ICH / GCP Mastery

Course Reference Document

Companion to the interactive online programme

Eight modules · Regulatory currency through June 2026

PROGRAMME COVERAGE

- ICH E6(R3) Good Clinical Practice — Principles, Annex 1, and Annex 2 (Step 4, June 2026)
- Global regulatory landscape: FDA (US), EMA (EU), MHRA (UK), Health Canada, PMDA (JP), NMPA (CN), TGA (AU), HSA (SG), MFDS (KR)
- Roles and responsibilities of sponsors, CROs, investigators, IRBs/IECs, DSMBs, regulators
- Quality and risk: QbD, RBQM, ALCOA+, 21 CFR Part 11, EU Annex 11, computer system validation
- Pharmacovigilance: AE/SAE/SUSAR taxonomy, reporting timelines, DSUR, safety oversight
- Trial Master File (TMF) management and regulatory inspection readiness

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How to Use This Document

This reference is a print-friendly companion to the interactive online programme delivered at your Aurelyn AI Clinical training portal. It mirrors the structure of the eight learning modules, provides the full text of the learning objectives, summarises the regulatory content covered in the course, and supplies primary-source links so that you can read original guidance from regulators. It is suitable as a self-study handbook, a refresher for experienced practitioners, and as a desk reference during the working day.

Learning objectives are framed using **Bloom's revised taxonomy** (Remember · Understand · Apply · Analyse · Evaluate · Create). Each module begins with explicit objectives at named taxonomy levels and concludes with a stated outcome — a behavioural expectation that you should be able to demonstrate after completing the lesson.

Important disclaimer. The information in this document is educational and illustrative. It is current as of the date of publication and reflects the state of guidance as adopted at the ICH Assembly held in Rio de Janeiro on 3 June 2026. It is not legal, regulatory, or medical advice. Always consult the operative version of any guideline published by the appropriate regulator before making operational, compliance, or commercial decisions.

MODULE 01

Foundations of Good Clinical Practice

LEARNING OBJECTIVES

• **Remember:** Identify the key ethical events that shaped modern clinical research, including the Nuremberg Code (1947), the Declaration of Helsinki (1964 and revisions), the Tuskegee Syphilis Study (1932–1972), and the Belmont Report (1979).

• **Understand:** Explain the three Belmont principles — respect for persons, beneficence, and justice — and how each maps to a contemporary GCP operational practice.

• **Apply:** Use the ICH guideline categories (Efficacy, Safety, Quality, Multidisciplinary) to correctly classify a given guideline by topic.

Outcome: Explain why GCP exists, what problem it solves, and how the regulatory architecture is organised.

1.1 Why GCP Exists

Good Clinical Practice is the body of international ethical and scientific quality standards for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Its purpose is to provide public assurance that the rights, safety, and well-being of trial participants are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that clinical-trial data are credible.

GCP did not emerge in a single document. It is the synthesis of nearly eighty years of ethical reflection, scientific failure, and regulatory reform — beginning with the trials of Nazi physicians at Nuremberg and continuing through the Tuskegee revelations, the Belmont Report, and the formation of the International Council for Harmonisation in 1990.

1.2 Timeline of Ethical Foundations

Milestone	Significance
1947 — Nuremberg Code	The first international codification of research ethics. Established voluntary consent as absolutely essential and prohibited research where serious injury or death was anticipated.
1964 — Declaration of Helsinki	Adopted by the World Medical Association. Articulated the duty of physicians to safeguard subject welfare and established principles that physician-researchers must follow. Revised most recently in October 2024.
1932–1972 — Tuskegee	The 40-year US Public Health Service study of untreated syphilis in Black men, conducted without informed consent. Its disclosure led directly to the National Research Act of 1974.
1979 — Belmont Report	Issued by the US National Commission for the Protection of Human Subjects. Codified three principles — respect for persons, beneficence, and justice — that underpin all subsequent GCP guidance.
1990 — ICH Formed	The International Conference on Harmonisation (now Council) was established by regulators and industry from the EU, Japan, and the US to harmonise technical requirements for pharmaceutical products.

1996 — ICH E6(R1)	The first consolidated ICH GCP guideline. Adopted into law in the EU, recognised by FDA in 1997, and accepted globally as the de facto baseline for the next 20 years.
2016 — ICH E6(R2)	Introduced risk-based monitoring, quality management systems, expanded sponsor oversight of CROs, and explicit data-governance expectations.
2025–2026 — ICH E6(R3)	A fundamental redraft. Principles separated from operational annexes. Adopted 6 Jan 2025 (Step 4). Annex 2 (non-traditional trials) adopted Step 4 at Rio Assembly on 3 Jun 2026.

1.3 The Three Belmont Principles

Every operational requirement of GCP — from informed consent to investigator qualifications to vulnerable-population safeguards — can be traced back to one of the three Belmont principles. Internalising these three ideas is the most efficient way to develop GCP intuition.

