

Unit 3: Clinical Trial Documentation, Monitoring and Adverse Drug Reactions

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3.1 Documentation: the essential documents

GCP's memory is paper, and its governing maxim is that if it was not documented, it was not done. The **essential documents** are those that individually and collectively permit evaluation of a trial's conduct and of the quality of the data produced: the protocol and its amendments, the investigator brochure, consent forms, ethics committee approvals and correspondence, regulatory permissions, investigator agreements and curricula vitae, product accountability records, case report forms and source documents, monitoring reports, safety reports, and the clinical study report, assembled in the trial master file. Preparation follows simple, examinable guidelines: documents are version controlled and dated, written in language their users understand, approved before use, and archived so that the trial can be reconstructed years later by an auditor or inspector who was never there.

3.2 The protocol

The **protocol** is the trial's constitution: the document that describes the objectives, design, methodology, statistical considerations and organization of the trial, fixed and approved before the trial begins. Its standard contents are:

Part of the protocol	What it fixes
Background and rationale	Why the trial is needed and what is already known
Objectives and endpoints	The primary and secondary questions and how success is measured
Design	Type of trial, arms, randomization, blinding, duration
Participants	Inclusion and exclusion criteria, recruitment, withdrawal rules
Treatment	Product, dose, schedule, compliance, prohibited medication
Assessments	Visits, procedures and measurements, with their timing
Safety	Adverse event definitions, recording and reporting procedures
Statistics	Sample size reasoning, analysis populations and methods
Ethics and administration	Consent, confidentiality, data handling, quality control, publication

Every later document answers to the protocol: the case report form collects exactly what it schedules, the monitor checks conduct against it, and the study report reports its questions. Deviations are therefore defined against the protocol, and amendments to it require the same ethics and regulatory approvals as the original before they take effect, urgent safety changes excepted.

3.3 The investigator brochure

The **investigator brochure (IB)** is the compilation of the clinical and nonclinical data on the investigational product that is relevant to its study in humans: the physical and pharmaceutical description, the animal pharmacology and toxicology, any human pharmacokinetic and earlier trial results, and a summary of known risks and anticipated benefits, ending in guidance to the investigator on recognizing and managing

adverse effects and overdoses. The sponsor prepares and updates it, at least annually or whenever significant new information appears, because the investigator's judgement at the bedside rests on it. Where the protocol is the plan of this trial, the IB is the dossier of everything known about the drug before this trial adds to it.

3.4 Case report forms

The **case report form (CRF)** is the printed or electronic document designed to record all of the protocol required information on each participant: eligibility, dosing, visit measurements, laboratory results, adverse events and outcomes. Good CRF design is a discipline of its own: one datum in one place, questions that cannot be misunderstood, no data collected that the protocol does not need, and a design that matches the source records from which coordinators transcribe. The electronic CRF (eCRF) inside an electronic data capture system adds edit checks at entry, an audit trail of every change, and controlled access; the rules of correction, date, sign, never obscure the original entry, apply in both media, because the CRF is a legal record of the trial.

3.5 The clinical study report

The **clinical study report (CSR)** is the trial's final, integrated account: a full description of the trial's planning, conduct, participant disposition, efficacy and safety results, statistical analysis and conclusions, in the structured format of ICH E3, with protocols, sample forms, investigator lists and key tables appended. It is written after database lock and unblinding, is signed by the sponsor's responsible medical officer, and becomes the primary source from which publications, licensing submissions and labelling statements are drawn. A trial that is never reported has, scientifically, not been run; the CSR is where the subject's first half discharges its duty to the patients of the second half.

3.6 Clinical trial monitoring

Monitoring is the act of overseeing the progress of a trial to ensure it is conducted, recorded and reported in accordance with the protocol, standard operating procedures, GCP and regulatory requirements. It is performed by **monitors** (clinical research associates) appointed by the sponsor, who act as the line of communication between sponsor and investigator. The monitor's cycle through a site is standard:

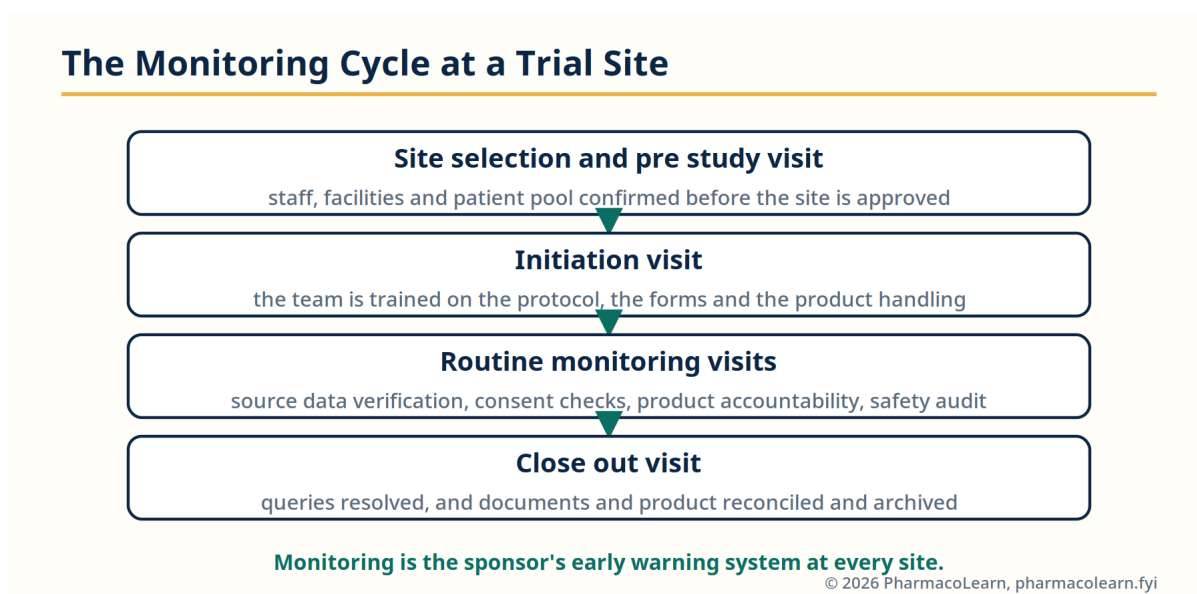


Figure: Monitoring follows a fixed cycle: qualify the site, initiate it, visit it regularly during the trial, and close it out.

At **selection and pre study visits** the monitor confirms the site's staff, facilities and patient pool. At the **initiation visit** the team is trained on protocol, forms and product handling before the first participant. At **routine monitoring visits** the monitor performs the craft's core act, **source data verification**: CRF entries are compared line by line with source documents, consent forms are checked for every participant, product accountability is reconciled, adverse event reporting is audited, and queries are raised for correction. At the **close out visit** outstanding data, documents and product are reconciled and archived. Monitoring reports after each contact document what was found; a monitor who finds a serious or persistent breach escalates it, because monitoring is the sponsor's early warning system, and Unit 3's next topic is its safety half.

3.7 Safety monitoring within the trial

Inside a trial, safety monitoring is the continuous collection, review and escalation of harm. Its vocabulary, fixed by ICH E2A, must be exact: an **adverse event (AE)** is any untoward medical occurrence in a participant administered a product, whether or not it is considered related to the product. Every AE is recorded; its relationship to the drug is assessed; and events meeting seriousness criteria or defying expectation follow the fast reporting path of section 3.9. For larger and longer trials, an independent **data safety monitoring board (DSMB)**, also called a data monitoring committee, reviews accumulating, often unblinded, safety and efficacy data at intervals and recommends whether the trial should continue, change or stop, protecting participants from an emerging imbalance no single site could see. Safety monitoring inside trials and pharmacovigilance outside them are one discipline at two scales, which is why the syllabus teaches them in one subject.

3.8 Adverse drug reactions: definition and types

An **adverse drug reaction (ADR)** is narrower than an adverse event: in the WHO definition, a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function. Causality, at least a reasonable possibility, separates a reaction from an event. ADRs are classified by the Rawlins and Thompson scheme extended to six types:

Type	Name and mechanism	Classic behaviour and example
A	Augmented: an exaggeration of the drug's known pharmacology	Dose related, predictable, common; bleeding on anticoagulants, hypoglycaemia on insulin
B	Bizarre: unrelated to known pharmacology, often immunological or idiosyncratic	Not dose related, unpredictable, uncommon but serious; penicillin anaphylaxis
C	Chronic: related to cumulative dose and duration	Appears with continued use; analgesic nephropathy, corticosteroid suppression of the adrenal axis
D	Delayed: appears long after exposure, sometimes in the next generation	Teratogenesis and carcinogenesis; thalidomide limb defects
E	End of use: withdrawal reactions on stopping	Rebound hypertension after abrupt clonidine withdrawal
F	Failure: unexpected failure of therapy	Contraceptive failure from enzyme inducing co medication

Side effects are unintended effects at normal doses related to the drug's pharmacological properties, often tolerable and sometimes useful; a side effect becomes spoken of as an ADR when it is noxious. Precision here is examinable: adverse event is the wider, causality free term of trial reporting; ADR asserts a suspected causal link; side effect describes mechanism, not harm.

