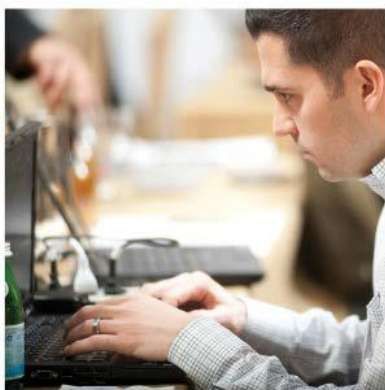


Summary of Themes from Executive Roundtable on Company Response to the New ICH E6 Revisions

Tufts CSDD



**Tufts Center for the Study of Drug Development
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Summary

The Tufts Center for the Study of Drug Development hosted an executive roundtable with R&D leaders from around the industry to gather feedback and collaborate on applying the International Conference on Harmonization's (ICH) addendum to the ICH E6 Guideline for Good Clinical Practice. Overall, companies are receptive to the recently updated ICH E6 Guidelines. The regulation provides standards and procedures for the use of IT tools, electronic records, and essential documents. With risk-based quality management (RBM) and quality-by-design (QbD) being the most pivotal aspects of R2, many companies have started to revise their current strategies and operating models to address site quality control and protocol risk assessment to meet the new requirements. ICH E6 R2 also has implications for critically important aspects of study quality and provides recommendations to facilitate modernized approaches to clinical trial conduct. Companies are addressing these implications by designing strategies and operating models that include statistics-driven data analysis to inform central monitoring practices that support the areas listed in the regulation. Attendees agree that the revised E6 guidance now reflects and embodies the principle of needing to be agile, lean, and to move efficiently.

How are companies responding to the addendum?

Many companies are still in the process of interpreting the guidance to translate recommendations into tangible operating practices. Attendees confirmed that most organizations have made significant progress and/or have the E6 amendment on their near-term roadmap. In order to begin the process of design and implementation, companies are developing risk based auditing programs to perform internal audits of their RBM approaches and identify critical variables for their trials early on (e.g., relevant critical-to-quality (CTQ) factors). Others are working with their technology departments to incorporate algorithms and account for the sensitivity of smaller trials. To address recommendations on documentation, some companies are stating their monitoring approaches in their quality management plans, creating data surveillance plans managed by statisticians, and including signatures on reports to confirm adherence to monitoring plans. Additional ways companies are responding:

- Reinforcing central monitoring programs to limit onsite monitoring and report on central monitoring activities
- Working with vendors to pilot trials with crowdsourcing to get feedback on feasibility assessments (i.e. the patient, caretaker, and physician experience)
- Cross-functional stakeholders are setting tolerance limits on key clinical data from electronic data capture (EDC) systems and key risk indicator (KRI) dashboards
- Creating education within the organization around everyone's role in the organization and how each department uses data
- Changing both the mindset and skill set of monitors to be more strategically-focused with sites and to embrace analytical methods to help identify risks.
- Creating an atmosphere where stakeholders share information informally and expectations are clear

What areas are most expected to be impacted?

Companies are starting to perform risk assessments and gap analyses of organizational procedures to identify where the organization stands and determine areas that both question the credibility of data and will be most impacted by ICH E6 R2. Cross functional discussions on protocol design, quality, risks and mitigation are suggested. Potential areas impacted are:

- Late stage processes
- Computer systems that will need to be validated against new requirements
- Documentation: Amending standard operating procedures (SOPs) and source doc implementation tools.
- Education: Training CRAs and those who interact with them.

Do companies anticipate having to make new investments?