Principle	Definition and GCP Expression
Respect for Persons	Treat individuals as autonomous agents and provide additional protection to those with diminished autonomy. **GCP expression:** informed consent, the right to withdraw, protection of vulnerable populations (children, pregnant participants, prisoners, individuals with impaired cognition).
Beneficence	Maximise possible benefits and minimise possible harms. **GCP expression:** favourable risk-benefit assessments, qualified investigators, validated systems, robust adverse-event reporting, data and safety monitoring boards (DSMBs).
Justice	Distribute the benefits and burdens of research fairly. **GCP expression:** inclusion and exclusion criteria that do not unfairly exclude or burden specific populations, equitable subject selection, attention to diverse representation.

1.4 The ICH Guideline Architecture

ICH publishes guidelines in four topical categories. GCP itself sits in the **Efficacy** series as E6. Understanding the broader architecture helps you locate adjacent guidance when designing or operating a trial.

Category	Scope	Examples
E — Efficacy	Clinical trial design, conduct, safety, and reporting	E6 (GCP), E8 (general considerations), E9 (statistical principles), E3 (study reports)
S — Safety	Non-clinical toxicology and pharmacology	S7A (safety pharmacology), S9 (oncology nonclinical)
Q — Quality	Chemistry, manufacturing, and controls	Q8 (pharmaceutical development), Q9 (quality risk management), Q10 (PQS)

M — Multidisciplinary	Topics that cross categories	M4 (CTD), M11 (clinical study protocol template), M14 (RWD)

MODULE 02

ICH E6(R3) Principles and Annex 1

LEARNING OBJECTIVES

- **Remember:** List the 11 principles of ICH E6(R3) and recognise the structural difference between Principles, Annex 1, and Annex 2.
- **Understand:** Explain Quality by Design (QbD), Critical to Quality (CtQ) factors, and the concept of proportionality in trial oversight.
- **Apply:** Distinguish a CtQ factor from a non-critical factor in a worked scenario and justify the classification.
- **Analyse:** Map a given operational decision (for example, the level of source data verification) to the underlying principle(s) and CtQ factor it addresses.

Outcome: Use the E6(R3) principles and Annex 1 fluently as the operational baseline for any interventional trial.

2.1 Structure of E6(R3)

E6(R3) is organised in three layers. The **Principles** are short, durable, and apply to every clinical trial regardless of design. **Annex 1** covers interventional trials and contains the operational requirements that were previously the bulk of E6(R2). **Annex 2**, adopted at Step 4 on 3 June 2026, extends the framework to non-traditional designs — decentralised, pragmatic, and real-world-data-enabled trials.

2.2 The 11 Principles

Each principle is intentionally written at a high level of abstraction so it can apply across the full diversity of trial types. Memorising them in plain language is more valuable than memorising their numbering.

Principle	Plain-language statement
P1 — Ethics	Trials must be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki.
P2 — Informed Consent	Freely given informed consent must be obtained from every subject prior to clinical trial participation.
P3 — Scientific Soundness	Trials must be scientifically sound and described in a clear, detailed protocol.
P4 — Benefit-Risk	The anticipated benefits to the individual subject and society must justify the foreseeable risks.
P5 — Investigator Qualifications	Investigators must be qualified by education, training, and experience for the tasks they perform.
P6 — IRB/IEC Review	A trial must receive favourable opinion or approval by an independent ethics committee before it begins.
P7 — Quality by Design	Quality must be built into the scientific and operational design of a trial — not inspected in at the end.

P8 — Risk Proportionality	The systems, processes, and oversight applied to a trial should be proportionate to the risks to participants and to the reliability of results.
P9 — Data Quality and Integrity	Trial-related information must be recorded, handled, and stored in a way that allows accurate reporting, interpretation, and verification (ALCOA+).
P10 — Subject Privacy	The confidentiality of records that could identify subjects must be protected, respecting privacy and confidentiality rules in accordance with applicable regulatory requirements.
P11 — Investigational Product Quality	Investigational products must be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice (GMP) and used in accordance with the approved protocol.

2.3 Quality by Design and Critical-to-Quality Factors

QbD is the discipline of identifying, at the design stage, the factors most likely to affect participant safety and the reliability of trial results, and then deliberately constructing processes that protect those factors. The factors themselves are called **Critical to Quality (CtQ) factors**. Anything that is not a CtQ factor is, by definition, a candidate for reduced oversight.

A CtQ factor has three characteristics: (1) an error in it would meaningfully harm participants or the integrity of the primary endpoint; (2) it is feasible to monitor; and (3) reasonable controls exist that can mitigate the risk. Identifying CtQ factors is a team activity that should involve clinical, operational, data, statistical, and quality functions.

Worked example — first-in-human oncology Phase 1

Factor	Classification and rationale
Eligibility criteria for organ-function thresholds	**CtQ.** Errors directly expose participants to unsafe dosing. Mitigation: independent eligibility review for first three subjects; central laboratory.
DLT assessment window adherence	**CtQ.** Errors corrupt the dose-escalation decision. Mitigation: protocol-mandated visit windows, real-time medical monitor review.
Concomitant-medication coding consistency	**Not CtQ.** Useful for analyses but does not change safety decisions. Mitigation: standard data review at database lock.
Quality-of-life questionnaire timing within ±3 days	**Not CtQ.** Secondary endpoint; small variation tolerable. Mitigation: site training; no extra monitoring.

