Regulatory Signal Brief™

The New Standard in Clinical Development: ICH E6(R3), Quality by Design (QbD), and Its Applied Domains (DCT, RWD, and AI)

Probio Corporation

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Purpose

The purpose of this report, *Regulatory Signal Brief*™, is not merely to understand global regulatory trends, but to enable action based on them.

Centered on ICH E6(R3), the implementation of the Quality by Design (QbD) principles defined in ICH E8(R1) is progressing as the standard framework for clinical quality management in pharmaceuticals, vaccines, and biological products.
(*Note: Medical devices and SaMD are outside the scope of E6(R3).*)

The challenge now facing organizations is not only *"understanding regulations,"* but *"aligning and operationalizing their internal processes accordingly."*

This report is designed as a shared language to accelerate execution decisions and organizational alignment.

Analytical Methodology

This report is generated using a **regulatory-specific AI analysis process** applied to primary-source documents (ICH, FDA, EMA, etc.).

Unlike general-purpose conversational AI models, the methodology is engineered to:

- Parse regulatory logic structures, hierarchical requirements, and dependencies
- Identify cross-document consistencies across guidelines, annexes, and Q&As
- Extract **granular verification points** often overlooked in manual reviews

The output serves as a **"working zero-draft"** for operational planning and risk assessment. Final determinations must be made by your organization's subject matter experts.

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Scope / Framework Positioning

ICH E6(R3) serves as the upper-level framework institutionalizing the concept of Quality by Design (QbD) in clinical development.
Annex 1 and Annex 2, as subordinate components, specify the implementation domains of QbD.

Hierarchy	Content	Target Domain
E6(R3) Core	Defines QbD principles, Critical-to-Quality (CtQ) factors, Quality Tolerance Limits (QTLs), risk-proportionate design, and baseline QMS standards	Interventional clinical trials for pharmaceuticals, vaccines, and biologics
Annex 1	Details QbD implementation methods for traditional interventional trials	Pharmaceuticals, vaccines, and biologics
Annex 2	Presents additional GCP considerations for decentralized (DCT), pragmatic, and real-world data (RWD) elements	Clinical trials incorporating decentralized, pragmatic, or RWD components

DCT and RWD correspond to the additional GCP considerations presented in Annex 2 – the practical implementation layer of QbD.
Annex 2 itself does not define AI-specific requirements.
When AI/ML systems are used in clinical trials, however, they must be governed under the E6(R3) core principles, particularly *Section 4: Data Governance*, and the *EMA Reflection Paper on the Use of AI in Medicinal Product Lifecycle*, including requirements such as pre-specification, model freezing, auditability, and performance monitoring.
If AI constitutes a medical device (AI-enabled software functions), it must comply with device-specific regulations such as the FDA's PCCP framework.

Accordingly, the implementation sequence is structured as follows:
Define the baseline for quality design under E6(R3) →
Reinforce operational detail in Annex 1 →
Add DCT/RWD-specific controls in Annex 2
(*AI lies outside Annex 2's scope.*)

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Executive Summary

On 6 January 2025, ICH E6(R3) reached Step 4 adoption, recommending regional regulatory authorities to proceed with local adoption.
Elements such as CtQ definition, QTL establishment, centralized monitoring, and data governance will be implemented sequentially in each region; there is no single effective date.

The QbD principle represents a paradigm shift – from audit-based assurance to proactive integration of quality at the design stage.

E6(R3) and Annex 1 formalize the structural components of quality, including CtQ identification, Quality Tolerance Limits (QTLs), centralized monitoring, and integration of data governance.
Annex 2 introduces additional GCP considerations for emerging elements such as DCT and RWD (e.g., remote visits, electronic informed consent, direct-to-patient IP shipment, remote data capture).
(AI model retraining and updating are outside Annex 2's scope.)

Revising SOPs alone is insufficient.
Cross-functional updates across protocols / DMPs / SAPs, QMS, and vendor agreements are urgently required.
Organizations capable of integrated design and execution of QbD, DCT, RWD, and AI will gain advantages in data reliability, inspection readiness, and development efficiency.

In the EU, E6(R3) (Principles + Annex 1) becomes effective on 23 July 2025.
Because timelines differ by region, implementation and transition planning must be region-specific.

Top 3 Strategic Actions (Management / Enterprise Level)

1. Executive approval of a QbD gap-closure plan, including internal standardization of CtQ, QTL, monitoring, and data-governance frameworks.
2. Finalization of operational criteria for the DCT "core three" set: electronic consent, direct-to-patient IP shipment, and audit trail.
3. Issuance of AI-monitoring SOPs (linked to PCCP) and RWD eligibility checklists. Cross-functional updates of design documents, QMS, and vendor contracts are essential to achieve unified operations of QbD, DCT, RWD, and AI, thereby forming a key source of competitive advantage.

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Overview of the Three Converging Trends

E6(R3): Reconstructing the Clinical Development OS through QbD Thinking (see Signal Card 1)

- Quality = Fit-for-Purpose; identify CtQs → apply risk-proportionate design → monitor boundaries via QTLs
- Standardization of sponsor QMS and centralized monitoring
- Data governance: protection of blinding, full data-lifecycle control, audit trails, computerized-system validation (CSV) using a risk-based approach

DCT: Operational Domain Implementing QbD (see Signal Card 2)

- Remote visits, local HCPs, DHT/BYOD, eConsent, direct-to-patient IP shipment, home-based elements
- eSource / audit trail compliance with 21 CFR Part 11 and alignment with EU DCT recommendations (ACT EU)
- Vendor oversight (home visits, logistics, cloud, IRT, DHT) and visibility of data flows

RWD and AI: Data-Driven Domains Extending QbD Implementation (Annex 2 for RWD; AI outside scope) (see Signal Card 3)

- Pre-specification of RWD reliability, relevance, traceability, and linkage processes
- AI used in clinical operations must comply with E6(R3) §4 (data governance): maintaining blinding, ensuring data-lifecycle finalization before analysis, and validating computerized systems for security and integrity
- If AI qualifies as a medical device, incorporate pre-defined learning plans under PCCP with operational monitoring (KPIs, drift, rollback)
- Align with the EMA AI Reflection Paper for design, data curation, and transparency. In high-impact settings, use pre-specified pipelines and frozen models (no incremental learning in pivotal trials) with ongoing performance monitoring.

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Signal Card 1 | Parent Theme: Overview of ICH E6(R3) and the Quality by Design (QbD) Principles

1. Card Summary

- ICH E6(R3) was adopted at Step 4 on 6 January 2025 (final version). It includes the Principles section, Annex 1 (detailed application to traditional interventional trials), and clarified data-governance requirements, establishing QbD (CtQ identification, risk-proportionate approach, QMS integration) as the standard for clinical development.
- Annex 2 (additional considerations for emerging models such as DCT and RWD) reached Step 2 (public consultation) on 6 November 2024. The timing of final adoption (Step 4) remains undetermined; implementation will depend on each regional authority (E6 core was already adopted at Step 4 on 2025-01-06).

