

ICH GCP E6 R3 and its implications for clinical trials

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Disclaimer

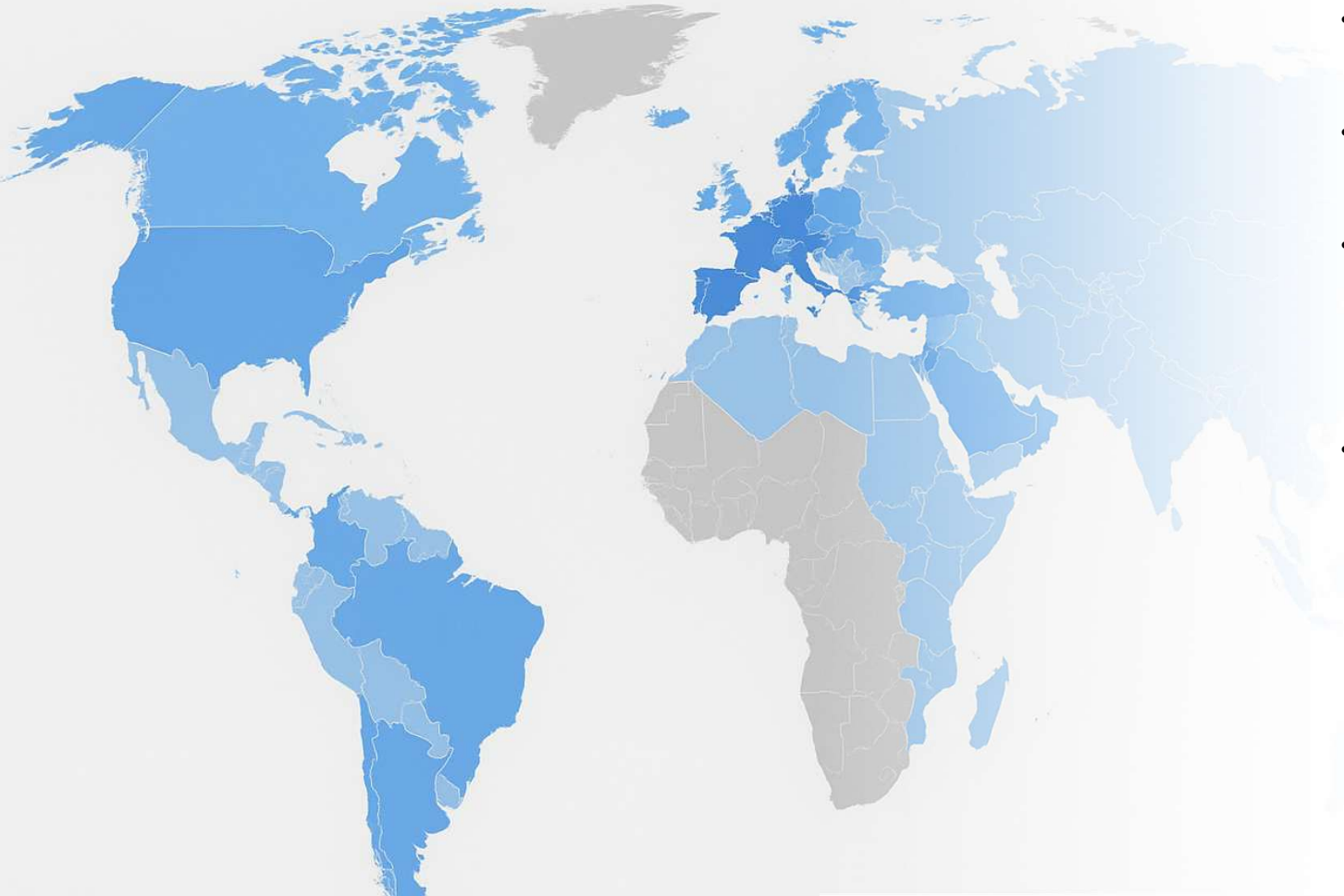
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Agenda

