

### Unit 5: Clinical Trials

Free notes at [pharmacolearn.fyi](https://pharmacolearn.fyi)

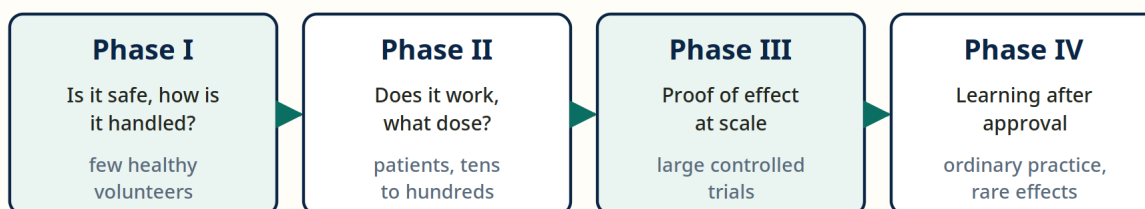
#### 5.1 Clinical trials and their phases

A **clinical trial** is a systematic study of a drug in human subjects to discover or verify its clinical, pharmacological or other effects, to identify adverse reactions, and to study its absorption, distribution, metabolism and excretion, with the object of ascertaining safety and efficacy. Trials are conventionally described in phases:

| Phase                 | Main question                                 | Typical subjects                                                                                                  | Notes                                                                                                               |
|-----------------------|-----------------------------------------------|-------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| Phase I               | Is it safe, and how does the body handle it?  | Small number of healthy volunteers (patients when the drug is too toxic for volunteers, as in much oncology work) | First in human dosing guided by the non clinical data; single and multiple ascending doses, food effect, early ADME |
| Phase II              | Does it work, and at what dose?               | Patients with the target condition, tens to a few hundred                                                         | Proof of concept, dose ranging, selection of the dose and endpoints for Phase III                                   |
| Phase III             | Is it effective and acceptably safe at scale? | Large patient groups, hundreds to thousands, usually controlled (randomised, blinded comparisons)                 | The pivotal evidence for the marketing application                                                                  |
| Phase IV              | What else is learned after approval?          | Patients in ordinary practice                                                                                     | Post marketing studies: rare adverse effects, long term outcomes, new populations and uses                          |
| Phase 0 (exploratory) | Early human signal at microdoses              | Very small numbers                                                                                                | Optional exploratory work under reduced non clinical requirements                                                   |

The phases are a development logic, not a legal straitjacket: programmes overlap, and adaptive and seamless designs combine phases, but an examination answer should always be able to place a study question in its phase.

#### Clinical Trial Phases I to IV



Phase 0 exploratory microdose studies are optional and sit before Phase I.

Figure: The four clinical trial phases and the question each phase answers.

#### 5.2 Developing a clinical trial protocol

The **protocol** is the master plan of the trial, written before the trial starts and approved by the ethics committee and, where required, the regulator. A protocol contains:

- Title, objectives and the scientific background and rationale.
- Trial design: type of study (randomised, blinded, controlled), treatment arms, and the plan that keeps bias out (randomisation and blinding procedures).
- Subject selection: inclusion and exclusion criteria defining the study population.
- Treatment details: product, dose, route, duration, permitted and prohibited concomitant medication, and compliance checks.
- Assessments: efficacy and safety variables, the schedule of visits and procedures, and laboratory work.
- Statistics: sample size reasoning, analysis populations and methods, interim analyses.
- Ethics and administration: informed consent arrangements, safety reporting procedures, data handling and record keeping, monitoring and quality control, publication and finance arrangements.

Changes after approval of the protocol are made by **protocol amendments**, which themselves need ethics and regulatory handling proportionate to their effect on subject safety and the study's science. A trial run materially off its protocol produces data a regulator may refuse to use, however expensive the trial was.