2. What changed? (Latest Developments / Sections)

E6(R3) Step 4 Adoption (Final Version)

- Adoption date and Step: 6 January 2025, Step 4 (recommendation for regulatory adoption). The document header includes its adoption history [Document History section].
- Structure: Principles (Section II), Annex 1 (IRB/IEC, Investigator, Sponsor, Quality Management, Monitoring, etc.), Data Governance (Section 4), and Appendices A–C [Sections II, III, 4].
- Implementation: Step 4 is an ICH-level recommendation; regional implementation is required. There is no single effective date [Introduction: “At Step 4… recommended for adoption”].

Positioning of Annex 1 and Annex 2

- Annex 1 provides application-level details (IRB/IEC, Investigator, Sponsor). Data Governance (Section 4: Data Governance – Investigator and Sponsor) is newly established as a separate chapter in the core document [Sections III (Annex 1) and 4].
- Annex 2 covers additional considerations for emerging models. It was signed at Step 2 on 6 November 2024; public-comment review and revision are ongoing, and the Step 3/4 timeline remains open [Annex 2 Step 2 Presentation p.3; Preface of Annex 2 Step 2 Draft].

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Introduction of QbD (Embedding Quality at the Design Stage)

- Identify Critical-to-Quality (CtQ) factors proactively and manage them in a risk-proportionate manner [Principles 6.2, 7, 3.10.1].
- Integrate QbD into the Quality Management System (QMS) and define Quality Tolerance Limits (QTLs) as thresholds for deviation and evaluation [3.10, 3.10.1.3].
- Adopt risk-based monitoring (RBM) combining centralized, remote, and on-site approaches with a mandatory monitoring plan [3.11.4, 3.11.4.3].
- Formalize data governance (data lifecycle, audit trail, computerized-system validation using a risk-based approach) [4.2, 4.3].

Conceptual Shift from Previous Practice

- Move from “post-hoc audit and QC focus” to “forward-looking design centered on CtQs to eliminate unnecessary complexity” [Principles 6, 7; E8(R1) ‘Considerations in Identifying Critical to Quality Factors’].

Transparency and Reliability of Results

- Strengthen trial registration and result-disclosure transparency, record retention and access, and data integrity [Principles 9.4–9.6, 3.16, 2.12, Appendix C].

3. So what? (Role-Specific Implications: SOP, QMS, RBM, Data Governance, Vendors)

	Key Operational Implications
Regulatory Affairs (RA)	• Standardize E6(R3) compliance review for protocols, IB, informed-consent documents, and safety reports (Appendix B, Appendix A, 2.8, 3.13). • Establish criteria for reporting quality issues such as QTL deviations and for notifying authorities or IRBs (3.10.1.3, 3.12, 3.13.3, 3.17). • Define procedures for trial registration, result disclosure, and lay summaries (Principles 9.6, 3.17.2(c)). • Clarify responsibilities and update contract clauses for outsourcing and co-development (3.6, 10.2); define submission and communication flows with authorities and IRB/IEC (3.8, 1.1).
Clinical Operations (ClinOps)	• Specify CtQs, risk controls, monitoring strategy, blinding protection, and data handling in protocols (Appendix B B.12, B.14, 3.11.4, 4.1–4.2). • Evaluate and oversee vendor/sub-contractor qualification (3.6, 3.9.5). Implement risk-based central/remote/on-site monitoring (3.11.4.1–3.11.4.6).

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	Key Operational Implications
	• Establish procedures for IMP supply, decentralized distribution, and home administration (2.10, 3.15.3). • Maintain blinding and define emergency unblinding procedures (2.11, 4.1).
Quality Assurance (QA)	• Renew the QMS to integrate QbD, risk management, oversight, audit, and CAPA consistency (3.10, 3.11.2, 3.12). • Define QTL setting, monitoring, root-cause analysis, CAPA, and quality-issue reporting (3.10.1.3, 3.10.1.6, 3.12.2). • Apply risk-based approaches to monitoring and audit plans (3.11.4.3, 3.11.2). • Standardize data-governance and computerized-system validation criteria (audit trail, access control, backup/DR, change management) (4.2, 4.3). • Establish escalation and authority-notification criteria for major non-compliance (3.9.6, 3.12.2–3).
Data Science	• Define data-lifecycle procedures (acquisition, metadata/audit trail, correction, transfer, finalization, archiving) (4.2.1–4.2.8). • Design central monitoring logic and KPIs (3.11.4.2, 3.11.4.5). • Plan statistical analysis, programming QC, traceability, and data lock (3.16.2, 4.2.6, 3.16.1(p)–(r)). • Control data access, sharing, and unblinding according to blinding requirements (4.1, 3.16.1(f)–(g)). • Ensure timely provision of external data to investigators for review-driven operations (2.12.3, 3.16.1(k)).

4. Operational Action Checklist (for Discussion at Working Level)

- Gap analysis between E6(R3) principles and current SOP/QMS for QbD, risk management, monitoring, and data governance (Principles 6–7, 3.10, 3.11, 4).
- Develop CtQ mapping by trial (define objectives, endpoints, participant risks, data criticality, and risk controls) (Principles 6.2, 7.1).
- Draft guideline for Quality Tolerance Limits (QTL): thresholds, detection, escalation, correction, authority/IRB communication (3.10.1.3, 3.10.1.6).
- Revise monitoring-plan template to combine central, remote, and on-site approaches and cross-vendor oversight (3.11.4, 3.11.4.3).
- Require protocol templates to include quality-design sections (CtQ, risk, QC/QA, data handling) (Appendix B B.12, B.14; Principles 8).

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- Update vendor qualification and responsibility definitions (including SLA/KPI and sub-contractor oversight) (3.6.6–3.6.10, 3.9.5).
- Define minimum data-governance standards (metadata/audit trail, computerized-system validation, access control, backup/DR) (4.2, 4.3, 3.16.1(x)).
- Reconfirm standard procedures for registration, result disclosure, and lay summaries (Principles 9.6).

5. Decision Prompts (Who Does What)

	Action	Relevant Clauses
Head of QA	Approve E6(R3) gap-analysis review and define CAPA priorities	3.10, 3.12
Head of ClinOps	Revise monitoring-plan template to reflect criteria for central and remote monitoring	3.11.4.3
Head of Data Management / Data Science	Issue provisional procedures for data-governance standards and risk-based computerized-system validation	4.2, 4.3
Head of RA	Establish a monitoring framework for Annex 2 finalization and regional implementation timelines	Introduction and Annex 2 Step 2 documents

6. FAQ

Q1. What is the relationship between QbD and RBM (risk-based monitoring)?

A. QbD identifies CtQs and manages risks proportionately (Principles 6.2, 7). RBM is the primary operational tool for that risk management (central, remote, on-site) and is implemented through the monitoring plan (3.11.4, 3.11.4.3).