3.9 Detection and reporting of ADRs in the trial setting

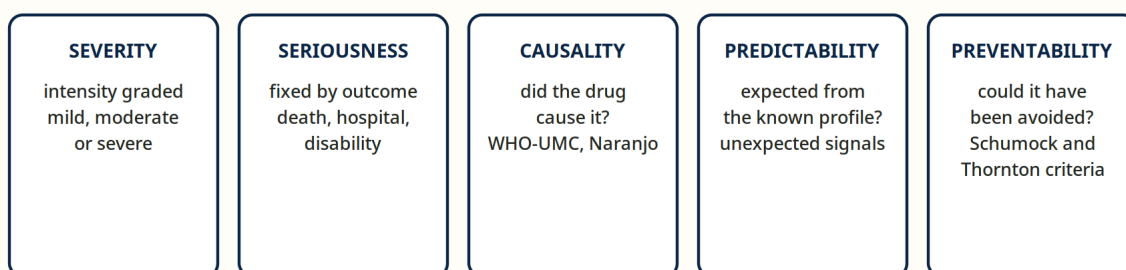
Within trials, detection is systematic by design: participants are questioned, examined and tested at scheduled visits, and every untoward occurrence is captured on the CRF whether or not the investigator suspects the drug. Reporting then splits by gravity. The investigator reports **serious adverse events to the sponsor immediately**, conventionally within 24 hours of awareness, and to the ethics committee as required; the sponsor evaluates seriousness, causality and expectedness, and expedites to regulators the events that are serious, unexpected and suspected adverse reactions (SUSARs), fatal or life threatening ones fastest. Under the Indian rules, trial related injury, disability or death must additionally be reported within prescribed timelines to the licensing authority and ethics committee, with compensation determined for the participant or family. The structure to remember is a relay: bedside to investigator, investigator to sponsor and committee, sponsor to regulator, each leg with its own clock.

3.10 Severity and seriousness: two different assessments

Students lose marks by confusing these twins, so the syllabus names them side by side. **Severity** grades the intensity of an event: mild, moderate or severe, a clinical description of how bad it felt and how much it interfered with activity or required treatment; a severe headache is intensely unpleasant and entirely non-serious. **Seriousness** is a regulatory category defined by outcome: an event is a **serious adverse event (SAE)** if it results in death, is life threatening, requires or prolongs hospitalisation, produces persistent or significant disability, is a congenital anomaly or birth defect, or is otherwise medically important. Seriousness, not severity, drives expedited reporting, insurance and regulatory attention. Severity is graded on scales, sometimes formal ones such as the Common Terminology Criteria for Adverse Events in oncology; seriousness is judged against the fixed outcome list.

The Five Assessments of an Adverse Reaction

Every suspected reaction is read five ways before it is reported onward



Seriousness drives the reporting clock; the other four assessments drive learning.

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Figure: Every adverse drug reaction is read through five assessments: severity, seriousness, causality, predictability and preventability.

3.11 Predictability and preventability assessment

Predictability, also called expectedness, asks whether the reaction is consistent with the information already known about the drug, the investigator brochure in trials and the approved product information after marketing. An expected reaction is already described; an unexpected one, in nature, severity or outcome, carries the greater signal value and the heavier reporting duties, since it may be the first sighting of a new harm. **Preventability** asks the harder human question: could this reaction have been avoided? The standard Schumock and Thornton approach examines whether the drug was inappropriate for the patient's condition, whether dose, route or duration was wrong, whether monitoring or a needed interaction check was omitted, and whether a known allergy or prior reaction was ignored, classifying reactions as definitely preventable, probably preventable, or not preventable. Preventability assessment converts an ADR from a

statistic into an audit, and it is the assessment that most directly reduces future harm.

3.12 Management of adverse drug reactions

Management follows a steady sequence. **Recognize**: suspect the drug in any new symptom, rash, or laboratory abnormality, and take a complete drug history including over the counter and traditional medicines. **Act on the suspect drug**: withdraw it where the reaction is serious or progressive, the commonest and most effective single step; reduce dose for dose related type A reactions; and never stop abruptly where withdrawal itself is dangerous. **Treat the reaction**: symptomatic and supportive care, specific antidotes where they exist, and specialist help for organ injury. **Avoid re exposure**: document the reaction prominently, inform the patient, and supply an alert the patient can show future prescribers; a deliberate rechallenge is justified only exceptionally, where the drug is irreplaceable and the reaction mild. **Report**: every suspected reaction, however managed, enters the reporting system of Units 4 and 5, because one clinician's case is the next patient's warning. Dechallenge, the improvement of a reaction after withdrawal, and rechallenge, its return on re exposure, are also the clinician's causality evidence, and link this section to the evaluation methods of Unit 4.

3.13 Terminologies of ADR

The safety vocabulary in one place, since the units that follow use it constantly:

Term	Working meaning
Adverse event (AE)	Any untoward medical occurrence during treatment, causality not implied
Adverse drug reaction (ADR)	Noxious, unintended response at normal doses, causality at least reasonably possible
Serious adverse event or reaction	Defined by outcome: death, life threatening, hospitalisation, disability, congenital anomaly, medically important
Unexpected ADR	Inconsistent with the applicable product information in nature, severity or outcome
Side effect	Unintended pharmacological effect at normal dose, not necessarily noxious
Adverse drug event	Harm arising from medication use, including errors, used widely in hospital safety work
Signal	Information suggesting a new potentially causal association, or a new aspect of a known one, judged to require verification

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