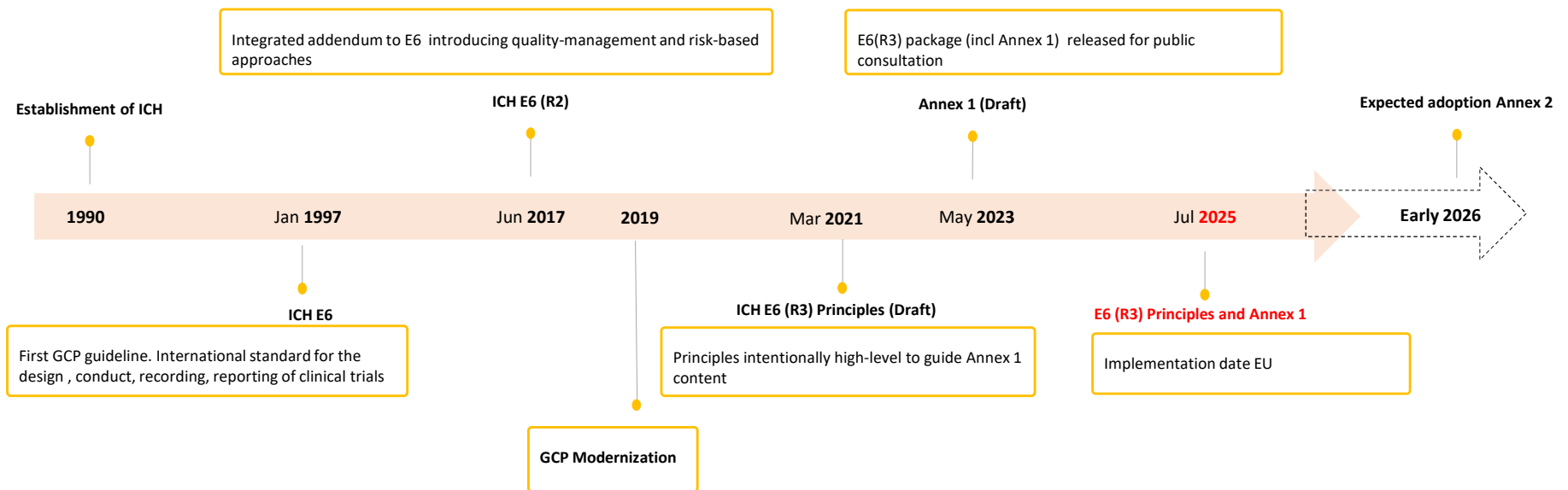
1. History and context
2. Regulatory scope and applicability
3. E6 R3 Structure and key changes
4. E6 R3 content topics
 - Roles and responsibilities
 - Essential records
 - IP management
5. Key takeaways

