

# Practical Guide on How to Adapt Your Auditing Practices for The Implementation of E6 (R3)

Erich Zirzow & Suheila Abdul-Karrim

## Practical Guide on How to Adapt Your Auditing Practices for The Implementation of E6 (R3)

With ICH E6 R3 being adopted and implemented across several countries, the landscape of auditing practices and audit scope have to evolve to align with these changes. This session will explore and discuss the implications of these changes for the auditor and sponsors, while focusing on how auditors may be required to adjust audit practices from R2 to R3. These include emphasizing the shift to a risk-based approach to ensure compliance and enhance the quality of clinical trials, as well as planning and time management which are often overlooked. Auditors are seeing major revisions in Standard Operating Procedures (SOPs). The revisions for E6 (R3) bring focus to the entire clinical trial process, advocating for flexibility and adaptability in auditing methodologies. The shift within the guidance encourages auditors to prioritize critical study elements and data integrity while incorporating technological advancements such as electronic records and data analytics.

The updated guidelines highlight the significance of collaboration among stakeholders, promoting a culture of transparency and continuous improvement in audit practices. Training and development are necessary for auditors to effectively navigate the complexities of the revised framework. Emphasizing patient-centric practices and Good Clinical Practice (GCP) underscores the need for auditors to fully understand and assess regulatory and ethical standards. Ultimately, adapting auditing practices to the changes from E6 (R3) aims to enhance the reliability of clinical trial data, ensuring that the rights and welfare of participants are safeguarded.

### CONTEXT & REGULATORY SHIFT Background

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) introduced E6(R3) to modernize GCP in response to:

- Increasing trial complexity
- Decentralized & hybrid designs
- Advanced digital systems
- Risk-proportionate oversight expectations
- Growing vendor ecosystems

#### Why E6(R3) Changes Auditing

R2 Paradigm	R3 Paradigm
Compliance-based	Risk-based & quality-driven
Retrospective review	Proactive system evaluation
Routine site audits	Risk-triggered audits
SOP adherence focus	Critical-to-quality protection

#### Core Principles of E6(R3)

- Risk proportionality
- Quality by Design (QbD)
- Critical-to-Quality (CtQ) factors
- Lifecycle quality management
- Technology-enabled oversight
- Patient safety & data reliability focus

### PRACTICAL ADAPTATION FRAMEWORK Risk-Based Audit Planning

**Shift:** Fixed audit schedules → Dynamic risk-informed strategy

#### Actions:

- Align audit plan with sponsor QRM
- Use KRIs & centralized monitoring outputs
- Prioritize critical data & processes
- Reduce low-risk procedural reviews

#### Audit Through a Quality-by-Design Lens

##### Evaluate:

- Protocol robustness
- Endpoint protection
- Feasibility assessments
- Vendor governance models

#### Hybrid & Centralized Auditing

E6(R3) supports digital oversight.

##### Audit Focus Areas:

- RBQM dashboards
- Remote source verification
- Data trend analysis
- eSystems validation (ePRO, eSource, CTMS)
- Competency Shift → Data literacy & systems thinking.

#### Vendor Oversight

Sponsor accountability remains.

##### Audit:

- CRO governance structures
- Delegation models
- Data flow integrity
- Risk escalation pathways

### IMPLEMENTATION & IMPACT AUDITORS ARE SEEING

- Sites struggling to move from traditional to risk-based methods
- Lack of Gap assessment of computerized systems utilized at sites for medical records
- Contracts not updated with
  - Vendors
  - Technology Company Providers
- SOPs updated but not all of them have been fully implemented
  - Not all staff have completed training on new SOPs
- Auditing in countries where E6 (R3) is not yet implemented:
  - Client/Sponsor Expectation vs local regulations not yet adopting R3

Foreseeable	Expected Impact
What should we anticipate	Anticipated Outcomes
Change in Processes	Updated SOPs
PI Oversight	Strengthening documentation of delegated tasks and supervision

### Implementation Roadmap

- **Phase 1 – Gap Assessment:** Compare SOPs vs R3
- **Phase 2 – Methodology Redesign:** Embed risk-based planning
- **Phase 3 – Training & Pilot:** Upskill auditors in QbD & RBQM
- **Phase 4 – Continuous Improvement:** Measure audit impact, not volume

### Key Takeaways

- Auditing becomes strategic quality assurance
- CtQ factors drive focus
- Reporting must link findings to patient risk
- Digital capability is essential
- E6(R3) demands system-level thinking

### Conclusion

Implementation of **ICH E6(R3) Good Clinical Practice** transforms auditors from compliance inspectors to proactive quality risk evaluators safeguarding:

- Patient safety
- Data integrity
- Ethical trial conduct



#### About the Authors:

Erich Zirzow is the Director of Project Management at FDAQRC.  
[e.Zirzow@fdaqrc.com](mailto:e.Zirzow@fdaqrc.com)

Suheila Abdul-Karrim is an independent clinical research consultant, auditor and trainer. [suheila@mweb.co.za](mailto:suheila@mweb.co.za)

### References

#### ICH Documentation:

- ICH E6(R3) Good Clinical Practice. International Council for Harmonisation (Final Version, 2023/2024).
- ICH E6(R2) Good Clinical Practice. International Council for Harmonisation (2016).
- ICH Reflection Paper on GCP Renovation (2017).
- ICH Quality Risk Management Guideline Q9(R1).

#### Peer-Reviewed & Regulatory Literature:

- TransCelerate Biopharma Inc. Risk-Based Monitoring methodology papers.
- FDA Guidance on Risk-Based Monitoring (2013).
- EMA Reflection Paper on Risk-Based Quality Management.
- Morrison BW et al. (2011). Risk-based monitoring in clinical trials. *Clinical Trials Journal*.
- Brosteanu O et al. (2009). Risk-adapted monitoring. *Clinical Trials*.