2.4 Proportionality in Practice

Proportionality is the operational consequence of QbD. It says: do not apply the same intensity of monitoring, source data verification, and documentation to everything. Focus your effort where it matters. In practical terms, a sponsor can defensibly reduce on-site monitoring frequency for a well-controlled, low-risk study while increasing it for high-risk procedures or first-in-human cohorts — provided the rationale is documented in the monitoring plan and connected to the CtQ factors identified during design.

MODULE 03

ICH E6(R3) Annex 2 — Non-Traditional Trials

LEARNING OBJECTIVES

- **Remember:** Identify Annex 2's adoption milestone (Step 4 on 3 June 2026) and its three main trial archetypes: decentralised (DCT), pragmatic, and real-world-data-enabled.
- **Understand:** Explain how the E6(R3) principles apply to a fully decentralised trial without modification, and where additional operational guidance is needed.
- **Apply:** For a given trial concept, decide whether DCT elements, pragmatic design, or RWD use are appropriate, and articulate the GCP implications.
- **Evaluate:** Critique a fit-for-purpose justification for using real-world data as a primary data source against the Annex 2 framework.

Outcome: Operate Annex 2 designs confidently and articulate where the boundaries of fit-for-purpose data lie.

3.1 Why Annex 2 Was Needed

The 2020–2022 period demonstrated, at global scale, that many trial activities traditionally performed at investigator sites could be performed remotely without compromising participant safety or data quality. Telehealth visits, direct-to-participant investigational product shipment, mobile phlebotomy, electronic informed consent (eConsent), and patient-reported outcomes via wearables all became routine. At the same time, regulators were increasingly receiving submissions that used real-world data — from electronic health records, claims, registries, and devices — as supporting or primary evidence. The need for unambiguous GCP guidance on these activities became acute.

Annex 2 was developed under ICH's expedited workstream and adopted at Step 4 on 3 June 2026 at the Rio de Janeiro Assembly. It does not replace Annex 1. It extends the framework to additional trial types and clarifies how the principles apply in non-traditional contexts.

3.2 The Three Archetypes

Archetype	Definition	Common applications
Decentralised (DCT)	Some or all trial activities occur outside traditional investigator sites: telehealth visits, home health, mobile phlebotomy, direct-to-participant IP shipment, eConsent, sensor-based data.	Pivotal CVD outcome trials using home visits and remote ECG; oncology supportive-care studies with telehealth follow-up.
Pragmatic	Conducted in routine-care settings using usual-care infrastructure. Eligibility is broad, interventions are administered as in normal practice, outcomes are clinically meaningful.	Comparative effectiveness studies for established interventions; cluster-randomised trials in primary care.
RWD-enabled	Real-world data (EHR, claims, registries, devices) is used as a data source — either to construct external control arms, to identify endpoints, or as the primary evidence source.	Single-arm oncology trials with EHR-derived external controls; safety-surveillance studies using claims data.

3.3 The Fit-for-Purpose Framework for RWD

RWD is acceptable as a primary or supportive evidence source if — and only if — it is fit for the purpose for which it is being used. This is not a binary judgement; it is a structured assessment across four dimensions, each of which must be documented in a fit-for-purpose justification submitted with the protocol.

Dimension	What it means in practice
Relevance	Does the dataset capture the population, intervention, comparators, outcomes, and timing relevant to the research question? Are key variables present and well-defined?
Reliability	Has the data been generated through processes with adequate quality controls? Are coding, linkage, and missingness rates documented? Has the data been validated against an external source?
Provenance	Is the original source of each data element traceable? Are changes and corrections logged? Does the data meet ALCOA+ expectations?
Transparency	Is the cohort definition, the analysis plan, and any data-curation step pre-specified and documented in a way that would allow another team to reproduce the study?

Worked example — REACT-AF style decentralised pragmatic trial

Consider a Phase 4 cardiovascular trial comparing two approved direct oral anticoagulants in patients with non-valvular atrial fibrillation. Eligible participants are identified via EHR within a participating health system, consented electronically through a patient portal, randomised, and managed entirely through their existing primary-care physician. Endpoints — stroke, systemic embolism, major bleeding — are ascertained from the EHR and a national claims database with adjudication by a blinded committee. There are no in-person study visits.

This design combines all three archetypes. The Annex 2 obligations are: a documented data-source selection rationale; pre-specified algorithms for case ascertainment; safety oversight independent of the routine clinical team; and an eConsent process validated for the populations and devices expected. None of the E6(R3) principles are weakened — participants must still consent freely, the trial must still be ethical and scientifically sound, and data must still satisfy ALCOA+.