### 5.3 Institutional review board and independent ethics committee

An **Institutional Review Board (IRB)** in US terminology, or **Independent Ethics Committee (IEC)** in ICH GCP terminology, is the independent body whose review and approval protect the rights, safety and well being of trial subjects. In India the same body is the ethics committee registered with the licensing authority under the New Drugs and Clinical Trials Rules.

- **Composition:** a multidisciplinary, plural group, conventionally at least five members, including medical and non medical members, at least one member whose primary interest is non scientific (a lay member), and members independent of the trial site and sponsor. GCP and the Indian rules both prescribe composition elements (chairperson from outside the institution, clinician, pharmacologist, legal expert, social scientist or community representative, lay person, member secretary).
- **Formulation and working procedures:** the committee works to written SOPs of its own: submission requirements and review timelines, quorum rules (decisions only at convened meetings with the prescribed minimum membership present), review of the protocol, consent documents, investigator qualifications, subject payment and compensation arrangements, and continuing review of the running trial, including protocol amendments, deviations, safety reports and the final report.
- **Powers in practice:** the committee can approve, require modifications before approval, disapprove, and suspend or terminate an approval it has given. No subject may be enrolled before written approval for that site, and the investigator must report serious adverse events and new risk information to the committee promptly (Section 5.7).

### 5.4 Informed consent: process and procedures

**Informed consent** is the process by which a subject voluntarily confirms willingness to participate, after being informed of every aspect of the trial relevant to the decision. It is a process, not only a signature: information, comprehension, voluntariness, and the right to withdraw at any time without penalty to the subject's care.

The information that must be explained, in a language and form the subject understands, includes: that the study is research, its purpose and expected duration, the treatments and the probability of random assignment, the procedures (and which are experimental), foreseeable risks and inconveniences, expected benefits (and that there may be none), alternative treatments, confidentiality and who may inspect the records, compensation and treatment arrangements for trial related injury, whom to contact about the trial

and about injury, and the voluntary nature of participation and withdrawal.

Procedural points that examiners and inspectors both check:

- Consent is taken **before** any trial procedure, by a person qualified and authorised to do so, with time for the subject to consider and ask questions.
- Both subject and the person taking consent sign and date the consent form, and the subject receives a copy.
- Special protections apply to vulnerable subjects: legally acceptable representatives consent for those who cannot (children, incapacitated adults), with the subject's assent added where the subject can give it.
- New information that may affect willingness to continue is communicated and re-consent taken where required, for example after a material IB update (Unit 4.6).
- In India, audio visual recording of the consent process is required in defined situations under the New Drugs and Clinical Trials Rules, and compensation for trial related injury or death follows the formula and procedures given in those Rules.

## 5.5 HIPAA and the privacy of health information

The **Health Insurance Portability and Accountability Act of 1996 (HIPAA)** is the US law whose Privacy Rule governs how identifiable health information may be used and disclosed. Clinical trials run directly into it, because trial records are built from patients' health information and sponsors, monitors and auditors need access to it.

For research, the Privacy Rule works through **authorisation**: a subject's written authorisation, usually combined with the informed consent document in US trials, permits the covered health care provider to use and disclose the subject's protected health information for the trial. Without authorisation, use is possible only under limited routes such as a waiver granted by an IRB or privacy board for defined low risk situations. De-identified data fall outside the Rule, which is one reason sponsors work with coded subject identifiers in their databases and reports. The trial consequences are concrete: consent forms carry HIPAA language, monitors verify source data under the authorisation, and breaches of confidentiality are both a privacy violation and a GCP finding.

## 5.6 Requirements of the clinical study process

Beyond protocol, committee and consent, a lawful and credible trial needs the whole **GCP system** (ICH E6) in place:

- **Approvals before start:** ethics approval and the regulatory trial authorisation (an IND in effect in the US, a CTA approval in the EU, CDSCO permission in India) both precede enrolment.
- **Qualified team and delegation:** the investigator is medically qualified and trained in the protocol and GCP; every task is delegated in writing to named, trained staff.
- **Investigational product control:** the product is made to GMP for clinical supplies, labelled for trial use, stored correctly, dispensed against the randomisation system, and accounted for unit by unit.
- **Data integrity and essential documents:** case report forms, source documents, consent forms, approvals, monitoring reports and correspondence are filed as the trial master file, the inspection ready record that the trial was run as approved; data changes carry an audit trail.

