Unlocking Success with ICH E6(R3) Implementation

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The International Council for Harmonisation (ICH) issued its final version of the Guideline for Good Clinical Practice (GCP) E6(R3) in January 2025. This revision represents the first comprehensive overhaul of the E6 GCP guideline since ICH E6(R2) was issued in 2016, and introduces a modernized framework for the design, conduct, and oversight of clinical trials.

ICH E6(R3) has been called an "important milestone [that] marks a significant evolution in the global clinical trial landscape." Its goal is to update GCP principles to reflect current scientific and technological advancements while being flexible enough to address the growing diversity of clinical trial design and data sources. Like the previous versions, safeguarding participants and ensuring the integrity of trial outcomes remain central tenets of this revision.

The guidance emphasizes flexibility and scalability across diverse trial types and is supported by a three-part structure: overarching principles, Annex 1 for interventional trials, and Annex 2 for decentralized and real-world data approaches. The guideline also builds on the concepts from ICH E8, reinforcing the importance of thoughtful protocol design and critical thinking throughout the trial lifecycle. Importantly, ICH E6(R3) should be leveraged in conjunction with other ICH guidance to ensure comprehensive and harmonized implementation.

In the months following adoption, a growing number of trial sponsors, sites, and service providers have begun assessing the practical implications of adopting ICH E6(R3). A particularly rich source of insight comes from WCG's 2025 Avoca State of the Industry Report, which sought to understand industry action toward adoption and implementation of ICH E6(R3).

Drawing on these early reflections, this playbook will offer a practical lens into some of the key elements within ICH E6(R3) and the strategies that support successful implementation. Specifically, we'll explore how:

- ICH E6(R3) emphasizes flexibility and proportionality, rather than applying rigid, one-size-fits-all requirements.
- Quality by Design (QbD) promotes embedding quality into trial planning to reduce complexity and support operational feasibility.
- Expanded data governance reinforces shared sponsor-investigator responsibilities for ensuring data integrity, security, and traceability — recognizing reliable data is essential to trial credibility and participant protection.

Successful implementation requires a mindset shift from rigid compliance to proactive, quality-focused thinking. It should be supported by strong cross-functional and cross-industry collaboration to align expectations, share best practices, and co-create fit-for-purpose solutions.

Understanding the updates

There were significant changes from ICH E6(R2) to ICH E6(R3) that will impact clinical trial design and execution. The principles in ICH E6(R3) have evolved from the more prescriptive and static guidance of ICH E6(R2) to a flexible, modernized framework that introduces two new principles — risk proportionality and roles and responsibilities — and places greater emphasis on critical thinking, quality by design, and shared accountability across stakeholders.

Key Changes in Principles from ICH E6(R2) and (R3)

1. Ethical Principles
- Combined R2 2.1, 2.2, 2.3, 2.7 & 2.11.
- Periodic, timely safety information review.
- Representative participant inclusion.

2. Informed Consent
- Clear & concise.
- Process per relevant aspects of trial.
- Technology use for informed consent.

3. IRB/IEC Review
- Periodic review per regulatory requirements.

4. Science
- Periodic scientific review.
- Reflect IP knowledge & experience.

5. Qualified Individuals
- Different expertise across all phases of a clinical trial.

6. Quality
- Quality = fitness for purpose.
- Prospective QbD/CtQ factors.

7. Risk Proportionality NEW!
- Processes proportionate to risks.
- Risk to participants beyond usual medical care.
- Proactive and ongoing risk management.
- Avoid unnecessary burden on participants and investigators.

8. Protocol
- Importance of well-designed protocol.
- Clear, concise & operationally feasible; includes study plans.

9. Reliable Results
- Processes support key objectives.
- Fit for purpose, operationally feasible, proportionate.
- Transparency of clinical trials.

10. Roles & Responsibilities NEW!
- Sponsor/investigator retain overall responsibility for transferred/delegated tasks.
- Agreements clearly define roles and responsibilities.
- Sponsor/investigator maintain appropriate oversight of transferred/delegated tasks.

11. Investigational Product (IP)
- IP management by treatment while protecting the blind.
- IP to participants retains quality.
- Processes for all IP related activity.

Source: WCG Webinar: ICH E6(R3) is Here – What You Need to Know [January 29, 2025]

One of the most talked-about changes in ICH E6(R3) is the emphasis on **proportionality** and **fit-for-purpose** thinking. The principle of proportionality states that "clinical trial processes, measures, and approaches should be implemented in a way that is proportionate to the risks to participants and the importance of the data collected and that avoids unnecessary burden on participants and investigators." This shift encourages trial teams to focus their efforts where they matter most — activities and data that are critical to quality — to ensure participant safety and reliable results while reducing unnecessary burden and complexity.