MODULE 04

Roles and Responsibilities Across the Trial Ecosystem

LEARNING OBJECTIVES

- **Remember:** Identify each major stakeholder in a clinical trial — sponsor, CRO, investigator, IRB/IEC, DSMB, regulator — and their core responsibilities.
- **Understand:** Explain the difference between delegation and transfer of obligations between sponsor and CRO, and why the sponsor's accountability is not transferable.
- **Apply:** Given a specific operational task (for example, safety database management), identify which stakeholder is responsible, accountable, consulted, and informed (RACI).

Outcome: Allocate trial responsibilities cleanly and explain why a specific party owns a specific task.

4.1 Sponsor

The sponsor is the individual, company, institution, or organisation that takes responsibility for the initiation, management, and financing of the clinical trial. The sponsor's accountability encompasses the trial's scientific quality, data integrity, participant safety, regulatory submissions, oversight of all parties to whom tasks are delegated, and final responsibility for the Trial Master File. The sponsor may delegate **tasks** to a contract research organisation but cannot delegate **accountability**. In every regulatory inspection, the sponsor is the entity ultimately answerable.

4.2 Contract Research Organisation (CRO)

A CRO is an organisation contracted by a sponsor to perform one or more of the sponsor's trial-related duties. Delegations must be documented in a written agreement that specifies the precise scope of services. The sponsor retains oversight obligations: written procedures for vendor qualification, ongoing performance monitoring, escalation paths for issues, and audit rights.

4.3 Investigator and Investigator Site

The investigator is the individual responsible for the conduct of a clinical trial at a trial site. Where the trial is conducted by a team, the investigator is the responsible leader of the team and may be called the **principal investigator**. Investigator obligations include: ensuring compliance with the protocol; obtaining informed consent; medical care of participants; reporting adverse events; preparing and retaining the Investigator Site File (ISF); ensuring qualified, trained, and delegated study staff; and ensuring data accuracy in the case report form.

4.4 Institutional Review Board / Independent Ethics Committee

An IRB or IEC is an independent body whose responsibility is to ensure the protection of the rights, safety, and well-being of human subjects in a trial. The committee reviews the protocol, the informed-consent materials, advertisements, the investigator's qualifications, and the suitability of facilities. It also conducts continuing review at intervals appropriate to the degree of risk. In the EU under CTR 536/2014, ethics review is integrated with regulatory review through the Clinical Trials Information System (CTIS).

4.5 Data Safety Monitoring Board (DSMB / DMC)

A DSMB — sometimes called a Data Monitoring Committee — is an independent group of experts that monitors accumulating safety and efficacy data during a trial. The DSMB is separate from the sponsor and investigators and provides recommendations to continue, modify, or stop the trial. DSMBs are typical for blinded, randomised studies with mortality or major morbidity endpoints; they are not required for every trial but are expected for any trial where the accumulating data could meaningfully change the benefit-risk profile during the study.

4.6 Regulators

Regulators issue trial authorisations, inspect sites and sponsors, and enforce GCP through their national legal frameworks. The major actors covered in Module 5 are the FDA (United States), the EMA together with national competent authorities under the EU framework, the MHRA (United Kingdom), Health Canada, the PMDA (Japan), the NMPA (China), the TGA (Australia), the HSA (Singapore), and the MFDS (Republic of Korea).

MODULE 05

Global Regulatory Landscape

LEARNING OBJECTIVES

• **Remember:** Identify the major regulators and their core GCP-relevant instruments in the United States, the European Union, the United Kingdom, Canada, Japan, China, Australia, Singapore, and Korea.
• **Understand:** Explain how the EU Clinical Trials Regulation (CTR 536/2014) changed the submission, ethics review, and transparency framework compared to the previous Directive.
• **Apply:** Choose the correct US Code of Federal Regulations citation for a given operational scenario (informed consent, IRB review, IND requirements, electronic records).
• **Analyse:** Identify the GCP-equivalent jurisdiction for a multi-country trial and the documents required for each.

Outcome: Speak with confidence about each major jurisdiction's framework and where to find the operative text.

5.1 United States — FDA

Instrument	Scope
21 CFR Part 11	Electronic records and electronic signatures.
21 CFR Part 50	Protection of human subjects — informed consent.
21 CFR Part 56	Institutional Review Boards.
21 CFR Part 312	Investigational New Drug Application (IND).
21 CFR Part 314	Applications for FDA approval to market a new drug (NDA / sNDA).
21 CFR Part 812	Investigational Device Exemptions (IDE).
FDA E6(R3) guidance	Final guidance issued 8–9 September 2025 under Docket FDA-2023-D-1955. Provides FDA's expectations for application of ICH E6(R3) in trials conducted in the United States or supporting US submissions.

5.2 European Union — EMA and CTR 536/2014

Clinical Trials Regulation (EU) No 536/2014 came into application on 31 January 2022 and was fully operational at the end of the three-year transition period in January 2025. It replaced the Clinical Trials Directive 2001/20/EC with a single submission portal — the Clinical Trials Information System (CTIS) — and harmonised assessment timelines across the EU. ICH E6(R3) became effective in the EU on 23 July 2025.