Q2. How are CtQs identified?

A. For each trial, CtQs are identified prospectively based on objectives, scientific rationale, endpoints, participant safety, and data criticality (Principles 6.2, 7.1). The protocol must describe quality design and risk controls (Appendix B B.12).

Q3. When does E6(R3) take effect (transition measures)?

A. ICH adopted E6(R3) at Step 4 on 6 January 2025 (recommendation for regional adoption). Effective dates depend on each authority's implementation [Introduction: "At Step 4… recommended for adoption"]. Monitor regional guidance for official adoption and implementation dates.

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7. Signal Priority Index (SPI)

- Reach: 5 (global ICH scope; affects all interventional trials and QMS/data/oversight domains)
- Magnitude: 5 (full renewal of design philosophy, QMS, and data governance)
- Urgency: 4 (Step 4 adopted; pre-implementation preparation required)
- Certainty: 5 (final guideline published)
- Total: (5 + 5 + 4 + 5) × 5 = 95

  (Interpretation scale: 95–90 = highest priority for immediate discussion; 85–80 = next update cycle; 70–60 = monitor and collect information; 59 or below = monitor only.)

8. Sources and References

- **ICH E6(R3) Guideline for Good Clinical Practice** (Final version, Step 4, adopted on 6 January 2025)
  - Contains adoption history (Document History), guideline structure, and key sections:
  - QbD and CtQ (Principles 6, 6.2, 7);
  - Sponsor QMS, risk management, and QTL (3.10, 3.10.1.3);
  - Monitoring (3.11.4, 3.11.4.3);
  - Data governance (Sections 4.2, 4.3);
  - Transparency (Principles 9.6);
  - Protocol quality design (Appendix B B.12).
  - https://database.ich.org/sites/default/files/ICH_E6(R3)_Step4_FinalGuideline_2025_0106.pdf

- **ICH "Good Clinical Practice – ICH E6(R3) Step 4 document – to be implemented" (Step 4 Overview Presentation)**
  - Official presentation explaining the Step 4 adoption (Principles + Annex 1) in January 2025.
  - https://admin.ich.org/sites/default/files/inline-files/ICH_E6(R3)_Step%204_Presentation_2025_0123.pdf

- **ICH E6(R3) Annex 2 (Step 2) Presentation (6 November 2024)**
  - Describes Step 2 signature, current review process, and projected Step 4 timeline during 2025 (p. 3).
  - https://database.ich.org/sites/default/files/ICH_E6(R3)_Annex%202_Step%202_Presentation_2024_1122_0.pdf

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- **ICH E8(R1) General Considerations for Clinical Studies** (Step 4: 6 October 2021)
    - Provides the foundational concepts for QbD and CtQ, especially the section "Considerations in Identifying Critical to Quality Factors."
    - https://database.ich.org/sites/default/files/E8-R1_Guideline_Step4_2021_1006.pdf

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Signal Card 2 | Sub-Theme: Applying QbD Principles (1): Decentralized Clinical Trials (DCT)

1. Card Summary

- ICH E6(R3) Annex 2 (Step 2, 2024-11-06) presents “additional GCP considerations” for emerging elements including DCT (decentralized elements). The Step 2 draft under public consultation systematizes points to consider across design, informed consent, data, investigational product (IP) management, vendor oversight, and safety.
- The US FDA published its final guidance “Conducting Clinical Trials With Decentralized Elements” (Sep 2024), clarifying implementation requirements for remote visits, local HCPs, DHTs, eConsent, direct-to-patient IP shipment, and Part 11/audit trails. In the EU, ACT EU/CTCG released recommendation materials on DCT. In Japan, MHLW issued a notification on eConsent (2023-03-30) specifying requirements for remote explanations and electronic signatures.

2. What changed? (Latest Developments / Sections)

- ICH E6(R3) Annex 2 (Step 2: Additional Considerations)
  - Positioning: additional GCP considerations for applying DCT/pragmatic elements/RWD (Introduction and Definitions) [Annex 2: Introduction, p.1–2].
  - Key points across trial design, consent, data, IP, safety, and sponsor oversight [Annex 2 §2.2 (remote consent), §2.3 (IP management and direct shipment), §2.4 (investigator oversight), §3.2 (protocol), §3.5.1 (RWD reliability and relevance), §3.5.2 (remote data collection), §3.6 (IP management: stability and protection of blinding), §3.7 (privacy/cybersecurity), §3.8 (sponsor oversight including vendors), §3.9 (safety signal acquisition and provision across multiple data sources)].
  - Source: ICH E6(R3) Annex 2 Step 2 Draft (2024-11-06) https://database.ich.org/sites/default/files/ICH_E6(R3)_Annex%202_Step2_DraftGuideline_2024_1024_0.pdf

- FDA Final Guidance (Sep 2024)
  - Remote visits (telehealth/home/local HCP) [§III.B]; considerations for DHT/BYOD (sponsor-provided devices recommended) [§III.C, second paragraph]; roles and responsibilities (positioning of local HCPs; whether to list on Form 1572) [§III.D.2]; eConsent/IRB [§III.F]; IP management, direct shipment, packaging/shipping [§III.G, §III.H]; safety monitoring [§III.I]; electronic systems/Part 11 and audit trails [§III.J].
  - Source: FDA Final Guidance (Sep 2024) https://www.fda.gov/media/167696/download; Guidance page (docket, etc.) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/conducting-clinical-trials-decentralized-elements

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- EU (ACT EU/CTCG)
  - Publication of EU recommendations on DCT (joint ACT EU) and overview of handling at the Member State level [EMA News 2022-12-19]; explanatory presentation (DCT elements and recommendations) [EMA Presentation].
  - Sources: EMA News "Facilitating Decentralised Clinical Trials in the EU" https://www.ema.europa.eu/en/news/facilitating-decentralised-clinical-trials-eu;
  - EMA Presentation https://www.ema.europa.eu/en/documents/presentation/presentation-eu-recommendations-decentralised-elements-clinical-trials-m-al-ccmo_en.pdf
  - eSource/audit trail (EU GCP Inspectors Working Group) [Reflection paper: eSource expectations] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/reflection-paper-expectations-electronic-source-data-data-transcribed-electronic-data-collection_en.pdf

- Japan (MHLW/PMDA)
  - Points to consider for remote acquisition of consent, electronic signatures, robust identity verification, document issuance/retention, cloud use, training, etc. [Notification: 4. Points to Consider; (1) identity verification; (4) electronic signature; (5) issuance; (6) document handling; (7) systems/training].
  - Source: MHLW "Points to Consider for Explanations and Consent Using Electronic Methods in Clinical Trials and Post-marketing Clinical Studies" (2023-03-30) https://www.mhlw.go.jp/web/t_doc?dataId=00tc7518&dataType=1&pageNo=1

- Cross-cutting issues (eSource/ePRO/eConsent/direct-to-patient IP/audit trails)
  - eSource/ePRO: data provenance; data flows and maintenance of source records; audit trails; Part 11 compliance (FDA §III.J); EU eSource expectations (terminology/standards/timestamps/traceability) [EMA eSource Reflection Paper].
  - eConsent: robust identity verification and electronic signatures; bidirectional remote explanations; issuance/retention; handling of video, etc. [MHLW 4.(1)–(6)]; IRB review and central IRB recommended (FDA §III.F).
  - Direct-to-patient IP: stability/temperature control; receipt confirmation; protection of blinding; retrieval/disposal of unused IP [FDA §III.H; ICH Annex 2 §2.3.1 on patient-direct shipment: privacy, recipient verification, storage/retrieval, protection of blinding; §3.6.1–3.6.3 (sponsor considerations for IP management)].
  - Audit-trail review: access control in electronic systems; management of data originators; use of centralized monitoring (FDA §III.J, §III.D on sponsor oversight/monitoring).

