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[DOI: 10.14524/CR-17-4031]

ICH E6(R2)—Impacts on Investigator Responsibilities

The International Council for Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP) dates back to 1996, when clinical trials were largely managed with paper documents. Since then, the scale and complexity of clinical trials have greatly increased. This has given rise to the need to revise ICH E6 to better reflect advances in technology, including the Internet, electronic data capture (EDC), cloud computing, and real-time review of clinical data, and how these impact oversight of people and documents as well as recording and reporting procedures.

ICH E6(R2) now mandates sponsor oversight of contract research organizations (CROs), and requires that investigators document and oversee any delegated tasks such as essential document control or study-specific procedures.

Therefore, ICH E6(R2) was introduced in November 2016; it was adopted in the European Union on June 14, 2017, but there is no specified date for adoption in the U.S. or Japan yet.

Understanding the Revisions

While it is important to educate investigators and their teams about the salient aspects of ICH E6(R2), it is essential that they grasp *how* the revised guidance will affect both their workflows and the tools they use to do their work.

For instance, in the old days a clinical research associate (CRA) would regularly travel to study sites to manage quality. Now, under the most recent revision to ICH E6, there will be a mix of onsite and centralized monitoring. Investigators should be aware that not only will CRAs do more by telephone and e-mail, they will also likely visit the site less frequently, freeing them up to go into greater detail regarding verification of procedures and how specific tasks are carried out. In addition, other sponsor staff such as data managers, statisticians, and medical monitors will monitor data remotely.

In particular, the latest revisions to the tenets of GCP are meant to address deficiencies at the site and investigator level—in record keeping, lack of rigorous oversight of individuals charged with conducting study tasks, deviations from trial protocols, inadequate storage and archiving of essential documents and data, and poorly documented assessment of third-party providers.

For instance, ICH E6(R2) now mandates sponsor oversight of contract research organizations (CROs), and requires that investigators document and oversee any delegated tasks such as essential document control or study-specific procedures. It is critical that this oversight is ongoing and documented.

Where clinical trials used to be managed by a single study nurse who executed most of the trial activities, now many more individuals and professionals are involved in trials. Investigators are now responsible for ensuring that third-party suppliers to whom they delegate trial-related duties and functions are qualified. They should also implement procedures to ensure the integrity of those parties' duties and functions, and of the data they generate.

Prior to implementation of ICH E6(R2), investigators would delegate a task and not revisit it, assuming it was satisfactorily completed unless told otherwise by a study monitor. Now, beyond simply delegating the task, investigators must supervise and moreover document that ongoing supervision and oversight throughout the life of the study. Document control (e.g., case reports, medical images) and standard operating procedures (SOPs) should be adapted to the demands of this new regulatory environment.

This new ICH revision will put a lot more focus on how sponsors and CROs interact. It will require that sponsors be able to manage risk and be clear about which risk management tasks they want to retain, and which ones they want to delegate to the CRO.

Targeting Technology and Clear Communications

Study teams now have the technology needed to review clinical data in real time. This can be critical in the case of a dose-escalation trial, where investigators must track safety data across trial participants in real time in order to know when to go to the next dose.

Sites should be staffed by people skilled in data integrity, including system access, version control, and audit trails. In addition, source data should be attributable, legible, contemporaneous, original, accurate, and complete.

Sites also must now ensure that communications with staff regarding studies are documented—particularly communications between investigators and individuals to whom tasks have been delegated. This could encompass telephone calls, study meetings, eligibility discussions, and so forth.

Sponsors and investigators will need to maintain records of the location of all records, including but not limited to essential documents and communications that would enable the reconstruction of the study. In many cases, documents such as medical records or CVs are stored offsite, and will require a documented method to be accessed when required. This underscores the importance of noting their specific location in an SOP.

Rising to the Challenge

In its own words, the ICH E6(R2) addendum "encourages the implantation of improved and more efficient approaches to clinical design, conduct, oversight, recording, and reporting." These new responsibilities fall on lead investigators and their key staff, and the changes will usher in a new era in how clinical monitoring and trial management are conducted.

If investigators are prepared for the new tasks they will have to execute and the new ways that their sites will be monitored—and how these will impact their workflows and responsibilities—then they will have no trouble in meeting the challenge.

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