addressed in previous versions and will address a broader approach to clinical trials incorporating the potential impact of technology.

Technology advances are a crucial driver for change

A recent presentation co-sponsored by the FDA and the Clinical Trials Transformation Initiative (CTTI), shared some of the stakeholder input into ICH E6 (R3). Describing a survey of 500+ industry stakeholders in 153 countries, Amy Corneli, PhD, MPH, Associate Professor, Duke University, Lead Social Scientist, CTTI, noted that 45% of respondents pointed to monitoring guidelines as the area most in need of updating. Further, there was a clear consensus that the revised standards must provide direction on the use of technologies that will ultimately reduce the burden on patients and sites, while simultaneously increasing participation and enrollment in clinical trials.

As Carla Brichesi, Regulation and Health Surveillance Specialist, ANVISA - Brazilian Health Surveillance Agency, noted, some of these new technologies have come to the fore during the COVID-19 pandemic—remote source data verification, ehealth forms, and patien t-reported data. Having shown their utility, they are likely to remain in effect post-pandemic.

Such new technologies—along with advances such as machine learning and artificial intelligence—have also enabled a range of innovative trial designs from master protocol trials and non-IND studies to adaptive and platform trials. These don't fit easily into the existing guidelines. Roger J. Lewis, MD, PhD, Professor of Emergency Medicine, David Geffen School of Medicine at UCLA spoke to some of the issues.

Both adaptive and platform trials, for instance, require ongoing interim data—snapshots of what is happening at a given moment. Under ICH E6 (R2) guidelines, this data needs to be verified with equal rigor and a greater frequency in comparison to a traditional trial; which creates a burden not seen before with clinical trials.

There are some like Dr. Carol Légaré, of Health Canada who feel that the industry has not properly interpreted ICH E6 (R2), emphasizing less important aspects of trials, such as the completeness and accuracy of every piece of data, at the expense of key critical trial principles. She feels the focus should be on carefully managing risks to the integrity of key outcome data. Further, she believes the new guidelines should distinguish between clinical trial activity and standard of care activity, and, most importantly, accommodate for various trial designs, data sources, and remote technologies.

Designing the foundation for modern clinical research

The CTTI reports that stakeholders want the new guidelines to have four attributes: flexibility, simplicity, transparency, and timeliness. All this supports the ability to continue to apply the guidelines universally, even as circumstances shift. The hope is to transition the guidelines from being a perceived checklist and policing tool for audits to being the guiding principles for research everywhere.

As Dr. Légaré stated, trials will continue to change. Enabled by technology, they will leverage an increasingly digital ecosystem with new data sources, more mHealth, patient-generated data, and remote assessments for both convenience and safety. With these shifts, trials designs will become more innovative and study conduct more agile, with new multimodal trials and new study roles and responsibilities.

M. Khair El Zarrad, Deputy Director, Office of Medical Policy Center for Drug Evaluation and Research of the FDA, framed it well by saying that the clinical trial community needs comprehensive principles that are flexible enough to remain relevant while guiding clinical trial conception, design, conduct and analyses—and ensuring a proportional risk-based approach. Furthermore, it will be critical to maintaining such standards while incorporating the technological advances and keeping an open mind for integrating non-traditional sources of data to complement our current view of clinical trials. The goal for ICH E6 (R3) is to be sufficiently adaptable to serve as the foundation for a new way of conducting clinical research.