5.3 United Kingdom — MHRA

The MHRA issued an annotated version of ICH E6(R3) on 12 January 2026, taking effect immediately. Trials in the UK are governed by the Medicines for Human Use (Clinical Trials) Regulations 2004 as amended, with the MHRA exercising regulatory authority and the Health Research Authority (HRA) coordinating ethics review.

5.4 Canada — Health Canada

Health Canada adopted ICH E6(R3) with an effective date of 1 April 2026 under Division 5 of the Food and Drug Regulations. Clinical Trial Applications are submitted to the Health Products and Food Branch.

5.5 Japan — PMDA

The Pharmaceuticals and Medical Devices Agency administers Japan's J-GCP under the Pharmaceuticals and Medical Devices Act (PMD Act). J-GCP follows ICH E6 with country-specific operational requirements for the head of the investigational site and the in-house GCP review committee.

5.6 Other Asia-Pacific Jurisdictions

Authority	Framework
China — NMPA	National Medical Products Administration. China-GCP took effect in 2020 and aligns substantially with ICH E6. Submissions go through the Center for Drug Evaluation (CDE).
Australia — TGA	Therapeutic Goods Administration. Clinical trials are conducted under the Clinical Trial Notification (CTN) or Clinical Trial Approval (CTA) scheme.
Singapore — HSA	Health Sciences Authority. Trials require a Clinical Trial Authorisation under the Health Products Act.
Republic of Korea — MFDS	Ministry of Food and Drug Safety. KGCP follows ICH E6 with local operational requirements; submissions through MFDS clinical trial approval.

MODULE 06

Quality, Risk, and Data Governance

LEARNING OBJECTIVES

- **Remember:** List the components of ALCOA+ (Attributable, Legible, Contemporaneous, Original, Accurate, plus Complete, Consistent, Enduring, Available).
- **Understand:** Explain Risk-Based Quality Management (RBQM) and how it operationalises QbD and CtQ from Module 2.
- **Apply:** Map a finding from a data review (for example, late entries in a paper diary) to the ALCOA+ component(s) it violates.
- **Analyse:** Distinguish 21 CFR Part 11 and EU Annex 11 expectations and identify where they differ in practice for the same system.

Outcome: Operate confidently in the day-to-day language of quality, risk, and data integrity.

6.1 Risk-Based Quality Management (RBQM)

RBQM is the operational expression of E6(R3)'s principles of Quality by Design and proportionality. It is a continuous, iterative process consisting of four activities: identify the critical-to-quality factors; assess the risks to those factors; control them through proportionate processes and monitoring; and communicate and review the risks throughout the trial. The output of RBQM is not a single document; it is a living set of decisions — captured in the integrated quality plan, the monitoring plan, the data management plan, and the risk register — that together demonstrate that the sponsor is focusing oversight where it matters.

6.2 ALCOA+ — The Data-Integrity Acronym

Component	What it means
Attributable	It must be clear who recorded the data and when.
Legible	It must be readable and permanent.
Contemporaneous	It must be recorded at the time of observation.
Original	The first record (or a verified true copy) must be preserved.
Accurate	It must be free from errors and reflect the observation.
Complete	All data, including repeats and metadata, must be present.
Consistent	Sequence and dating must be coherent across the record.
Enduring	It must be preserved for the required retention period.
Available	It must be retrievable for review or audit.

6.3 21 CFR Part 11 and EU Annex 11

FDA's 21 CFR Part 11 and the EU's Annex 11 of the GMP guidelines both govern electronic records and electronic signatures used in regulated activities — including clinical trials. The two are largely compatible. Both require validated systems, audit trails capturing user, action, and timestamp, secure user authentication and authorisation, controlled changes to records (changes must not obscure prior values), and procedures for backup, archive, and disaster recovery. EU Annex 11 puts additional emphasis on the user organisation's responsibility for the supplier of the system, documented through a quality agreement.

6.4 Computer System Validation (CSV)

CSV is the documented process by which a system is shown to consistently produce a result meeting predetermined specifications. The depth of validation should be proportionate to the system's risk to participant safety and data integrity — a CTMS used to track milestones is not validated to the same depth as an eCOA used to capture the primary efficacy endpoint. The GAMP 5 framework (ISPE) is the dominant industry methodology and is consistent with both Part 11 and Annex 11 expectations.

MODULE 07

Safety Reporting and Pharmacovigilance

LEARNING OBJECTIVES

• **Remember:** Define adverse event (AE), adverse reaction (AR), serious adverse event (SAE), suspected unexpected serious adverse reaction (SUSAR), and individual case safety report (ICSR).
• **Understand:** Explain SUSAR reporting timelines (7 days for fatal/life-threatening, 15 days for other) and the destinations for each region.
• **Apply:** Given a case description, classify it correctly across the AE / SAE / SUSAR taxonomy and identify the reporting obligations.