As companies await the regulation, new investment options may drive them to rethink their sourcing options. Some companies are eliminating CRAs in order to adapt and change but have found that return on investment is a tradeoff. Companies are committing to improving data quality with a longer term goal of eliminating cost. There is agreement that R&D organizations have a responsibility to patients to improve the effectiveness of the drug development cycle, which include improving patient safety and data integrity through technology-driven oversight. Possible anticipated investments are in:

- Creating, or consolidating roles and delineating responsibilities of roles in quality management plans. Examples include:
 - *Data Quality Lead (DQL)*
 - *Internal Manager* within the quality department to help facilitate communications.
 - *Clinical Data Scientist* to understand data integrity and determine what and how a protocol should be implemented.
 - *Site Lead* (replaces the person who oversees CRAs) works with Clinical Data Scientist and the Central Monitor to help manage the signals received from monitoring tools.
- Using several utilization tools to measure how action plans are discussed among the different roles (i.e. clinicians, statisticians, etc.).
- Analytical systems and technologies

What revision elements show the widest differences in interpretation between companies?

Deciding on a monitoring plan (centralized, decentralized approach, or both) and finding the balance between centralizing the central monitors, appears to be the most variable decision among companies as a result of the R2 revision. Some monitoring plans have been decided on a site-by-site basis. Conversations throughout the process on how to integrate signals and make

monitoring decisions have been found to be essential. Elements with the widest differences in interpretation:

- Accepting risks to the point of diminishing returns
- Addressing ICH E8 in addition to ICH E6
- How to best collaborate with CROs over documentation and the translation of forms, and accessing the real-time data of CROs
- Simplifying vendor oversight by implementing tools that oversee vendor quality compliance. Reviewing sponsor oversight policies of sites and CROs in regards to the regulation.
- Establishing and deciding on definitions for predefined quality tolerance limits

What challenges have companies seen?

One of the major challenges companies face is transforming the organizational culture to change the way risks are identified and managed in clinical research. Further barriers encountered:

- Challenges to the process of site selection when developing an RBM approach
- Challenges in the adoption of risk-based monitoring approaches
- Establishing algorithms that are specific but can be applied to a broad set of therapeutic areas
- Aligning with CRO partners on incentives and leveraging CRO expertise to evolve models

In what specific areas are companies looking for more regulatory clarity and input?

Determining how regulators will assess quality risk management plans, and deciding on the acceptable amount of noise in the data if not undergoing 100% source data verification and review (SDV and SDR). If errors are distributed evenly among patient groups then the data may be able to handle a lot of noise, but the data should still be reliable. Companies are also looking for regulatory clarity when identifying the acceptable applications for validation (e.g. Excel, SharePoint), the frequency of documentation, and determining data quality parameters for a successful trial.

In light of these trends we can anticipate that the following is next to come:

- Adoption of the guidance by the regulators (i.e. FDA, EMA, HC)
- Evolution of models to include learning-algorithms that are trial specific
- Next-generation CRO partnerships that incorporate risk-adjusted modeling and oversight (i.e. risk-based oversight), etc.

Background about the Executive Roundtable

On April 11, the Tufts Center for the Study of Drug Development held a Management Roundtable among senior R&D executives to discuss the challenges and implications of the new ICH E6 R2 regulatory guidelines on drug development performance and collaborative effectiveness. The executive roundtable was produced and facilitated by Ken Getz, MBA, Research Associate Professor and Yaritza Peña, Research Analyst. In addition, select roundtable sessions were also facilitated by Patrick Hughes, Anup Kharode, Francois Torche, and Brian Slizgi.

34 participants attended the roundtable from a large number of companies including Allergan, Johnson & Johnson, Pfizer, GSK, Novartis, Biogen, Takeda, and Amgen. The agenda began with a strategic overview and panel discussion of the key components of ICH E6 R2 guidelines and technology implications, followed with case examples from organizations developing and implementing response, and ended by addressing barriers, anticipated challenges and discussing the changing regulatory environment.

The primary author of this report was Yaritza Peña.

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About Tufts Center for the Study of Drug Development

Established in 1976, the Tufts Center for the Study of Drug Development at Tufts University provides strategic information to help drug developers, regulators, and policy makers improve the quality and efficiency of pharmaceutical development, review, and utilization. The Tufts Center conducts a wide range of in-depth analyses on pharmaceutical issues and hosts symposia, workshops, and public forums on related topics, and publishes the *Tufts CSDD Impact Report*, a bi-monthly newsletter providing analysis and insight into critical drug development issues.



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