This principle aligns closely with the concept of QbD, which also promotes thoughtful planning that prioritizes what is critical to quality, rather than applying uniform procedures across all trials. QbD ensures that clinical trials are intentionally structured around factors critical to quality — proactively embedding quality from the outset and enabling early identification and management of risks to safeguard participant safety and ensure data reliability.

"The concept of quality by design isn't a new concept — it is outlined in ICH E8(R1) — but this is the first time we see it explicitly called out in ICH E6(R3) with a direct reference to ICH E8(R1)," explains Karen Harvey, senior director, Avoca Quality Consortium at WCG. "Even though [those key concepts] were here, there really is more emphasis on … putting that effort in up front to identify what's important to your trial, and then monitoring the risk to those important things throughout."

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> Avoca Quality Consortium at WCG

The ICH E6(R3) guidance also introduces substantial changes to **data governance**, offering a more robust and structured approach that reflects the evolution of trial complexity and increasing reliance on digital systems. Notably, it establishes a dedicated section on data governance — absent in ICH E6(R2) — that defines shared responsibilities between sponsors and investigators, ensuring a lifecycle-wide framework for data integrity and oversight. This includes comprehensive coverage of the data lifecycle, strengthened expectations for validated and access-controlled computerized systems, and the introduction of a source data plan and audit trail requirements to ensure transparency, traceability, and secure data handling.

While data governance is a new section in ICH E6(R3), Harvey notes that much of the language in that new section is aligned with the European Medicines Agency (EMA) guidance on computerized systems released in 2023, which means that organizations working under European guidance will be better prepared to adapt to the new expectation for data governance.

"It sets the responsibilities for data governance both at a sponsor level, which is not new, but it pulls the investigators in and names investigators as responsible parties," Harvey says. "Investigators need to ensure that the systems they implement are fit for purpose with appropriate user management."

A **shift in mindset** is reinforced throughout ICH E6(R3), which emphasizes proportionate, risk-based approaches and shared responsibilities across stakeholders. The guidance calls for **early and intentional collaboration** between sponsors, investigators, and other responsible parties to ensure data integrity, operational feasibility, and participant protection. By **embedding quality into trial design and execution** — and by co-creating fit-for-purpose solutions — organizations can better navigate the increasing complexity of clinical research and the demands of digital transformation. This spirit of co-creation is actively supported by WCG's Avoca Quality Consortium (AQC), which brings stakeholders together to collaboratively develop practical tools and frameworks that drive quality and compliance across the ecosystem.

"Effective upfront collaboration between stakeholders takes time and critical thinking — especially early in the study when there is a rush to meet milestones," says Harvey. "The shift in mindset to slow down and think strategically from the start may be just as important as the implementation activities."

Insights into impacts

As part of its industry-informed quality advancement, the AQC explored how organizations are adopting and implementing ICH E6(R3), as well as its impact on clinical trial design and execution, with findings published in the 2025 Avoca State of the Industry Report. This research provides a multifaceted view with perspectives from more than 250 sponsors, providers, and sites.

Key findings include:

- **87% of all survey respondents reported at least some familiarity with the new guidance** — a 31% increase compared to the previous year — indicating strong industry engagement.
- **Four out of five respondents believe clinical trial quality will improve** with implementation of the new guidance.
- **76% of all respondents anticipate moderate to significant impact** on how they conduct studies.
- **Innovative trial design and technologies were cited as the most difficult to implement** due to **cost, complexity, and regulatory uncertainty.**
- **Sites expressed concern about increased workload and the need for training,** especially around new technologies and investigator responsibilities.

These figures indicate that the industry perceives the transition to ICH E6(R3) not simply as a regulatory obligation, but as an opportunity to enhance scientific rigor and oversight. While optimism exists around the potential benefits, the report also highlights concern regarding the operational impact. **More than 70% of respondents acknowledged that adopting ICH E6(R3) will require internal transformation,** and around 60% of sponsors anticipate moderate to significant organizational change. Oversight responsibilities are expected to demand more time from sponsors. Meanwhile, sites foresee the need for greater investment to support training on new processes and systems, provider oversight, and documentation of risk assessments.

