ICH E6 (R3) ANNEX 2 RELEASED:
KEY UPDATES FOR DECENTRALIZED AND MODERN CLINICAL TRIALS

Finalized on June 3, 2026

Annex 2 complements E6 (R3) by extending Good Clinical Practice (GCP) principles to decentralized trials, pragmatic design approaches, and the use of real-world data—reflecting how clinical research is evolving.

WHERE ANNEX 2 FITS WITHIN E6 (R3)

E6 (R3) is structured into three components:

1. **GCP PRINCIPLES**
   Foundational ethical and scientific standards
2. **ANNEX 1**
   Core guidance for traditional interventional trials
3. **ANNEX 2**
   Additional considerations for modern, non-traditional trial designs

Annex 2 is not a standalone framework. It extends existing GCP principles to ensure they remain applicable as clinical trials evolve beyond traditional, site-based models.

ANNEX 1 vs. ANNEX 2: KEY DIFFERENCES

	ANNEX 1 (Core Guidance)	VS.	ANNEX 2 (Additional Considerations)
FOCUS	Traditional interventional trials conducted at investigator sites		Modern, non-traditional approaches (decentralized, pragmatic, RWD)
SCOPE	Site-based activities and established processes		Activities conducted beyond sites; use of technology and real-world data
DESIGN	Conventional protocol design and execution		Simplified, pragmatic, and technology-enabled designs
DATA SOURCES	Study data collected per protocol		Protocol data + RWD from EHRs, registries, claims, devices, and more
OVERSIGHT	Risk-based monitoring within site-based context		Proportionate oversight across distributed and hybrid models

KEY COMPONENTS OF ANNEX 2

Annex 2 focuses on how GCP should be applied in more flexible and technology-enabled trial environments.

DECENTRALIZED TRIAL ELEMENTS

GCP guidance now formally addresses trial activities conducted outside traditional investigator sites. Includes remote interactions, home-based care, and digital tools for data collection—supporting decentralized and hybrid trial models to improve access and engagement.

PRAGMATIC CLINICAL TRIAL DESIGN

Supports trial designs that align more closely with routine clinical practice through broader eligibility criteria, streamlined data collection, and integration into real-world care settings—generating results that better reflect actual patient populations and treatment environments.

USE OF REAL-WORLD DATA (RWD)

Introduces considerations for incorporating data from EHRs, registries, claims databases and more. Sponsors must ensure RWD used in trials is:

- Fit for purpose
- Reliable and traceable
- Appropriately governed, especially when managed by third parties

RISK-BASED AND PROPORTIONATE OVERSIGHT

Reinforces a flexible, risk-based approach to trial oversight. The intensity and nature of GCP processes should be proportionate to the trial's risks, complexity, and the importance of the data to protect participants and ensure data integrity.

WHAT CHANGED FROM THE 2024 DRAFT?

Based on public feedback, key refinements include:

- Stronger emphasis on participant protection in decentralized and remote settings
- More clarity on data privacy, security, and governance of digital tools and platforms
- Clearer expectations for the quality, traceability, and fitness for purpose of real-world data
- Greater alignment with Annex 1 responsibilities for IRB/IEC, investigators, and sponsors
- Additional flexibility in applying risk-based and proportionate oversight in practice

REGULATORY CONSIDERATIONS

- Annex 2 is expected to be adopted by regulatory authorities throughout ICH regions.
- Sponsors should assess how decentralized, pragmatic, and RWD-enabled elements may impact trial design, operations, and oversight.
- Documentation of risk assessments, data governance, and technology controls will be critical.
- Early engagement with regulatory authorities is encouraged for innovative trial designs and use of real-world data.

WHY ANNEX 2 MATTERS

It ensures GCP remains fit for purpose in a rapidly evolving research landscape—supporting innovation while maintaining participant protection and data integrity.

FINAL TAKEAWAY

Annex 2 completes the modernization of E6 (R3), empowering the clinical research community to deliver more accessible, patient-centered, and real-world relevant evidence.