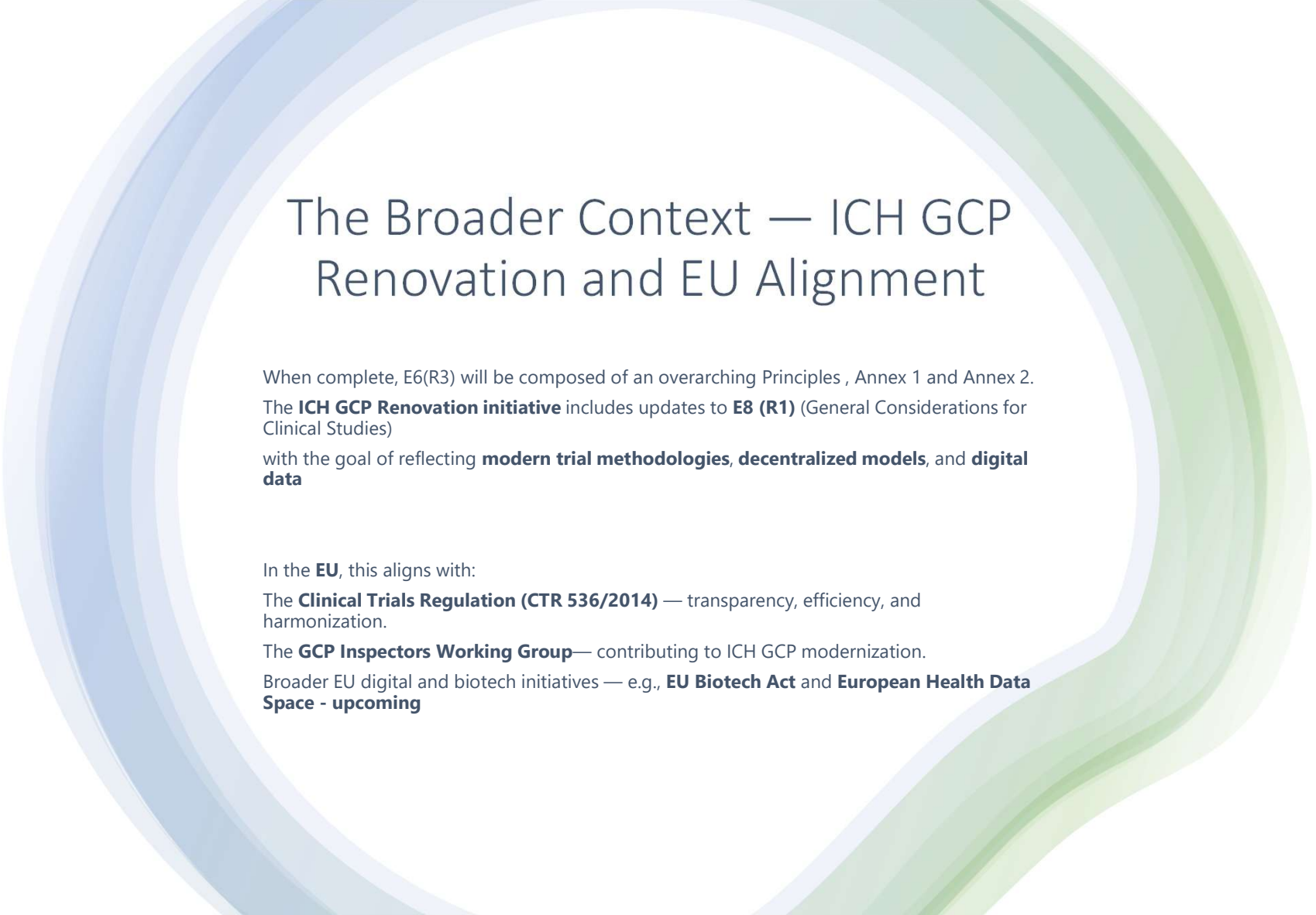
ICH outreach



- The *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use* (ICH) was established in 1990
- Founding members: Europe (EC), the U.S. (FDA), and Japan (PMDA) and industry associations (EFPIA, PhMRA, JPMA)
- **May 1996, *Good Clinical Practice: Consolidated Guideline*.** First global, unified standard describing ethical and scientific quality requirements for designing, conducting, recording, and reporting trials involving human subjects
- GCP “Renovation” 2019: ICH program (CP/ RP/ business plan) to modernize and restructure E6 and related guidance (E8), making GCP fit for modern trial designs, data sources and technologies

ICH GCP E6 timeline





The Broader Context — ICH GCP Renovation and EU Alignment

When complete, E6(R3) will be composed of an overarching Principles, Annex 1 and Annex 2.

The **ICH GCP Renovation initiative** includes updates to **E8 (R1)** (General Considerations for Clinical Studies)

with the goal of reflecting **modern trial methodologies, decentralized models, and digital data**

In the **EU**, this aligns with:

The **Clinical Trials Regulation (CTR 536/2014)** — transparency, efficiency, and harmonization.

The **GCP Inspectors Working Group**— contributing to ICH GCP modernization.

Broader EU digital and biotech initiatives — e.g., **EU Biotech Act** and **European Health Data Space - upcoming**

Regulatory scope

In the EU :

- Formally adopted by ICH on Jan 2025
- **Principles and Annex 1 came into effect** as of 23 July 2025, Annex 2 still under development, expected to be adopted early 2026
- For other regions, stakeholders should track **when** their region requires compliance

Primarily written for interventional clinical trials of **investigational medicinal products**, intended to be submitted to reg authorities; may be applicable to other interventional clinical trials of investigational products that are not intended to support MAAs

For EU medical-device clinical investigations you must follow the MDR (Regulation (EU) 2017/745) and device-specific GCP standard ISO 14155:2020

Regulatory applicability

What effective means

- Sponsors will need to assess, on a **case-by-case basis**, whether (and when) to apply R3 principles to **ongoing trials**
 - Not necessarily required to 'restart' under R3
 - Any substantial amendment needs to comply with R3 (principles and annex 1)
- If you are running or planning trials that start *NOW*, build in ICH E6(R3)-compliance from the start rather than retrofitting
- SOPs, training, quality systems should be timely updated to reflect requirements of the E6 (R3)

Structure

11 foundational Principles

2 Annexes (basis for appropriate interpretation and application of principles)

- Annex 1: Considerations for interventional clinical trials
- Annex 2: Additional GCP considerations, focusing on examples of trials that incorporate decentralised elements, pragmatic elements and/or real-world data (RWD)- *not yet ready*

Appendices

App A- IB, App B- Protocol and Protocol amendments, App C- Essential Records for the conduct of a trial- significantly revised from the R2 version

- All appendices are part of Annex 1

Glossary of terms

What's changed/new ?