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> **"Organizations that are compliant with ICH E6(R2) expectations will have an easier time achieving ICH E6(R3) compliance. While organizations that are not aligned with ICH E6(R2) will have a much heavier lift with ICH E6(R3) implementation."**
>
> **Karen Harvey,** senior director,
> Avoca Quality Consortium at WCG

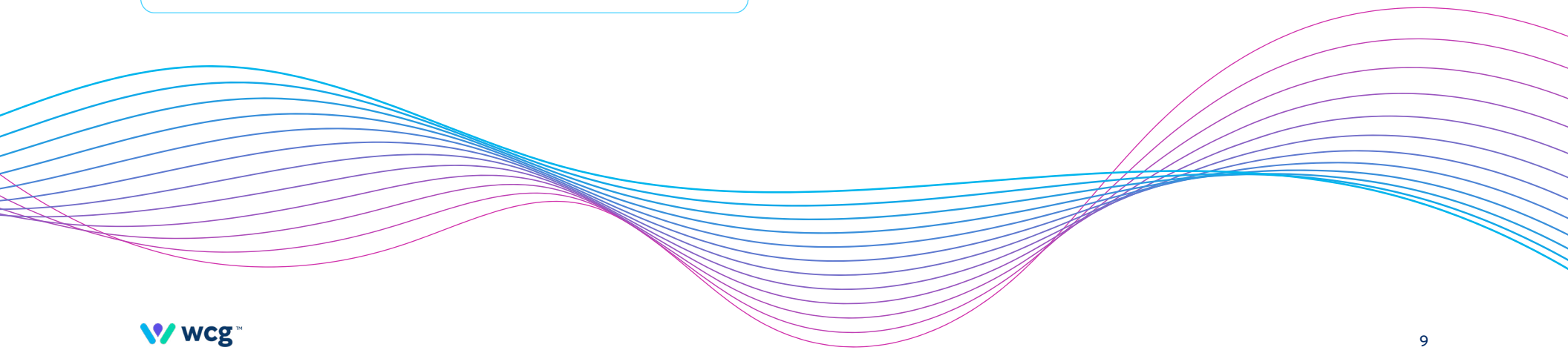
While many organizations are still navigating the demands of ICH E6(R2), the shift to E6(R3) is expected to be even more transformative. In this context, respondents identified three priority areas that will require focused attention and investment:

- **Risk-Based Approaches:** Shifting from traditional approaches to a more proactive and systematic evaluation.
- **Quality by Design:** Proactively building quality into trial design and execution.
- **Data Governance:** Implementing systems to ensure proper documentation, security, and integrity of study data that is in compliance with regulatory requirements.

"Each of these areas represents a shift from reactive to proactive thinking; sites and sponsors are being asked not just to respond to issues, but to anticipate and prevent them," says Michelle Webb, vice president, Avoca Quality Consortium, Quality Solutions & Strategic Partnering at WCG.

"The organizations that feel most prepared are the ones investing in strong data infrastructure, cross-functional collaboration, and early planning to embed quality and risk management into every stage of a trial."

Michelle Webb, vice president, Avoca Quality Consortium, Quality Solutions & Strategic Partnering at WCG



Despite broad optimism about the potential of ICH E6(R3) to elevate trial quality, the survey revealed persistent concerns about **increased site burden**. Over half of respondents believe the new guideline will place greater demands on sites, particularly in areas like oversight, technology adoption, and documentation. This is compounded by the fact that sites lag behind sponsors in both awareness and readiness. While many sponsors have begun structured change management and gap analysis efforts, most sites remain in early stages of preparation or are still unfamiliar with key elements of the guidance. This disparity highlights the need for targeted support and investment to ensure sites can meet these new expectations.