- **Monitoring and quality assurance:** the sponsor monitors the trial (on site and increasingly risk based and centralised) and may audit it; regulators may inspect sites, sponsors and CROs, and inspection findings can lead to data rejection or enforcement action.
- **Safety management:** the reporting system of Section 5.7 runs for the entire study and into the development safety update reporting that accompanies the programme.

## 5.7 Pharmacovigilance and safety monitoring in clinical trials

**Pharmacovigilance in a trial** is the continuous collection, assessment and reporting of adverse events so that subjects are protected in real time and the product's safety profile is built honestly. The working vocabulary:

- **Adverse event (AE):** any untoward medical occurrence in a subject given the product, whether or not it is caused by the product.
- **Adverse drug reaction (ADR):** an AE for which a causal relationship to the product is at least a reasonable possibility.
- **Serious adverse event (SAE):** an event that results in death, is life threatening, requires or prolongs hospitalisation, causes persistent or significant disability, is a congenital anomaly, or is otherwise medically important.
- **SUSAR:** a serious unexpected suspected adverse reaction: serious, causally suspected, and not described in the reference safety information (the IB for an investigational product); SUSARs are the core of expedited reporting.

The reporting duties run on two levels:

- **Investigator to sponsor and ethics committee:** the investigator reports SAEs to the sponsor immediately (conventionally within 24 hours of awareness) and reports serious events to the ethics committee within the timelines of the applicable rules.
- **Sponsor to regulators:** the sponsor assesses seriousness, expectedness and causality and submits expedited reports of SUSARs to the regulators (in the US, IND safety reports; fatal or life threatening unexpected suspected reactions are reported fastest, others on the standard expedited clock, exact day counts following the governing rule of the region), notifies all investigators and ethics committees, and keeps the IB and consent information updated as the profile changes.
- **Independent oversight:** many trials appoint a **Data Safety Monitoring Board (DSMB)**, an independent group that reviews accumulating, often unblinded, safety and efficacy data at intervals and can recommend continuing, modifying or stopping the trial; stopping rules for safety are defined in advance in the protocol or the DSMB charter.

Safety reporting inside a clinical trial  
 Subject has a serious adverse event  
 -> investigator assesses, treats, reports to sponsor at once  
 -> investigator also reports to the ethics committee  
 -> sponsor assesses: serious? expected? causally suspected?  
 -> if SUSAR: expedited report to regulators, inform all investigators and ethics committees  
 -> DSMB reviews accumulating data and may advise stopping  
 -> IB and consent updated if the risk picture has changed

## Safety Reporting Inside a Clinical Trial

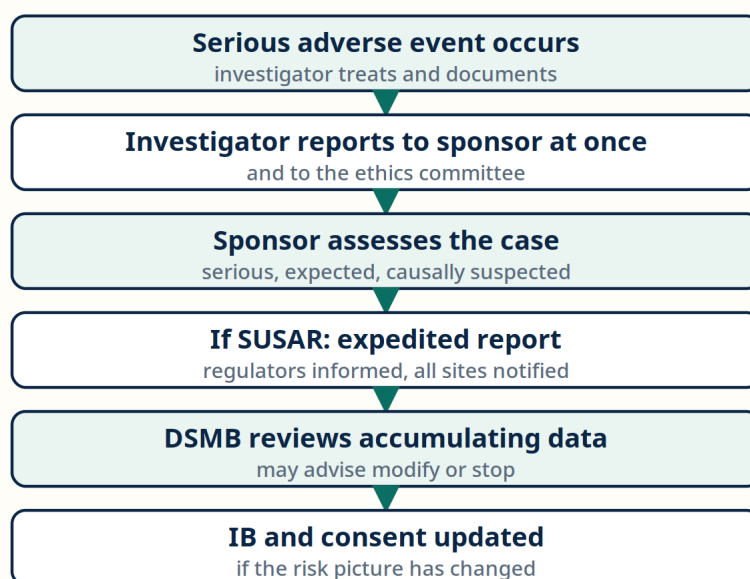


Figure: Safety reporting inside a trial: the event travels from bedside to sponsor to regulator, with independent DSMB oversight alongside.