	E6 R2	E6 R3
Overall focus	Strengthened global consistency in GCP implementation More structure for handling increasing trial complexity	More flexible, modern, and risk-proportionate Builds on critical thinking, not checklists Supports digital, decentralized, and adaptive trial design
Roles and responsibilities	Sponsor oversight of CROs formalized Functional responsibilities for monitoring, data handling, and quality systems	Sponsors & Investigators shared responsibility Service providers (not just CROs) - explicit oversight Clearer task delegation + required documentation of oversight
Documentation	Electronic systems validation required Documentation-heavy Recording, storing, and safeguarding trial data	Streamlined, fit-for-purpose documentation Data governance introduced: integrity, traceability, audit trails Essential records formally recognized
Quality	Introduced Risk-Based Monitoring (RBM) Risk identification & mitigation processes	Strong shift to Quality by Design (QbD) Identify and protect Critical-to-Quality Factors (CtQFs) RBQM expanded beyond monitoring → end-to-end quality management
Data sources	Guidance for eData capture and eSource Expectations for proper recording, handling, review, and archiving of clinical data	Acceptance of digital tools, sensors, eSource "Source records" now include data + metadata Strong emphasis on full data lifecycle management
Investigational Product	Site-based control of IP Does not explicitly address decentralized or direct-to-patient IP management	Decentralized/remote handling (incl direct shipment and administration outside trial sites) Requires stronger quality measures to ensure IP integrity across flexible delivery models

Roles and responsibilities

Redefined roles and responsibilities



Sponsors and investigators
shared accountability: Principle 10

Each retains within their respective sphere (*sponsor transfers and investigator delegates*) **for overall trial quality and participant protection** *

Investigators and site-> more flexibility, but also greater responsibility in ensuring **data reliability and integrity**



Cross-functional **quality culture** replaces siloed accountability



Operational staff : not only what tasks are performed, but **why they are critical to quality**

* Sponsor remains responsible for establishing, implementing and maintaining quality control processes and procedures to ensure that trials are conducted and data are generated, recorded and reported in compliance with the protocol, GCP and the applicable reg requirements



Imagine this scenario

Participant (home)

└─> Daily BP reading via connected device(**sponsor deployed**)



Automatic transmission to EDC



Investigator-managed EDC system

└─> Monitor data integrity, traceability

└─> Detect missing/inconsistent readings

└─> Document any issues



Sponsor/Regulatory Reporting

Remote BP data collection using connected devices

E6 R2 approach

- Monitoring is focused on SDV from site system/papers
- Assumes manual or site-entered data
- Limited detail on direct participant-to-EDC flow
- Device-level audit trails rarely addressed

New E6 R3



Electronic data (wearables, sensors) is recognized as **source data**



Data capture from participants, (remote, but source). Validation, security, and traceability of data flow.



Audit trail expectations across ***the entire data lifecycle***, from capture to storage

* Investigator is ultimately responsible for trial data reliability, as such ensuring data have audit trails and essential records are accessible.

Published info

	Objectives	Relevance
Digital Health Interventions for Hypertension Management in US Populations Experiencing Health Disparities: A Systematic Review and Meta-Analysis (2024) (JAMA Network)	28 studies, ~8,257 participants using digital health interventions (many including remote BP monitoring) in underserved populations. • Mean reduction in systolic BP of ~4.24 mmHg at 6 months and ~4.30 mmHg at 12 months compared to standard care. (JAMA Network)	Demonstrates that digital remote monitoring solutions can deliver measurable BP reductions , particularly relevant for home use and automated data collection . supports their use in large-scale interventional trials.
Digital Remote Monitoring Using an mHealth Solution for Survivors of Cancer: Protocol for a Pilot Observational Study (Digital Remote Monitoring Using an mHealth Solution for Survivors of Cancer: Protocol for a Pilot Observational Study – PubMed)	Pilot observational feasibility study aiming to test an mHealth solution for multidimensional longitudinal monitoring in cancer survivors	If feasibility confirmed, study paves the way for future interventional studies (digital coaching, tailored lifestyle interventions, AI predictive models) in future oncology trials .
Data Flow Construction and Quality Evaluation of Electronic Source Data in Clinical Trials: Pilot Study Based on Hospital Electronic Medical Records in China (JMIR Medical Informatics - Data Flow Construction and Quality Evaluation of Electronic Source Data in Clinical Trials: Pilot Study Based on Hospital Electronic Medical Records in China)	How to extract trial-related data from a hospital's EHR system, transform that data into a format required by an electronic data capture (EDC) system. evaluate the transferred data sets in terms of availability, completeness, and accuracy of constructing an eSource data flow from EHR to EDC	Demonstrates that an EHR → EDC data pipeline <i>can</i> be set up; strong de-identification, audit trails, secure transfers are critical; Unstructured/paper data remains a significant barrier

Essential records

Trial integrity should start with relevance

In E6 R2, documentation was about *reconstruction*; in E6 R3, it is about *understanding* — can your records tell the **story of the trial**, not just replay it ?