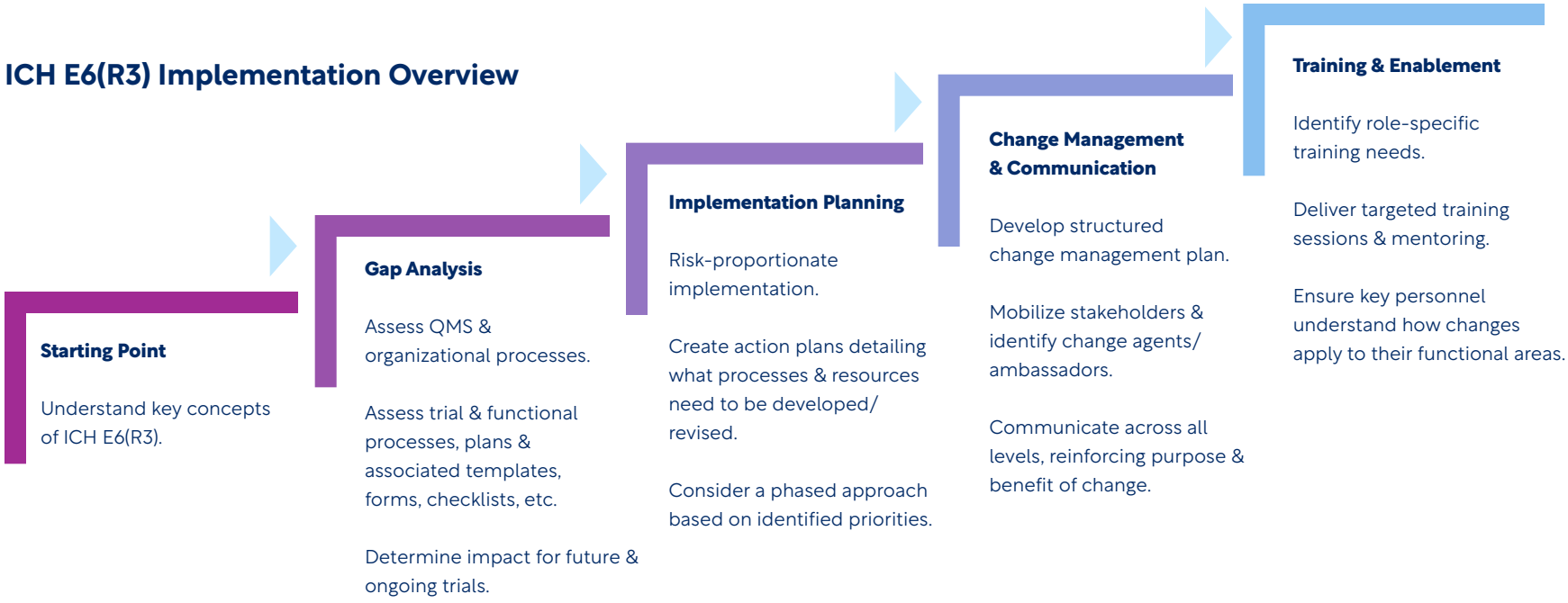
Unlocking success

Successful implementation of ICH E6(R3) requires more than procedural updates. It demands a strategic mindset that prioritizes risk and impact.

Rather than attempting to meet every new requirement equally, "organizations should take a proportionate, risk-based approach that first targets the gaps with the highest potential impact," says Webb. "Documenting gap analyses, action plans, and decision rationales not only supports alignment with ICH E6(R3), but it also provides regulators with clear evidence of how your organization has implemented ICH E6(R3) expectations."

"Additionally, it can be the foundation for building a culture of continuous improvement that strengthens quality and compliance over time." Educating stakeholders and adapting to uncertainties around proportionality and fit-for-purpose guidance are essential steps in this process.

ICH E6(R3) Implementation Overview



Longstanding industry challenges — limited time, fragmented collaboration, and inconsistent transparency — may complicate implementation. Organizations that prioritize speed may find it difficult to pause for deliberate risk planning or to build the internal alignment needed for strategic execution.

Achieving this alignment is not a solo effort. Without cross-functional coordination, implementation efforts risk stalling or creating blind spots. Organizations must work together to ensure consistent interpretation and execution of the guidance. As Harvey notes, "It's going to take sponsors, CROs, providers, and sites all working collaboratively in a transparent way."

The AQC supports these efforts by offering leading practices, tools, templates, and peer-to-peer forums. It sets organizations up for successful implementation and actively fosters the spirit of co-creation, bringing stakeholders together to collaboratively develop practical resources and frameworks that drive quality and continuous compliance.

Rather than viewing the new guidance as a regulatory burden, Harvey encourages teams to embrace its transformative potential: "It gives us more flexibility to have a much more meaningful impact on the health of people — and hopefully get us there in a more efficient manner."

Learn how WCG's Avoca Quality Consortium membership and consulting solutions can enable your organization's successful implementation of ICH E6(R3) guidance.

Get Involved →

Join over 200 organizations and become part of a global community committed to shaping the future of clinical trials.

With uncertainty around ICH E6(R3) implementation across the industry, WCG's Avoca Quality Consortium provides the tools, peer insights, and collaborative forums organizations need to navigate change with confidence. AQC members gain access to proven frameworks, co-created solutions, and a trusted network of sponsors, CROs, providers, and sites — all working together to elevate quality, streamline compliance, and drive meaningful impact across the clinical research ecosystem.

WCG is at the forefront of accelerating clinical research worldwide, serving as the trusted and preferred partner to biopharmaceutical and medical device companies, CROs, research institutions, and site partners. Offering a unique combination of expertise, next-generation data and insights, and tech-enabled solutions, WCG reduces complexity and optimizes study operations and outcomes while maintaining the highest standards of human participant protection.
For more than 55 years, WCG has maintained a relentless commitment to efficiency, safety, and impact, empowering clinical trials to deliver life-improving therapies swiftly.

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