Outcome: Make safety reporting decisions confidently and explain the boundaries between the categories.

7.1 The Safety Taxonomy

Term	Definition
AE — Adverse Event	Any untoward medical occurrence in a participant administered an investigational product. Causality is not required — every AE is recorded regardless of whether it is believed to be related to the product.
AR — Adverse Reaction	An AE for which there is a reasonable possibility of a causal relationship with the investigational product. Determined by the investigator and/or sponsor.
SAE — Serious Adverse Event	An AE that results in death, is life-threatening, requires hospitalisation, results in persistent or significant disability, is a congenital anomaly, or is otherwise medically important. 'Serious' is a regulatory term, not a severity assessment.
SUSAR — Suspected Unexpected Serious Adverse Reaction	A serious AR that is not consistent with the applicable product information (the Investigator's Brochure for an unapproved product, or the SmPC/label for an approved product). SUSARs are individually reportable to regulators in strict timelines.
ICSR — Individual Case Safety Report	The structured electronic submission used to report SUSARs to regulators, typically in E2B(R3) format.

7.2 SUSAR Reporting Timelines

Category	Timeline
Fatal or life-threatening SUSAR	Initial report within **7 calendar days** of the sponsor first becoming aware. Follow-up information within a further 8 days (total 15 days).
All other SUSARs	Initial report within **15 calendar days** of the sponsor first becoming aware.

7.3 Reporting Destinations

Region	Destination
United States — FDA	MedWatch / FAERS via FDA Gateway in E2B(R3) format under 21 CFR Part 312 IND safety reporting requirements.
European Union	EudraVigilance (EVCTM module for clinical trials) as ICSRs in E2B(R3). Mandated under CTR 536/2014.
United Kingdom	MHRA via the ICSR submission portal. Aligned with E2B(R3).
Other jurisdictions	Each regional authority maintains an equivalent destination — Health Canada Vigilance, PMDA, NMPA, TGA, HSA, MFDS — generally accepting E2B(R3) submissions.

7.4 The DSUR — Development Safety Update Report

ICH E2F defines the Development Safety Update Report — an annual cumulative review of the safety profile of an investigational product. The DSUR is submitted to all regulators where the product is under investigation. It is the primary mechanism by which the cumulative benefit-risk profile is communicated, contrasted with the per-case SUSAR reporting described above. The DSUR data-lock point is typically the anniversary of the first regulatory authorisation, with submission within 60 days of that date.

MODULE 08

Trial Master File and Inspection Readiness

LEARNING OBJECTIVES

- **Remember:** Distinguish the Sponsor TMF (sTMF) from the Investigator Site File (ISF) and identify the DIA TMF Reference Model v3.3.
- **Understand:** Explain the 'contemporaneous, complete, and inspection-ready' standard and what that requires of day-to-day TMF operations.
- **Apply:** For a given trial activity, identify the artifact(s) that must be filed in the TMF and which TMF zone they belong to.
- **Analyse:** Read a regulatory inspection finding (for example, FDA Form 483) and identify the underlying TMF or process gap that produced it.

Outcome: Treat TMF management as a continuous process — not an end-of-trial scramble — and explain why.

8.1 Sponsor TMF vs Investigator Site File

File	Description
Sponsor TMF (sTMF)	Owned by the sponsor. Demonstrates the conduct of the trial and the quality of the data generated. Includes regulatory submissions, protocols, oversight records, safety reports, monitoring reports, quality records, vendor management, statistical and clinical study reports.
Investigator Site File (ISF)	Owned by the investigator. Demonstrates the conduct of the trial at the site. Includes the investigator-relevant essential documents — signed protocol and amendments, IRB approvals, signed informed consents (or a log thereof), delegation log, training records, source documents, investigator brochure receipts, drug accountability records.

8.2 The DIA TMF Reference Model

The DIA TMF Reference Model is an open-source taxonomy maintained by the Drug Information Association. Version 3.3 organises trial documents into **11 zones** (for example, Trial Management, Central Trial Documents, Regulatory, IRB/IEC and other Approvals, Site Management, Investigational Product, Safety Reporting, Central and Local Testing, Third Parties, Data Management, Statistics), which are further divided into **48 sections** containing more than **249 individual artifacts**. Use of the Reference Model is not mandatory but is the de facto industry standard and is recognised by all major regulators.

8.3 Inspection Readiness as a Continuous Discipline

The most important thing a quality function can do for inspection readiness is to refuse to treat it as an event. Inspections occur with little notice. The artifacts that an inspector reviews — monitoring reports, signed consents, training records, delegation logs, deviations and CAPAs, safety reports, vendor oversight records — are exactly the artifacts that should already be complete and current in the day-to-day operation of the trial. Five disciplines, applied continuously, materially reduce inspection risk:

- **Contemporaneous filing.** Documents are filed as soon as they are generated or received, not in retrospective filing campaigns.
- **Quality control on intake.** Every artifact is reviewed against a checklist for completeness and correctness before filing.
- **Periodic TMF health reviews.** Sponsor quality reviews a sample of the TMF on a scheduled cadence — at minimum, before every major milestone.
- **Site-level mirror.** The sponsor maintains visibility into the ISF at each site, either through electronic ISF integration or through monitoring-visit verification.
- **Mock inspections.** Periodic mock inspections — internal or external — test both the artifacts and the people. Findings are tracked through the CAPA system.