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3. So What? (Role-Specific Implications: Adoption Decisions and Risks)

Role	Key Operational Implications
Regulatory Affairs (RA)	• Bridge and align regional differences. Reflect ICH Annex 2 additional considerations, FDA final DCT guidance, EU recommendations, and domestic notifications in the protocol/ICF/IB. • Clarify legality and submission strategy for local HCP use, remote elements, and direct-to-patient IP. • Clarify eConsent IRB review, electronic signature, and identity-verification requirements. • Translate electronic-system requirements (audit trails/Part 11/EU eSource) into submission documentation.
Clinical Operations (ClinOps)	• Standardize operational criteria and decision rules for remote visits (telehealth/home/local HCP). • Define DHT/BYOD policy, provision of alternative devices, and training/support. • Standardize eConsent operations (two-way remote explanations, issuance/retention, identity verification). • Implement SOPs for direct-to-patient IP (temperature control, receipt confirmation, retrieval, protection of blinding) and clarify safety information flows and escalation across multiple data sources.
Quality Assurance (QA)	• Confirm fitness of electronic systems/cloud (Part 11/audit trails/access control/change control) and design risk-based audit plans. • Establish procedures for audit-trail review aligned with EU eSource expectations and computerized-system guidance. • Ensure qualification/oversight and evidence chain for DCT vendors (home visits/logistics/IRT/DHT/cloud), including sub-delegation chains. • Update centralized-monitoring indicators.
Data Science	• In the Data Management Plan (DMP), specify data provenance/flows/providers (local HCPs/labs/vendors), and metadata/audit-trail requirements. • Define quality criteria for DHT/remote collection (accuracy/completeness/timestamp/synchronization) and strategies for missing data. • Embed RWD reliability/relevance assessment. • Implement role-based access, alerting, and linkage/mapping strategies with protection of blinding.

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4. Operational Action Checklist (Working Level)

- Revise DCT design SOPs/work instructions (remote visits, local HCP, telehealth, home sampling) (FDA §III.B, §III.D.2; Annex 2 §2.4, §3.2).
- Standardize eConsent operations: robust identity verification/electronic signatures; bidirectional remote explanations; issuance/retention; IRB review (MHLW 4.(1)–(6), 3.; FDA §III.F).
- Validate ePRO/DHT; formalize BYOD policy and rules for sponsor-provided devices (FDA §III.C; Annex 2 §3.5.2).
- Update SOPs for direct-to-patient IP: stability/temperature control/receipt tracking/retrieval; protection of blinding; access/authorization controls (FDA §III.H; Annex 2 §2.3.1, §3.6).
- Amend the DMP to list data provenance/flows/providers (local HCPs/labs/vendors) and audit-trail requirements (FDA §III.D (data-management items listed), §III.J).
- Establish an audit-trail review plan (Part 11/EU eSource compliance) and update centralized-monitoring indicators (FDA §III.J; EMA eSource Reflection Paper).
- Reflect vendor oversight (home visits/logistics/cloud/IRT/DHT) roles, KPIs, and sub-delegation controls in contracts/SLAs (Annex 2 §3.8; FDA §III.D on sponsor responsibilities).
- In safety-monitoring plans, specify signal acquisition/provision/escalation from multiple data sources (DHT/remote/local HCP/labs) (Annex 2 §3.9.1–3.9.2; FDA §III.I).

5. Decision Prompts (Who Does What)

Role	Action	Relevant Clauses
Head of ClinOps	Approve SOP revisions for operational criteria for remote visits, local HCPs, and telehealth	FDA §III.B, §III.D.2
Head of QA	Approve Part 11 compliance of electronic systems/cloud and audit-trail review plan	FDA §III.J; EMA eSource RP
Head of Data Management / Data Science	Issue DMP revision (data provenance/flows/providers; linkage strategy)	FDA §III.D, §III.J; Annex 2 §3.5.1–3.5.2
Head of RA	Present a traceability matrix showing differences across Annex 2 (Step 2), FDA final, and EU recommendations	Annex 2; FDA Final; EMA News/Presentation
Head of Supply Chain	Launch operational pilots for direct-to-patient IP (temperature control/blinding/retrieval)	FDA §III.H; Annex 2 §2.3.1, §3.6

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6. FAQ

Q1. How far must audit trails go in the cloud?

A. Electronic systems are subject to 21 CFR Part 11. Ensure data reliability, security, privacy, confidentiality, audit trails, a register of data originators, and access controls (FDA §III.J). The EU eSource Reflection Paper also sets expectations on terminology, standards, and traceability.

Q2. How can we maintain blinding while operating remotely?

A. For direct-to-patient shipment/home use, require procedural safeguards for blinding at each stage (shipping/receipt/storage/use/retrieval) (Annex 2 §2.3.1(d), §3.6.1–3.6.3). FDA §III.H also specifies packaging, shipping, tracking, and handling of unused IP.

Q3. What tasks can be delegated to local HCPs? Must they be listed on Form 1572?

A. Routine clinical activities (vitals/basic examinations) that do not require protocol-specific knowledge may be performed by local HCPs and, in drug trials, do not necessarily make them sub-investigators listed on Form 1572 (FDA §III.B, §III.D.2). Activities requiring protocol knowledge and directly contributing to trial data must be appropriately listed and supervised as trial personnel (FDA §III.D.2).

7. Signal Priority Index (SPI)

- Reach: 5 (broad applicability across ICH/EU/US/JP; covers design, consent, IP, data/IT, and oversight)
- Magnitude: 5 (cross-functional renewal across operations, systems, supply, and audit)
- Urgency: 4 (FDA finalized; Annex 2 in progress; early SOP/system preparation required)
- Certainty: 4 (FDA/JP finalized/notice; ICH Annex 2 at Step 2; EU recommendations established)
- Total: (5 + 5 + 4 + 4) × 5 = 90
  (Interpretation: 95–90 = top priority for immediate discussion; 85–80 = next update cycle; 70–60 = information gathering / follow-up in next issue; 59 or below = monitor only.)