## Frequently Asked Questions

**Q: What is a Drug Master File and is it ever approved by FDA?** A DMF is a confidential file submitted to FDA holding detailed information about a facility, process or material, most often the API. It is never approved or disapproved on its own; it is reviewed only when an application such as an ANDA or NDA refers to it with a letter of authorisation from the DMF holder, and it stands or falls as part of that application's review.

**Q: What did the Hatch-Waxman Act actually change?** The Drug Price Competition and Patent Term Restoration Act of 1984 created the ANDA pathway, so a generic could be approved on quality data plus bioequivalence instead of repeating clinical trials. In exchange it gave innovators patent term restoration of up to five years, data exclusivities such as five years for a new chemical entity, the Orange Book patent listing and paragraph certification system, the 30 month litigation stay, and 180 days of exclusivity for the first Paragraph IV generic filer.

**Q: What are the four paragraph certifications in an ANDA?** Paragraph I states that no patent information is filed for the reference drug; Paragraph II that the patent has expired; Paragraph III that approval is sought only after patent expiry; Paragraph IV that the patent is invalid, unenforceable or not infringed. Only Paragraph IV invites immediate litigation and the chance of 180 day first filer exclusivity.

**Q: How is bioequivalence decided statistically?** The 90 percent confidence interval for the ratio of test to reference geometric means of AUC and Cmax from the BE study must lie entirely within 80.00 to 125.00 percent. AUC carries the extent of absorption and Cmax the rate, and both must pass.

**Q: What is the difference between tentative approval and final approval of an ANDA?** A tentative approval means the application is scientifically complete but a patent or exclusivity still blocks marketing, so the product cannot be sold. Final approval, granted when the block clears, is what allows the generic to enter the market.

**Q: What are the five modules of the CTD?** Module 1 is regional administrative information and labelling; Module 2 holds the summaries and overviews; Module 3 is Quality (the CMC evidence); Module 4 is the non clinical study reports; Module 5 is the clinical study reports. Only Module 1 changes between regions.

**Q: How does the EU authorise a medicine, and how many routes are there?** There are four routes to an EU marketing authorisation: the centralised procedure through EMA and the European Commission, the mutual recognition procedure based on an existing national authorisation, the decentralised procedure for simultaneous authorisation in several states, and the purely national procedure for one state.

**Q: What is the difference between an IND, an IMPD and an investigator brochure?** An IND is the US filing that exempts an unapproved drug from the ban on interstate shipment so it can be tested in humans. The IMPD is the EU trial dossier carrying the quality, non clinical and clinical data behind a clinical trial application. The investigator brochure is the sponsor's compiled briefing on the product given to investigators, and it forms part of the support for both routes.

**Q: Who can sit on an ethics committee and what can it do?** An IRB or IEC is a multidisciplinary independent body, conventionally at least five members, including medical and non medical members and at least one lay or non scientific member, working to its own written procedures. It can approve a trial, require changes, refuse approval, and suspend or terminate an approval, and no subject may be enrolled before its written approval.

**Q: What is a SUSAR and who reports it to whom?** A SUSAR is a serious unexpected suspected adverse reaction in a clinical trial: serious, not described in the reference safety information, and with at least a reasonable possibility of causality. The investigator reports serious events to the sponsor and the ethics committee at once; the sponsor then files expedited reports of SUSARs to the regulators and informs all investigators, with the fastest handling for fatal or life threatening cases.