8.4 Common FDA Form 483 Findings

The patterns below are recurring observations from FDA bioresearch monitoring inspections of sponsors and sites. Each maps to a TMF or process discipline that, if applied consistently, would have prevented the finding.

Finding pattern	Underlying gap and mitigation
Failure to follow the protocol	Deviations not recorded; eligibility criteria not enforced. Mitigation: protocol training, deviation log discipline, monitoring focus on inclusion/exclusion.
Inadequate informed consent	Wrong version used; signature dates not contemporaneous; assent missing for paediatric subjects. Mitigation: ICF version-control register; consent verification at every monitoring visit.
Inadequate investigator oversight	Tasks performed by unqualified staff; delegation log incomplete. Mitigation: delegation log review at every monitoring visit.
Inaccurate or incomplete records	Source data missing or contradicting the eCRF. Mitigation: source data verification proportionate to CtQ; query resolution discipline.
Inadequate drug accountability	IP receipt, dispensing, and return records do not reconcile. Mitigation: pharmacy oversight; IP accountability reconciliation at every monitoring visit and at close-out.

Glossary of Key Terms and Acronyms

ADR	Adverse Drug Reaction — an unwanted effect of a marketed medicinal product.
AE	Adverse Event — any untoward medical occurrence in a clinical trial participant.
ALCOA+	Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring, Available.
Annex 1	ICH E6(R3) Annex 1 — operational requirements for interventional trials.
Annex 2	ICH E6(R3) Annex 2 — additional considerations for non-traditional trials (Step 4, June 2026).
AR	Adverse Reaction — an AE assessed as having a causal relationship to the investigational product.
Audit Trail	A secure, computer-generated, time-stamped electronic record showing user, action, and timestamp.
Belmont Report	1979 US report establishing respect for persons, beneficence, and justice as ethical principles for research.
Bloom's Taxonomy	Educational classification of cognitive objectives: Remember, Understand, Apply, Analyse, Evaluate, Create.
CAPA	Corrective and Preventive Action — quality-system response to issues.
CDISC	Clinical Data Interchange Standards Consortium — global non-profit defining clinical data standards (SDTM, ADaM, USDM).
CFR	Code of Federal Regulations — codified US federal rules.
CIOMS	Council for International Organizations of Medical Sciences — international body for biomedical research ethics guidelines.
CRO	Contract Research Organisation.
CSV	Computer System Validation.
CtQ	Critical to Quality — factor identified as essential to participant safety or trial-result reliability.
CTIS	Clinical Trials Information System — EU portal for trial submissions under CTR 536/2014.
CTR	Clinical Trials Regulation — EU Regulation (EU) No 536/2014.
DCT	Decentralised Clinical Trial.
DSMB	Data Safety Monitoring Board (also called DMC, Data Monitoring Committee).
DSUR	Development Safety Update Report — annual ICH E2F safety summary.
EHR	Electronic Health Record.
EMA	European Medicines Agency.
ETMF	Electronic Trial Master File.

EU CTR	EU Clinical Trials Regulation 536/2014, in force from 31 January 2022.
FDA	United States Food and Drug Administration.
GAMP 5	ISPE Good Automated Manufacturing Practice framework v5 — industry standard for computer system validation.
GCP	Good Clinical Practice.
Helsinki Declaration	WMA Declaration of Helsinki — foundational ethical statement for medical research involving human subjects (current revision 2024).
HSA	Health Sciences Authority (Singapore).
ICF	Informed Consent Form.
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.
ICSR	Individual Case Safety Report — structured ICH E2B(R3) safety submission.
IEC	Independent Ethics Committee (European term, equivalent in function to an IRB).
IND	Investigational New Drug application (FDA, 21 CFR Part 312).
IRB	Institutional Review Board (United States term).
ISF	Investigator Site File.
J-GCP	Japan GCP, administered by PMDA under the PMD Act.
MFDS	Ministry of Food and Drug Safety (Republic of Korea).
MHRA	Medicines and Healthcare products Regulatory Agency (United Kingdom).
NDA	New Drug Application (FDA).
NMPA	National Medical Products Administration (China).
Nuremberg Code	1947 international codification of research ethics following the Nuremberg trials.
PMDA	Pharmaceuticals and Medical Devices Agency (Japan).
Pragmatic Trial	Trial conducted in routine-care settings, often with broad eligibility.
Part 11	21 CFR Part 11 — FDA regulation on electronic records and electronic signatures.
PV	Pharmacovigilance — science and activities concerned with detection, assessment, and prevention of adverse effects.
QbD	Quality by Design.
RBQM	Risk-Based Quality Management.
RWD	Real-World Data — data on health status or care delivery routinely collected from EHRs, claims, registries, devices.
RWE	Real-World Evidence — clinical evidence derived from RWD.
SAE	Serious Adverse Event.
SCORM	Sharable Content Object Reference Model — e-learning content packaging standard.