8. Sources and References

- ICH E6(R3) Annex 2 Draft (Step 2, 2024-11-06)
  - Definitions/application of DCT/RWD (Introduction); remote consent (§2.2); IP management/direct-to-patient shipment (§2.3, §3.6); investigator oversight (§2.4); protocol (§3.2); RWD reliability/relevance (§3.5.1); remote data collection (§3.5.2); privacy/security (§3.7); sponsor oversight (§3.8); safety signal acquisition/provision across multiple sources (§3.9).
  - https://database.ich.org/sites/default/files/ICH_E6(R3)_Annex%202_Step2_DraftGuideline_2024_1024_0.pdf

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- FDA Final Guidance: Conducting Clinical Trials With Decentralized Elements (Final, Sep 2024)
  - Remote visits (§III.B); DHT/BYOD (§III.C); roles/Form 1572/local HCPs (§III.D.2); IRB/eConsent (§III.F); IP (§III.G–H); safety (§III.I); electronic systems/Part 11/audit trails (§III.J).
  - PDF: https://www.fda.gov/media/167696/download
  - Guidance page (docket, etc.): https://www.fda.gov/regulatory-information/search-fda-guidance-documents/conducting-clinical-trials-decentralized-elements

- EMA (EU DCT recommendations and information)
  - News: Facilitating Decentralised Clinical Trials in the EU (ACT EU recommendations) https://www.ema.europa.eu/en/news/facilitating-decentralised-clinical-trials-eu
  - Presentation: EU Recommendations on Decentralised Elements in Clinical Trials (CTCG/CCMO) https://www.ema.europa.eu/en/documents/presentation/presentation-eu-recommendations-decentralised-elements-clinical-trials-m-al-ccmo_en.pdf
  - Guideline on computerised systems and electronic data in clinical trials (latest EU GCP Inspectors WG guideline; Reflection Paper superseded) https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-computerised-systems-and-electronic-data-clinical-trials_en.pdf

- MHLW (Japan)
  - "Points to Consider for Explanations and Consent Using Electronic Methods in Clinical Trials and Post-marketing Clinical Studies" (Notification, 2023-03-30), Chapters 3–4 (identity verification/authentication/issuance/retention/cloud/training).
  - https://www.mhlw.go.jp/web/t_doc?dataId=00tc7518&dataType=1&pageNo=1

Notes

- Article numbers from the E6(R2) version (e.g., §5.2.3) have been reorganized under E6(R3)/Annex 1/Annex 2. For IP management, refer to Annex 1 §3.15.3, Annex 2 §2.3 and §3.6, and FDA §III.H.

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Signal Card 3 | Sub-Theme: Applying QbD Principles (2): Designing Reliability for Real-World Data (RWD) and Framework for AI Oversight (Annex 2 + Related Guidelines)

Note: AI is not directly within the scope of Annex 2. When AI is used in clinical trials, it must be governed under the principles of E6(R3) Section 4 (Data Governance) and the EMA Reflection Paper on AI, with pre-specification and monitoring consistent with QbD. If AI qualifies as a medical device, the FDA PCCP applies.

1. Card Summary

- ICH E6(R3) Annex 2 (Step 2, 2024-11-06) systematizes, in the QbD context, assessments of RWD reliability and relevance, data linkage, remote data collection, and sponsor oversight (Annex 2 §3.5.1, §3.5.2, §3.8). RWD may be used for purposes such as external controls (Annex 2 I. INTRODUCTION).
- The FDA has issued the final PCCP guidance for AI-Enabled Device Software Functions (2024-12) and a draft on AI-Enabled lifecycle management (covering TPLC). The EMA's adopted Reflection Paper clarifies principles for AI design, data curation, and "frozen model" approaches.
- RWD is treated as an additional consideration in Annex 2; AI lies outside Annex 2's scope but, as a quality design and monitoring domain aligned with QbD, should be cross-referenced against adjacent frameworks (FDA PCCP / EMA Reflection Paper).

2. What Changed? (Latest Developments)

- **ICH E6(R3) Annex 2 (Step 2, 2024-11-06)**
    - Position: Additional GCP considerations for DCT/pragmatic elements/RWD (I. INTRODUCTION), explicitly identifying RWD uses (e.g., endpoint ascertainment, external controls).
    - RWD quality: Fit-for-Purpose is determined by reliability (accuracy, completeness, traceability) and relevance (availability of exposure, outcomes, covariates) (§3.5.1(b)). Consider variable formats, non-standard timing, missingness, EHR/claims data quality, de-identification, and registry validation status (§3.5.1(a)(i)–(vi)).
    - Data linkage: Requires accurate matching, privacy protection, and pre-specification in the protocol/SAP (§3.5.1(d)).
    - Remote collection: Security/cybersecurity and privacy for DHT and EHR extraction (Annex 2 §3.5.2(a)); see also E6(R3) §4.3.3 (Security). Sponsor oversight and quality management must be CtQ/risk-proportionate (§3.8).

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- Safety: Provide multi-source safety information to investigators in a timely manner to support decision-making (§3.9.1–3.9.2).
- Source: ICH E6(R3) Annex 2 Draft (Step 2) https://database.ich.org/sites/default/files/ICH_E6(R3)_Annex%202_Step2_DraftGuideline_2024_1024_0.pdf

- **FDA (RWD/RWE)**
  - Final: *Real-World Data: Assessing EHR and Medical Claims* (2024-07) – detailed evaluation of reliability, relevance, traceability, and data linkage when proposing RWD (Final Guidance, 2024-07). Guidance page/PDF: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-electronic-health-records-and-medical-claims-data-support-regulatory | https://www.fda.gov/media/152503/download
  - Related: Package includes final guidance on registries and drafts on non-interventional RWE.

- **FDA (AI)**
  - Final: *Marketing Submission Recommendations for a Predetermined Change Control Plan for AI-Enabled Device Software Functions* (PCCP, 2024-12). Recommends including modification types, development/validation methods, implementation approach, and impact assessment. Guidance page: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/marketing-submission-recommendations-predetermined-change-control-plan-artificial-intelligence | Webinar (2025-01-14): https://www.fda.gov/medical-devices/cdrhnew-news-and-updates/webinar-final-guidance-marketing-submission-recommendations-predetermined-change-control-plan
  - Draft: *AI-Enabled Device Software Functions – Lifecycle Management and Marketing* (TPLC), noticed in the Federal Register on 2025-01-07; public comment closed 2025-04-07 (Docket FDA-2024-D-4488): https://www.federalregister.gov/documents/2025/01/07/2024-31543/artificial-intelligence-enabled-device-software-functions-lifecycle-management-and-marketing
  - Background: GenAI TPLC (CDRH) https://www.fda.gov/media/182871/download

