Global Harmonization Center Clinical Trials Webinar Part 2:

Adaptive Design Clinical Trials under Draft ICH E20

Regulatory Expectations, Remaining Uncertainties and Strategic Considerations for Global Development

Andreea Szentannai, OPIS



Why Does Draft ICH E20 Matter?

Drug development is becoming increasingly complex

- Precision medicine
- Rare diseases
- Cell & gene therapies
- Smaller patient populations
- Faster development timelines

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Traditional fixed trial designs are often no longer optimal

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Adaptive designs offer greater flexibility—but also greater regulatory complexity



The Regulatory Journey Towards ICH E20

Timeline

FDA Adaptive Design Guidance

EMA Reflection Papers

COVID-19 Platform Trial Experience

Growing use of Master Protocols

Draft ICH E20 (2025)

Global harmonisation of regulatory expectations

Adaptive designs are no longer considered experimental—they are becoming part of mainstream clinical development.



Draft ICH E20: From Acceptance to Implementation

- **ICH E20 establishes common regulatory principles**
- **The public consultation demonstrates that implementation questions remain**

The discussion has shifted from:
"Should adaptive designs be accepted?"

to
"How should adaptive designs be implemented consistently?"



What Draft ICH E20 Clearly Establishes

Four fundamental principles

1. Prospectively planned adaptations
2. Preservation of trial validity
3. Protection of trial integrity
4. Reliable and interpretable evidence for regulatory decision-making

Flexibility is acceptable.
Uncontrolled flexibility is not.





Prospectively Planned Adaptations

Adaptive modifications should be predefined



Examples include:

- Sample size re-estimation
- Treatment selection
- Population enrichment
- Dose selection
- Randomisation changes

Decision rules should be specified **before** unblinded interim data become available.



Validity and Reliability: The Core Regulatory Question

Every adaptive design should answer four questions

1. Will bias be introduced?
2. Is trial integrity preserved?
3. Is Type I error appropriately controlled?
4. Will the final results remain clinically interpretable?

The objective is not simply to complete the trial.
The objective is to produce evidence that regulators can trust.



Simulation: From Statistical Exercise to Regulatory Evidence

Draft ICH E20 elevates simulation to a key component of trial justification

Simulation should demonstrate:

- Control of Type I error
- Adequate statistical power
- Robust operating characteristics
- Performance under multiple plausible scenarios

Simulation is no longer supporting evidence—it is part of the regulatory evidence package.



Trial Integrity: The Human Element

Maintaining trial integrity requires more than sound statistics. Critical governance elements include:

- Independent Data Monitoring Committee (IDMC)
- Controlled access to interim results
- Clear decision-making responsibilities
- Operational firewalls
- Documented governance procedures



Adaptive trials succeed through governance—not statistics alone.



The Guideline is Clear on Principles…

Less Clear on Implementation

Draft ICH E20 answers:

✓ What should be protected
✓ Why adaptations require planning
✓ Why simulations matter

Less clear is:

- How much simulation is enough?
- Which adaptive methods are "well established"?
- How much flexibility remains after trial initiation?
- What level of documentation is expected?



Bayesian Methods:

Innovation or Source of Regulatory Uncertainty?

Draft ICH E20 discusses:

- Bayesian adaptive designs
- Borrowing external information
- Prior distributions
- Decision rules

Industry comments highlight several unresolved questions:

- Bayesian ≠ External borrowing
- Frequentist borrowing also exists
- Hybrid approaches are increasingly used
- Greater clarity is needed



Platform Trials, Basket Trials and Master Protocols

Adaptive designs continue to evolve beyond traditional models.
Increasingly used in:

Oncology | Rare diseases | Precision medicine | Cell & gene therapies

Yet Draft ICH E20 provides only limited discussion of:

- Platform trials
- Basket trials
- Umbrella trials
- Adding new treatment arms
- Non-concurrent controls



Where Draft ICH E20 Leaves Sponsors Without Clear Answers

Examples of topics suitable for early Scientific Advice

- Simulation strategy
- Bayesian methodology
- External data borrowing
- Complex adaptive decision rules
- Platform and master protocols
- Interim governance
- Documentation expectations



The guideline establishes principles.
Scientific Advice establishes confidence.



Scientific Advice: From Regulatory Milestone to Development Strategy

Scientific Advice should not validate an adaptive design. It should reduce uncertainty around its implementation.

Scientific Advice is particularly valuable when:

- Novel adaptive features are proposed
- Multiple adaptation rules interact
- Bayesian methodologies are used
- External information is incorporated
- Regulatory expectations remain uncertain





Questions Worth Bringing to Scientific Advice

Methodology

- Is the proposed adaptive strategy appropriate?
- Are the adaptation rules sufficiently justified?
- Is the simulation strategy adequate?

Operations

- Is the governance model acceptable?
- Are interim procedures sufficiently robust?

Regulatory Documentation

- Is additional justification expected?
- Are the proposed documentation plans sufficient?



Five Strategic Principles for Protocol Authors



1. Design adaptations prospectively—not retrospectively.
2. Build governance before writing statistics.
3. Treat simulation as regulatory evidence.
4. Plan documentation from Day 1.
5. Discuss uncertainty before submission—not during review.



Looking Beyond Draft ICH E20

Future evolution is likely to include:

- Greater acceptance of master protocols
- Increased use of Bayesian methodologies
- Wider use of external and real-world data
- AI-assisted trial monitoring
- Greater international harmonisation



Draft ICH E20 is the beginning—not the end—of adaptive regulation.



Key Take-Home Messages



- Adaptive designs are becoming mainstream.
- Remaining uncertainties are implementation challenges.
- Governance is as important as statistics.
- Early regulator interaction reduces development risk.
- Flexibility requires greater planning—not less.



Closing thoughts

The success of an adaptive clinical trial is determined long before the first interim analysis. It is determined during protocol development.