SmPC	Summary of Product Characteristics (EU labelling document).
Sponsor	The individual, company, institution, or organisation that takes responsibility for initiation, management, and financing of a clinical trial.
STMF	Sponsor TMF.
SUSAR	Suspected Unexpected Serious Adverse Reaction.
TGA	Therapeutic Goods Administration (Australia).
TMF	Trial Master File.
TMF Reference Model	DIA-maintained open taxonomy of trial documents (current v3.3 — 11 zones, 48 sections, 249+ artifacts).
Tuskegee	US Public Health Service study (1932–1972) of untreated syphilis in Black men conducted without informed consent.
USDM	CDISC Unified Study Definitions Model — machine-readable protocol representation.
WHO	World Health Organization.
WMA	World Medical Association — issuer of the Declaration of Helsinki.

Appendix A — Primary-Source Reference Library

Always consult the operative version of each guideline at the issuing regulator's website. Listed below are the canonical entry points.

ICH

- ICH official guideline portal — https://www.ich.org/page/efficacy-guidelines
- ICH E6(R3) Step 4 document — https://www.ich.org/page/efficacy-guidelines
- ICH E8(R1) — General Considerations for Clinical Studies — https://www.ich.org/page/efficacy-guidelines
- ICH E9(R1) — Statistical Principles / Estimands — https://www.ich.org/page/efficacy-guidelines
- ICH E2A — Safety Definitions and Reporting — https://www.ich.org/page/efficacy-guidelines
- ICH E2F — Development Safety Update Report — https://www.ich.org/page/efficacy-guidelines

United States — FDA

- 21 CFR Part 11 — Electronic Records / Signatures — https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-11
- 21 CFR Part 50 — Protection of Human Subjects — https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-50
- 21 CFR Part 56 — IRBs — https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-56
- 21 CFR Part 312 — IND Application — https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312
- FDA E6(R3) Final Guidance Docket FDA-2023-D-1955 — https://www.regulations.gov/docket/FDA-2023-D-1955

European Union — EMA

- CTR 536/2014 Full Text — https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32014R0536
- Clinical Trials Information System (CTIS) — https://euclinicaltrials.eu/
- EMA Clinical Trials page — https://www.ema.europa.eu/en/human-regulatory-overview/clinical-trials-human-medicines

United Kingdom — MHRA

- MHRA Clinical Trials page — https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency
- Health Research Authority (HRA) — https://www.hra.nhs.uk/

Canada — Health Canada

- Drugs and Health Products — Clinical Trials — https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/clinical-trials.html

Japan — PMDA

- PMDA English portal — https://www.pmda.go.jp/english/

Other APAC

- NMPA — China — https://english.nmpa.gov.cn/
- TGA — Australia — https://www.tga.gov.au/
- HSA — Singapore — https://www.hsa.gov.sg/

- MFDS — Republic of Korea — https://www.mfds.go.kr/eng/index.do

Standards Bodies and Ethics

- CDISC — https://www.cdisc.org/
- DIA TMF Reference Model — https://tmfrefmodel.com/
- WMA Declaration of Helsinki — https://www.wma.net/policies-post/wma-declaration-of-helsinki/
- Belmont Report — https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html
- ISPE GAMP 5 — https://ispe.org/publications/guidance-documents/gamp-5-guide-2nd-edition
- CIOMS International Ethical Guidelines — https://cioms.ch/

Appendix B — Regulatory Currency Snapshot (June 2026)

This snapshot reflects the state of guidance as of the date of publication. Verify all dates with the issuing regulator before making compliance decisions.

Item	Status
ICH E6(R3) Principles + Annex 1	Adopted Step 4 on 6 January 2025.
EMA — adoption of E6(R3)	Effective 23 July 2025.
Swissmedic — adoption of E6(R3)	Effective 15 August 2025.
FDA — E6(R3) Final Guidance	Issued 8–9 September 2025 (Docket FDA-2023-D-1955).
MHRA — annotated UK E6(R3)	Effective 12 January 2026.
Health Canada — adoption of E6(R3)	Effective 1 April 2026.
ICH E6(R3) Annex 2	Adopted Step 4 on 3 June 2026 at the Rio de Janeiro ICH Assembly. Covers decentralised, pragmatic, and RWD-enabled trials.
EU CTR 536/2014	Fully operational since January 2025 (transition complete).
Declaration of Helsinki	Current revision adopted October 2024 (WMA General Assembly).
DIA TMF Reference Model	Current version 3.3.

End of document. *For the interactive version of this programme — with knowledge checks, auto-saving progress, downloadable certificate of completion, and ongoing updates to regulatory currency — visit your Aurelyn AI Clinical training portal.*