- **EMA (AI)**
  - Reflection Paper (adopted): principles for AI across the medicinal product lifecycle, including design, data curation, pre-specified pipelines, frozen/documented model sets, and impacts on statistical inference. Adopted page/PDF: https://www.ema.europa.eu/en/use-artificial-intelligence-ai-medicinal-product-lifecycle | https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-use-artificial-intelligence-ai-medicinal-product-lifecycle_en.pdf

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3. So What? (Role-Specific Implications)

Role	Key Operational Implications
RA (Regulatory Affairs)	• Pre-specify RWD criteria for reliability/relevance/traceability in protocol, SAP, and DMP (incl. applicability conditions, linkage, inspection access, privacy). • Establish justification and bias control when using external controls. • For AI-DSF, incorporate PCCP content (modification types, methodology, implementation, impact assessment) into submissions; align with lifecycle draft. • In the EU, align with EMA Reflection Paper and clarify regulatory impacts via early consultation.
ClinOps	• Design operations by RWD source (EHR/claims/registries), accounting for availability, missingness, timing differences; define data-linkage responsibilities and records. • Standardize security, privacy, and consent handling for remote collection/DHT. • Operationalize AI monitoring (performance KPIs, drift detection, rollback) per PCCP. • Maintain blinding and formalize bias control for external controls or algorithmic support.
QA	• Audit data governance for RWD/remote collection (provenance, audit trails, access control, cybersecurity); ensure inspection access to third-party data. • Verify traceability & reproducibility for multi-source linkage. • Integrate AI change control, performance monitoring, CAPA under QMS per PCCP. • Re-evaluate CtQ/QTL-based metrics and central monitoring KPIs.
Data Science	• In the DMP, document data origins/flows/providers, linkage specs, quality metrics, and audit trails to support Fit-for-Purpose determinations. • In the SAP, pre-specify handling of non-standard timing, missing data, measurement error, with sensitivity analyses. • For AI, align training/validation/inference data management and KPIs/drift thresholds/rollback with PCCP; ensure log/model integrity. • Implement blinding protection, access-control design, and alert operations.

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4. Operational Action Checklist (Working Level)

- Revise the standard DMP template for RWD use: require data origins, flow diagram, provider list, linkage specifications, audit trails, and access rights (FDA DCT Guidance §III.D The Sponsor [data management plan]; ICH E6(R3) Annex 2 §3.5.1(d), §3.8).
- Update external-control guidance: codify RWD reliability/relevance criteria, pre-specify linkage, ensure inspection access, and define privacy safeguards (ICH E6(R3) Annex 2 §3.5.1(b),(c),(d); INTRODUCTION).
- Update the AI monitoring SOP: reflect PCCP structure (modification types; development/validation/implementation; impact assessment) and operations (monitoring KPIs, drift detection, rollback, escalation) (FDA PCCP Final, 2024-12).
- Amend the SAP: pre-specify handling of non-standard timing, missingness, and intercurrent events, with sensitivity analyses (ICH E6(R3) Annex 2 §3.2).
- Update remote collection/cloud security and audit-trail review plans (cybersecurity, access control, audit trails) (ICH E6(R3) Annex 2 §3.5.2(a); §3.7).
- Add vendor-oversight roles/KPIs/inspection-access clauses to contracts (registries/EHR providers/cloud/DHT) (ICH E6(R3) Annex 2 §3.8; §3.5.1(c)).
- Prepare an RA differential matrix across FDA RWD Final, PCCP Final, FDA AI Lifecycle Draft, and the EMA Reflection Paper (with pinpointed sections).

5. Decision Prompts (Who Does What)

Role	Action	Reference
Head of Data Science	Approve AI monitoring plan (KPIs/drift/rollback) reflecting PCCP requirements	FDA PCCP Final
Head of RA	Determine need and plan for pre-submission consultation on external controls/RWD use	FDA RWD Final; ICH E6(R3) Annex 2 §3.1
Head of QA	Approve protocol for audit-trail and reproducibility checks of the RWD linkage process	ICH E6(R3) Annex 2 §3.5.1(d), §3.8
Head of ClinOps	Issue SOP revision on security operations and privacy notices for remote collection/DHT	ICH E6(R3) Annex 2 §3.5.2(a), §3.7

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6. FAQ

- **Q1. When and how is AI model re-training approved?**

  A. Define, in the PCCP, the allowable scope of change, methodology, validation, implementation, and impact assessment; changes within scope may be implemented without additional pre-market submissions (FDA PCCP Final). Include monitoring KPIs and rollback/corrective actions.

- **Q2. Where does PCCP apply? Is it required for all AI?**

  A. PCCP applies to AI-Enabled Device Software Functions (AI-DSF) within 510(k)/De Novo/PMA routes (including device-led combinations) (FDA PCCP Final). Confirm classification and device definition case-by-case.

- **Q3. How are RWD "reliability" and "relevance" determined?**

  A. Reliability = accuracy, completeness, traceability; Relevance = availability of exposure, outcome, and covariates addressing the clinical question (ICH E6(R3) Annex 2 §3.5.1(b); consistent with FDA RWD Final). For multiple-source linkage, pre-specify methods and ensure accurate matching, privacy protection, and inspection access (§3.5.1(c),(d)).

7. Signal Priority Index (SPI)

- Reach: 5 (RWD under Annex 2 and AI under related guidelines affect development through post-marketing across ICH/FDA/EMA).
- Magnitude: 5 (Re-design across study design/analysis, QMS, change control, and vendor oversight).
- Urgency: 4 (FDA RWD/PCCP finalized; Annex 2 at Step 2; EMA Reflection operational).
- Certainty: 4 (Multiple finalized guidances plus established international drafts).

  Total: (5 + 5 + 4 + 4) × 5 = 90

  Priority: 95–90 = immediate discussion; 85–80 = next update; 70–60 = information gathering; ≤59 = monitor only.

8. Sources and References

- **ICH E6(R3) Guideline for Good Clinical Practice** (Final, Step 4, 2025-01-06)
  - §4 Data Governance – Investigator and Sponsor
  - 4.1 Safeguard Blinding; 4.2 Data Lifecycle (esp. 4.2.6 Finalisation of data sets prior to analysis); 4.3 Computerised Systems
  - https://database.ich.org/sites/default/files/ICH_E6(R3)_Step4_FinalGuideline_2025_0106.pdf

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- **ICH E6(R3) Annex 2 Draft** (Step 2, 2024-11-06)
    - INTRODUCTION (purpose/scope; additional GCP considerations for DCT/pragmatic/RWD);
    - RWD Considerations (esp. (b) Reliability and Relevance; (d) Data linkage);
    - Remote Data Collection; 3.7 Privacy and Confidentiality; 3.8 Sponsor Oversight; 3.9.1–3.9.2 Safety Assessment and Reporting
    - https://database.ich.org/sites/default/files/ICH_E6(R3)_Annex%202_Step2_DraftGuideline_2024_1024_0.pdf