Are we building *evidence of compliance* or ***evidence of understanding*** ?

How confident are we that digital systems can trace the ***meaning of data***, not just store it?

Do audit trails help inspectors find **answers** — or hide them under layers of redundancy?

Essential trial records - new concept

E6 R2

- Section 8 – Essential Documents, which listed **specific document types** (e.g. IB, signed protocol, subject ID log, CRFs).
- **What documents (hard-copies)** to be kept to demonstrate adherence with GCP and enable trial reconstruction
- Split into *Before trial* and *During trial* conduct. Sometimes led to overly rigid document management without context or **proportionality**.

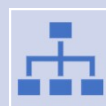
E6 R3



Essential record (all types of records) if supports the reliability of trial results and protection of participations and demonstrates GCP compliance



Essentiality of records criteria provided (appendix C, Section C.3.1)



Shifts the focus from *collect everything* to *justify* what's essential and *ensure it's complete, traceable, and accessible*. Also records related to metadata (especially audit trails of data which was corrected)

Essentiality of trial records

28 criteria

- (a) Is a document that is submitted to or issued by the regulatory authority or IRB/IEC, including related correspondence and those documenting regulatory decisions or approvals/favourable opinions;
- (b) Is a trial-specific procedure or plan;
- (c) Is relevant correspondence or documentation of meetings related to important discussions and/or trial-related decisions that have been made related to the conduct of the trial and the processes being used;
- (d) Documents the conduct of relevant trial procedures (e.g., database lock checklist produced from following data management standard operating procedures (SOPs));
- (e) Documents the arrangements between parties and insurance/indemnity arrangements;
- (f) Documents the compliance with the requirements and any conditions of approval from the regulatory authority or the favourable opinion of the IRB/IEC;
- (g) Documents the composition and, where appropriate, the functions, correspondence and decisions of any committees involved in the trial approval or its conduct.
- (h) Demonstrates that a trial-specific computerised system is validated and that non-trial-specific systems (e.g., clinical practice computerised systems) have been assessed as fit for purpose for their intended use in the trial;
- (i) Is a document that has been authorised/signed by the sponsor and/or investigator to confirm review or approval;
- (j) Is, where necessary, documentation that demonstrates signatures/initials of staff undertaking significant trial-related activities; for example, completing data acquisition tools;

Essential records

New elements

Security-breach / incident-response processes are essential (where applicable)	bb) "Defines processes/practices in place in the event of a security breach in order to protect participants' rights, safety and well-being and the integrity of the data."
Service-provider selection, assessment and oversight records made explicit	(p) "Documents that service providers are suitably qualified for conducting their delegated or transferred activities;"
Stronger focus on computerised systems: validation, failure handling, user management and security	(h) "Demonstrates that a trial-specific computerised system is validated and that non-trial-specific systems (e.g., clinical practice computerised systems) have been assessed as fit for purpose for their intended use in the trial;"
Inclusion of data <i>and relevant metadata</i> as essential	(n) "Contains the data as well as relevant metadata that would be needed to allow the appropriate evaluation of the conduct of the trial."

Essential trial records - implications



E6 R3 supports **risk-proportionate documentation** — allowing flexibility for decentralized trials and digital records, as long as essentiality criteria are met.



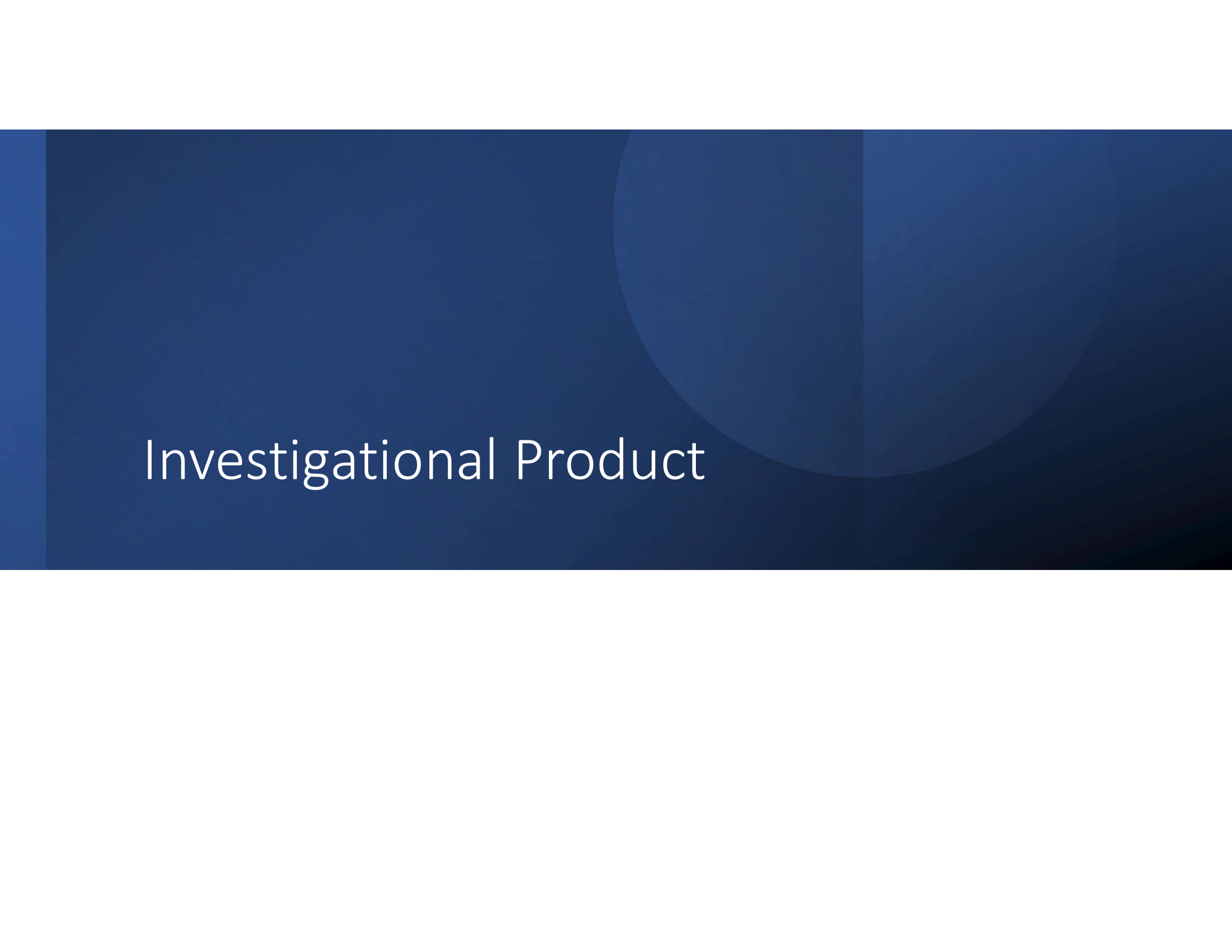
Record management plans or TMF plans should explicitly describe how essentiality is assessed and maintained.



Systems used to store essential records (including electronic systems, eSource, vendor portals) must ensure **traceability, version control, and accessibility for inspection.**



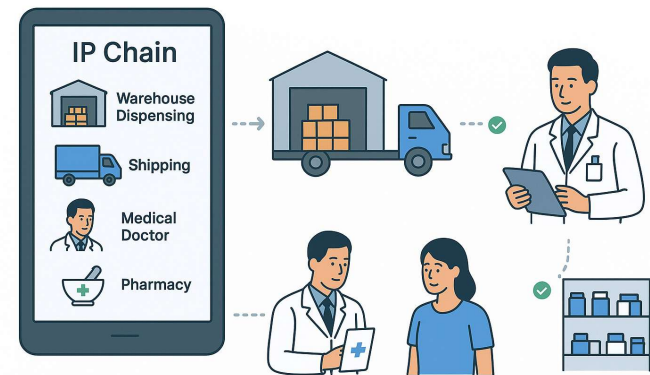
Higher-quality documentation aligned with purpose — not volume.



Investigational Product

IP traceability : how confident are we ?

- ✓ When a temperature deviation happens, **how fast** can we identify impacted kits and participants?
- ✓ Can our systems **demonstrate full chain-of-custody** — or are we still relying on email threads and spreadsheets?
- ✓ What can we do to keep pace with decentralized supply chains and direct-to-patient models ?