- **EMA Reflection Paper on the use of AI in the medicinal product lifecycle** (Adopted)
    - 2.3.3.1 Clinical trials: GCP compliance and inspection scope;
    - 2.3.3.3 Pre-specification and frozen models (no incremental learning in pivotal trials);
    - 2.5.6 Performance monitoring and lifecycle management (drift monitoring; criteria for halt/re-training)
    - https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-use-artificial-intelligence-ai-medicinal-product-lifecycle_en.pdf

- **FDA Final Guidance:** *Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence-Enabled Device Software Functions* (Final)
    - Scope: AI-enabled devices (including device-led combination products);
    - Pathways: 510(k)/De Novo/PMA;
    - PCCP structure: modification types; development/validation; implementation; impact assessment
    - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/marketing-submission-recommendations-predetermined-change-control-plan-artificial-intelligence
- **FDA Final Guidance:** *Real-World Data – Assessing Electronic Health Records and Medical Claims Data* (Final)
    - Evaluation of reliability/relevance/traceability/data linkage for RWD use
    - Guidance page: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-electronic-health-records-and-medical-claims-data-support-regulatory
    - PDF: https://www.fda.gov/media/152503/download

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Notes:

- Annex 2 is a Step 2 draft and may be updated upon finalization. The FDA RWD and PCCP guidances are final. The EMA document is a Reflection Paper indicating the current position.
- In this report, in addition to Annex 2's formal scope (DCT/RWD), AI is addressed in a referential manner where QbD principles connect in practice (model change control and monitoring). AI is not directly covered by Annex 2, but shares the common concept of "embedding quality at the design stage" through frameworks such as the PCCP.

Supplement:

Scope delineation for application (quick reference for regulatory applicability of AI use)

1. When AI/ML is used in the design, conduct, or analysis of clinical trials

   [Applicable requirements]

   - E6(R3) core data governance provisions (§4)
   - General GCP requirements
   - EMA AI Reflection Paper principles

   [Cases requiring explicit measures (high-impact cases)]

   When AI use may materially affect trial results or participant safety, specify the following in the protocol and the statistical analysis plan (SAP):

   - Pre-specification of the AI model (intended use, functions, data pipeline)
   - Model freezing (version fixed before trial start)
   - Prohibition of incremental learning (no automatic learning/updates during pivotal trials)
   - Monitoring plan (performance KPIs, drift detection, rollback procedures)

   [Examples]

   - Use of AI image analysis in central assessment
   - Use of AI for automated adverse event detection
   - Use of AI for risk stratification of participants

   [References]

   - ICH E6(R3) §4 (4.1–4.3)
     https://database.ich.org/sites/default/files/ICH_E6(R3)_Step4_FinalGuideline_2025_0106.pdf
   - EMA Reflection Paper on AI: §2.3.3.1, §2.3.3.3, §2.5.6
     https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-use-artificial-intelligence-ai-medicinal-product-lifecycle_en.pdf

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2. When AI is regulated as a medical device

[Cases in scope]

AI software used for medical purposes such as diagnosis, treatment, or prediction is regulated as a medical device. Examples include:

- AI-enabled diagnostic decision-support software
- AI tools that support treatment decision-making
- AI systems for patient monitoring
- AI systems that support medicinal product dosing decisions (including combination products)

[Applicable requirement]

FDA PCCP Final Guidance (AI-Enabled Device Software Functions)

[Submission pathways]

510(k) / De Novo / PMA

[Content required at submission (to be included in the PCCP)]

- Types of modifications (e.g., algorithm improvement, addition of training data, performance enhancement)
- Development and validation methodology
- Implementation approach
- Impact assessment (effects on safety and effectiveness)

Within the approved PCCP scope, post-approval AI model updates may be implemented without an additional pre-market submission.

[Reference]

- FDA PCCP Guidance (scope for AI-enabled medical devices)
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/marketing-submission-recommendations-predetermined-change-control-plan-artificial-intelligence

3. Relationship to Annex 2 (additional considerations when using DCT/RWD)

[Scope of Annex 2]

ICH E6(R3) Annex 2 presents additional GCP considerations for the following emerging trial models:

- Decentralized clinical trials (DCT)
- Pragmatic trial elements
- Use of real-world data (RWD) (no AI-specific clauses)

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[Key provisions relevant when AI is used]

- Remote data collection: §3.5.2 (Remote Data Collection Considerations)
- RWD reliability and relevance (Fit-for-Purpose): §3.5.1(b)
- Data linkage (accurate matching, privacy protection, pre-specification): §3.5.1(d)
- Security and privacy (privacy/confidentiality): §3.7
- Sponsor oversight (including vendor oversight): §3.8 (see also safety information collection and provision: §3.9.1–3.9.2)

[Practical implication]

When AI is used in DCT operations or when RWD is analyzed by AI, the additional Annex 2 requirements for data quality, linkage, remote collection, privacy/security, and sponsor oversight must be met alongside E6(R3) core requirements (§4).

[Reference]

- ICH E6(R3) Annex 2 Step 2 Draft
  I. INTRODUCTION / §3.5.1 (especially (b), (d)) / §3.5.2 / §3.7 / §3.8 / §3.9.1–3.9.2
  https://database.ich.org/sites/default/files/ICH_E6(R3)_Annex%202_Step2_DraftGuideline_2024_1024_0.pdf

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Business Implications Matrix (Impact by Function and Recommended Actions)

Function	E6(R3)	DCT	RWD & AI
Clinical Development	Impact: High. Completion criteria: Before the next protocol freeze, finalize the CtQ map and issue the monitoring-plan template.	Impact: High. Completion criteria: Before IRB/IEC submission for trials including DCT elements, activate the SOPs and initiate the first pilot.	Impact: Medium. Completion criteria: Before receipt of external data or start of remote collection, finalize the operational flow and blinding procedures.
Quality Assurance	Impact: High. Completion criteria: Before the next quality committee meeting, complete the QMS gap analysis and issue QTL operating standards.	Impact: High. Completion criteria: Before the next system release and contract renewals, approve the audit-trail review plan and oversight standards.	Impact: Medium. Completion criteria: Before the first RWD linkage and before any AI model update, issue QMS procedures covering audit items and, where applicable for AI-DSF, PCCP integration steps.
Regulatory Affairs	Impact: High. Completion criteria: Before the next authority submission, have the tracking system in operation and agree on the QTL deviation reporting policy.	Impact: High. Completion criteria: By the internal design review (final protocol review), complete legality assessments and present a differential matrix.	Impact: High. Completion criteria: Before protocol freeze, finalize RWD eligibility proposals, determine PCCP applicability for any AI-DSF, and set the plan for agency consultations.
Data Science	Impact: High. Completion criteria: Before issuing the next SAP revision (vX), add data lifecycle and central monitoring KPIs to the DMP/SAP.	Impact: High. Completion criteria: Before DHT deployment and the start of remote collection, establish the validation plan, data flows, and timestamp operations.	Impact: High. Completion criteria: Before first receipt of external data and before any AI model update, finalize linkage specifications, quality metrics, monitoring KPIs, and drift thresholds.