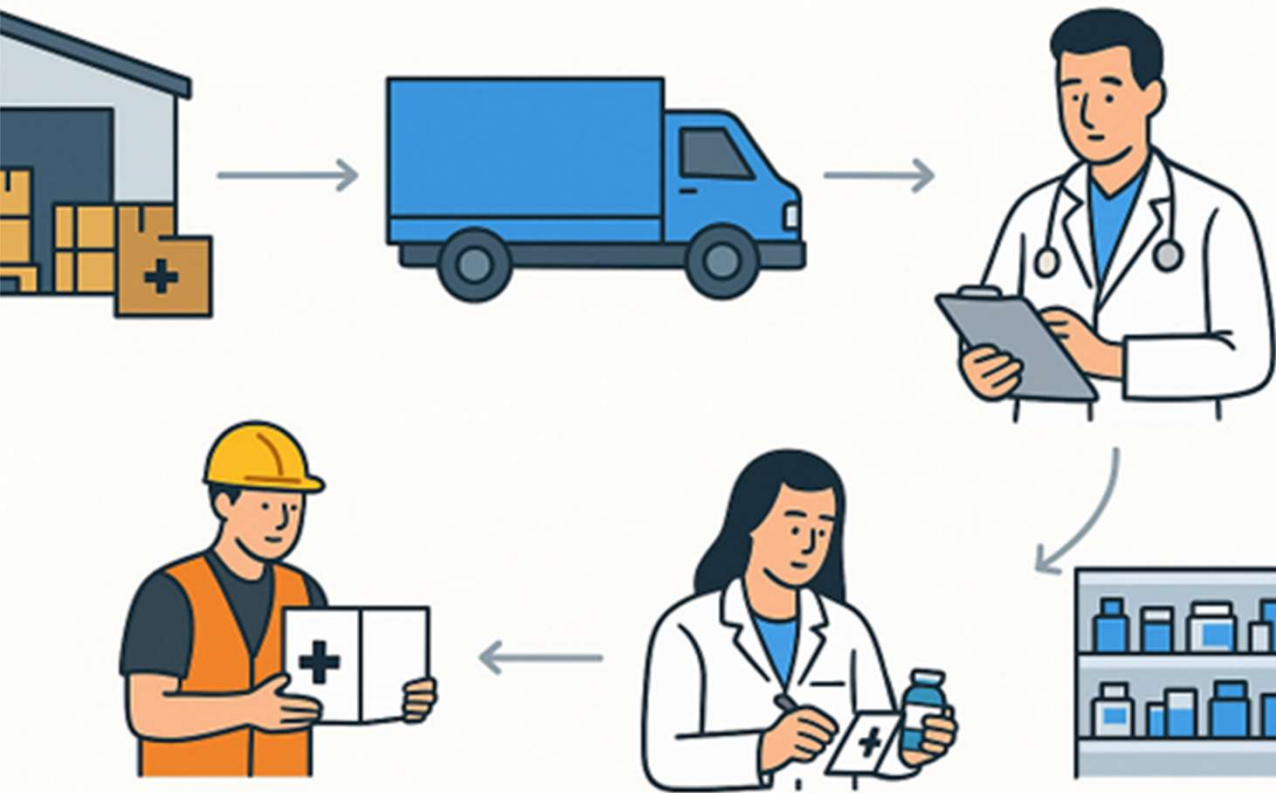


In a 2025 audit-based study of IP management, missing shipment records and incorrect labels were the most common errors, highlighting the operational imperative for full-lifecycle traceability (shipment → receipt → dispensing → return/destruction) in clinical trials

[Audit experiences in investigational medicinal product management and errors in clinical trials - PMC](#)



Evolving role of IP management



Quality Focus: Protects what's *Critical to Quality* (CtQ)

Data Integrity: Extends oversight to systems and digital tools

Participant Safety: Ensures product and process reliability

IP management shifts

E6 R2 traditional approach

- Primarily site-based, site pharmacy or PI dispensing product under local manual or trial SOP
- Monitoring largely via on-site checks
- Novel dispensing models (and PI oversight) not clearly mentioned

E6 R3 new approach



Delegate model * (investigator delegates IP dispensing to site pharmacy, local healthcare provider or local pharmacy)



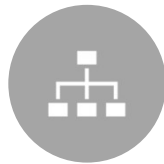
Systems and records must support **traceability of IP:** shipment/receipt/distribution/return, linking participants to dispensing events, documenting cold chain or special storage

*explicit recognition that IP may be shipped to the participant's location or supplied closer to the participant (e.g., local pharmacy or healthcare centre) (Section 2.10.8)

IP for clinical operations



Investigator retains full **responsibility for IP management** even when external dispensing/distribution modes are used.



SOPs must cover participant-location dispensing, shipping, return, and link to product accountability records.



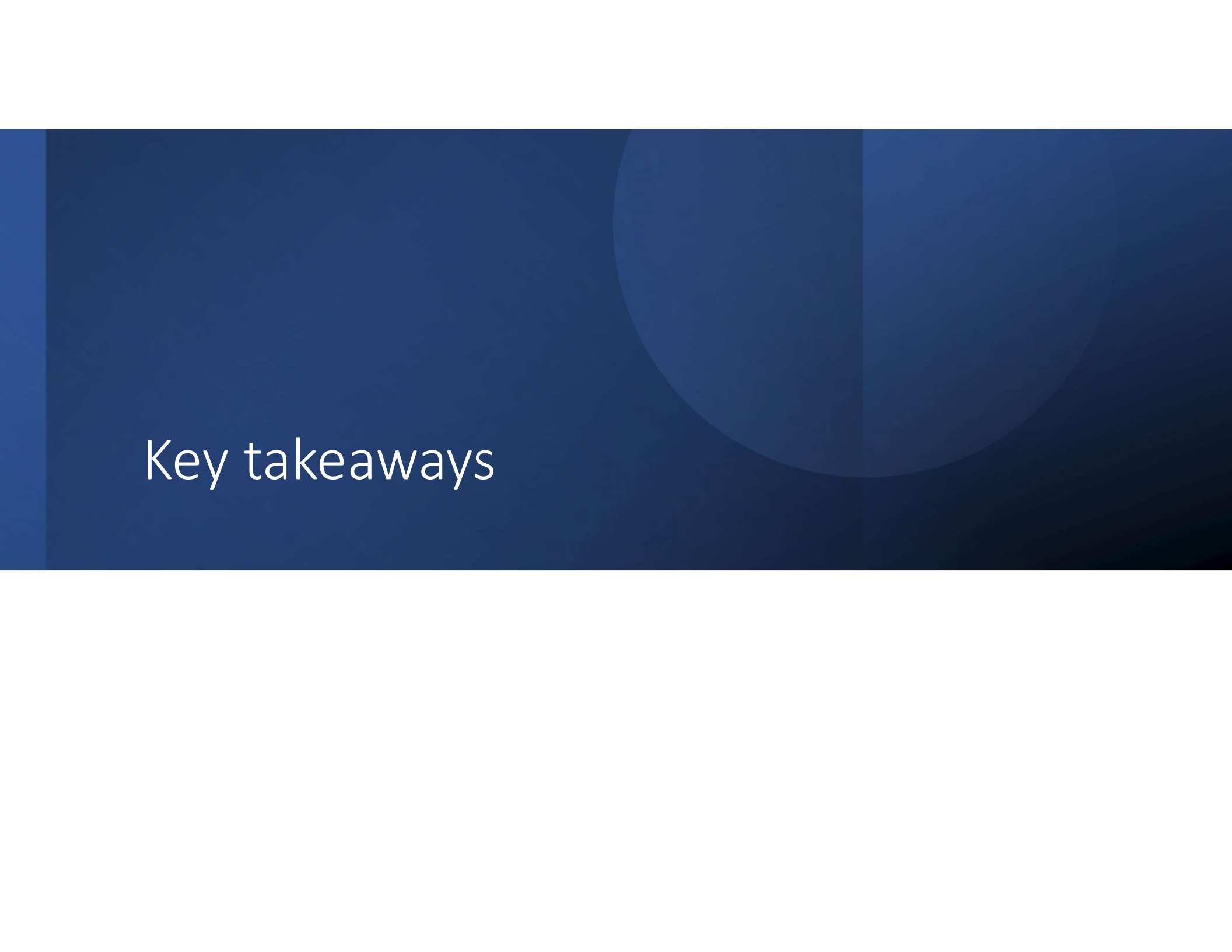
Monitoring plans must include risk-based oversight of IP workflows outside the site pharmacy.



Documentation must capture the **full lifecycle of IP** (shipment → dispensing → return/destruction) with traceability and audit trail consistent with data integrity principles.



Sites may need to train local pharmacies or home-care services, ensure documentation, delegation logs and oversight mechanisms.



Key takeaways

E6 (R3) recognizes that

Oversight now happens through **data flow**, not just site visits

Participant interaction extends **beyond physical locations**

Quality management must evolve to match this **digital reality**



E6 R3 introduces new expectations for

Vendor oversight

Quality by design

Data governance

Systems validation

All directly impacting service providers that supply devices, manage logistics, or operate digital platforms



ICH E6(R3): Key takeaways

Principles-based guidance rather than prescriptive requirements

Quality by Design (QbD) – quality built into systems and decisions

Risk-proportionate approaches – focus where it matters most

Supports innovation – digital tools, connected devices, and DCTs

Transparency and traceability of data

Sponsor and investigator **shared** accountability

Participant at the forefront

Moving from Regulation to Operations



**Participant at the
forefront**



**Shared sponsor—
investigator accountability**



**Focus on what's
Critical to Quality (CtQ)**



Build systems that embody QbD



**Risk-based oversight &
monitoring**



**Transparency and traceability
across data and systems**



Flexibility is not 'freedom'
from responsibility

If the new E6 is about
proportionate quality...
What comes next ?

Thank you!

Questions ?