Each cell records “Impact level + completion criteria (event-based).”

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Future Outlook

The following section summarizes expected milestones over the next 12 months (approx. Nov 2025 → Nov 2026) based on verified primary sources. Items not yet confirmed are marked "TBD."

Milestones by Topic

E6(R3) (Clinical Development OS: QbD)

- **Nov 15–19 2025:** ICH Assembly (Singapore) scheduled. Minutes note: "E6(R3) EWG has no meeting request for Singapore (Nov 2025)" (under E6(R3) item).
- **Q3–Q4 2025:** Acceleration of training module development (Principles + Annex 1). Core modules 1–4 targeted for completion within 2025; most E6-related training expected to conclude by year-end.
- **Annex 2 (DCT/RWD add-on):** Over 1,000 public comments received after Step 2 publication; substantial revisions expected. Timeline extension for Steps 3/4 shared during the Assembly. Adoption timing = TBD.
- **May 30–Jun 3 2026:** ICH Assembly (Rio de Janeiro).
- **Nov 14–18 2026:** ICH Assembly (Europe/Africa/Middle East region; location TBD).

DCT (Decentralized Elements – Annex 2 Implementation Domain)

- Annex 2 revision work ongoing after Nov 2024 public comment period. Step 3/4 adoption = TBD (Assembly minutes note possible extension).
- **Nov 2025 (Singapore meeting):** Progress report on Annex 2 expected (details to be updated post-meeting).
- New FDA revisions or deadlines for its Final DCT Guidance (Sep 2024) = TBD.
- Updated EU recommendations (ACT EU / CTCG) = TBD.

RWD and AI (Data-Driven Domain – Quality and Change Control)

- **ICH M14 (Non-Interventional Safety Studies using RWD):** Adopted at Step 4 on 2025-09-04; now in implementation and training phase.
- **FDA AI (PCCP):** Final guidance issued late 2024; Federal Register notice posted end-2024 to early 2025 (Public Inspection FR Doc. 2024-28361). Refer to FR page for exact posting date (Webinar held 2025-01-14).
- **FDA AI Lifecycle Draft (AI-Enabled Device Software Functions):** Published in FR on 2025-01-07; public comment closed 2025-04-07 (Docket FDA-2024-D-4488). Finalization = TBD.
- **FDA Request for Comments on AI Performance in Real-World Use:** The comment period closed on 2025-12-01 (input sought on measurement of AI performance in practice).

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- **FDA RWD Final Guidance (July 2024):** No announced revisions or deadlines as of now (TBD).

Upcoming Meetings / Public Comment Deadlines / Adoptions

- **ICH Assembly:** Nov 15–19 2025 (Singapore: concluded); May 30–Jun 3 2026 (Rio); Nov 14–18 2026 (Europe/Africa/Middle East, venue TBD)
- **E6(R3) Annex 2:** Step 2 (public consultation) document published Nov 6 2024; review of >1,000 comments ongoing; Steps 3/4 adoption = TBD (extension noted in Assembly minutes).
- **FDA AI Lifecycle (Draft):** FR publication Jan 7 2025 / comment deadline Apr 7 2025 (closed).
- **FDA RfC (AI Real-World Performance):** Comment deadline Dec 1 2025.

Monitoring Focus (Operational Attention Points)

- **Extent of Annex 2 revision:** Magnitude of updates across DCT, RWD, privacy/security, and sponsor-oversight sections (to address >1,000 comments).
- **Notice of E6 training completion:** Publication timing of E6 (EWG) / MRCT training modules and implementation announcements.
- **Finalization of FDA AI Lifecycle:** Alignment with PCCP Final (monitored via KPIs, drift detection, rollback processes, documentation).
- **Outcome of FDA RWP public comments:** Subsequent actions (e.g., guidance development, workshops).

Monitoring Items (Topic / Schedule / Authority / Source Links)

Item	Schedule	Authority	Source Link
ICH Assembly (Singapore)	2025-11-15 to 19 (Concluded)	ICH	https://ich.org/page/ich-public-events
ICH Assembly (Rio de Janeiro)	2026-05-30 to 06-03	ICH	https://admin.ich.org/sites/default/files/2025-06/ICH50_MC_Minutes_MadridMeeting_Final_2025_0611.pdf
ICH Assembly (Europe/Africa/Middle East)	2026-11-14 to 18 (location TBD)	ICH	https://admin.ich.org/sites/default/files/2025-06/ICH%20Assembly%20Madrid%20Meeting,%2013-14%20May%202025.pdf
E6(R3) Annex 2 (DCT/RWD Add-on) Steps 3/4	Adoption TBD (Assembly minutes suggest timeline extension)	ICH E6(R3) EWG	https://admin.ich.org/sites/default/files/2025-06/ICH%20Assembly%20Madrid%20Meeting,%2013-14%20May%202025.pdf

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Item	Schedule	Authority	Source Link
E6(R3) Training (Principles + Annex 1)	Target completion of main modules within 2025	ICH (E6 EWG / MRCT)	https://admin.ich.org/sites/default/files/inline-files/ICH_E6(R3)_Step%204_Presentation_2025_0123.pdf
E6(R3) EWG Work Plan (Annex 2 Schedule)	Prior plan: Step 4 by Jul 2025 → currently extension possible	ICH	https://database.ich.org/sites/default/files/ICH_E6(R3)EWG_WorkPlan_2025_0214.pdf
FDA AI Lifecycle (Draft)	FR notice 2025-01-07 / comment deadline 2025-04-07 (closed)	FDA (CDRH/CBER/CDER)	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/artificial-intelligence-enabled-device-software-functions-lifecycle-management-and-marketing
FDA PCCP (AI-DSF) Final	Final Dec 2024 / Webinar Jan 14, 2025 / next revision TBD	FDA (CDRH)	https://www.fda.gov/medical-devices/cdrhnew-news-and-updates/webinar-final-guidance-marketing-submission-recommendations-predetermined-change-control-plan
FDA RfC (AI Real-World Performance Measurement)	Comment period closed on 2025-12-01	FDA (DHCoE/CDRH)	https://www.fda.gov/medical-devices/digital-health-center-excellence/request-public-comment-measuring-and-evaluating-artificial-intelligence-enabled-medical-device
ICH M14 (RWD Non-Interventional Safety Studies)	Step 4 adopted 2025-09-04 (finalized, now in implementation and training)	ICH	https://admin.ich.org/sites/default/files/2025-06/ICH%20Assembly%20Madrid%20Meeting,%2013-14%20May%202025.pdf

Note:

- The above summary is based on primary information sources (ICH minutes, EWG work plans, FDA official guidances, event and notice pages). The adoption timeline for Annex 2 remains undecided (as noted in Assembly minutes).
- In practice, track monthly updates from the Singapore Assembly (Nov 2025), Rio Assembly agenda (May 2026), and FDA Docket updates for AI Lifecycle and AI Real-World Performance.

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