

Unit 2: Clinical Trials: Types and Design

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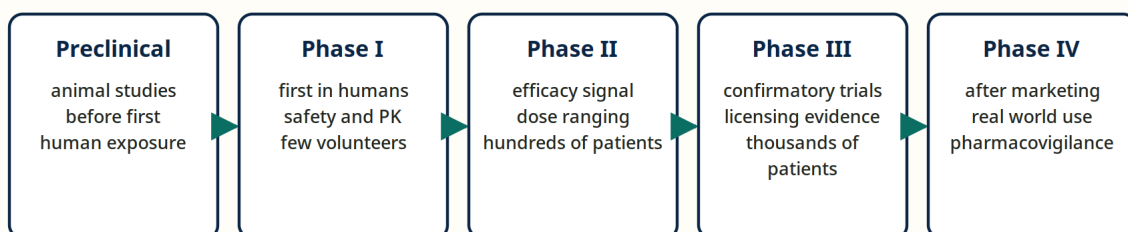
2.1 What a clinical trial is, and the phases in which trials run

A **clinical trial** is a systematic study of a drug in human subjects, conducted to discover or verify its clinical, pharmacological or pharmacodynamic effects, to identify its adverse reactions, or to study its absorption, distribution, metabolism and excretion, with the object of ascertaining safety and efficacy. Trial types are classified two ways in this subject: by the development phase they belong to, and, which is what the PCI unit examines, by study design.

The phases are the conventional frame. **Phase I**, first in humans, studies safety, tolerability and pharmacokinetics in a small number of healthy volunteers, or patients where the drug class demands it. **Phase II** studies efficacy signals and dose ranging in a few hundred patients with the target disease. **Phase III** is the large, usually randomized confirmatory stage in hundreds to thousands of patients, whose results support licensing. **Phase IV** covers studies after marketing, where the drug meets the general population and pharmacovigilance, the second half of this subject, takes over the watch. The design classification that follows cuts across the phases: a Phase III trial is typically an RCT, and a Phase IV commitment is typically observational.

The Phases of Clinical Development

Participant numbers grow as the questions move from safety to confirmation to real world use



Phase IV hands the safety watch to pharmacovigilance (Units 4 and 5).

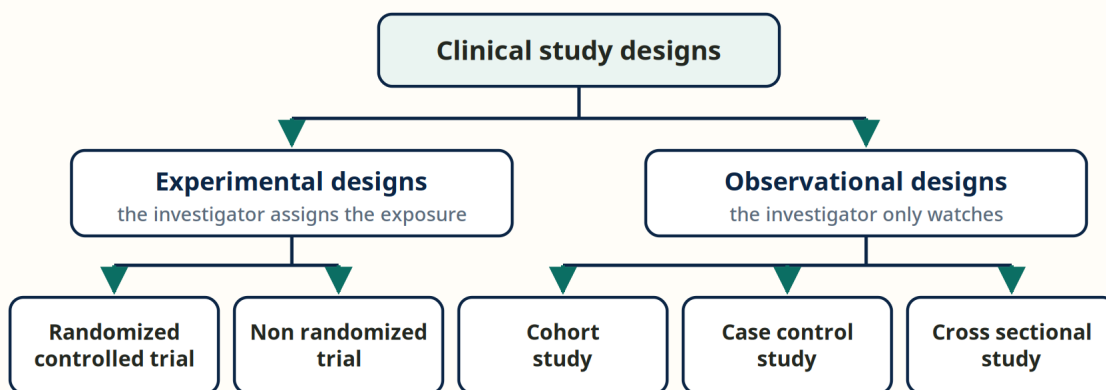
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Figure: The phases of clinical development. Numbers grow and questions change stage by stage, and Phase IV hands the safety watch to pharmacovigilance.

2.2 Two families of design: experimental and observational

Designs divide by one question: does the investigator assign the exposure? In an **experimental study** the investigator allocates participants to interventions, test drug against control, and compares outcomes; the randomized controlled trial and its non randomized relatives live here. In an **observational study** the investigator assigns nothing: exposure has already happened, or happens by ordinary clinical choice, and the study watches, records and compares. Cohort, case control and cross sectional studies live here. Experimental designs can approach causal proof because allocation, properly randomized, breaks the link between exposure and every other characteristic; observational designs trade that strength for realism, size, speed and the ability to study exposures, rare harms and long latencies that no trial could ethically or practically assign. Unit 2 teaches the experimental family; the observational family returns in Unit 5, where it becomes the engine of pharmacovigilance.

The Family Tree of Clinical Study Designs



Experimental designs allocate; observational designs watch. Both return in Unit 5 as safety tools.

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Figure: Study designs divide by whether the investigator assigns the exposure: experimental designs allocate, observational designs watch.

2.3 Randomized controlled trials

The **randomized controlled trial (RCT)** is the reference design of clinical research. Participants meeting the protocol's criteria are allocated **at random** to the test intervention or to a control, which may be placebo, standard treatment, or a different dose, and the groups are then treated and followed identically apart from the intervention. Randomization is the design's genius: done properly and in sufficient numbers, it distributes known and unknown confounders, age, severity, habits, genes, evenly between groups, so that a difference in outcome can be attributed to the intervention with a confidence no observational comparison can match.

Three supporting techniques protect that attribution. **Blinding** (masking) hides allocation: single blind from the participant, double blind from participant and investigator, so that expectations cannot bend care, reporting or assessment. **Allocation concealment** hides the upcoming assignment from the person enrolling, so selection cannot creep back in before randomization. **Analysis by intention to treat** keeps every randomized participant in the group to which chance assigned them, preserving the balance randomization bought even when participants stray. RCT variants the examiner expects named include parallel group and crossover layouts, and superiority, equivalence and non inferiority questions; each is a way of arranging the same machinery.

2.4 Non randomized experimental studies

Not every experimental question can or should be randomized. In a **non randomized controlled trial** the investigator still allocates the intervention, but by a non random rule: alternation, date of birth, centre, or patient choice, and the groups are compared with the standing warning that allocation bias and confounding may explain part of any difference. **Uncontrolled studies**, a single arm treated and described with no comparator, answer feasibility and safety questions, dominate early Phase I and II work, and can occasionally settle efficacy where the untreated course is uniform and catastrophic and the effect is dramatic. The design lesson is symmetrical: removing randomization does not make a study useless, it makes its conclusions graded, and the report must carry the grading honestly.

2.5 Cohort studies

A **cohort study** assembles groups by exposure and follows them forward to outcomes. A defined population is classified as exposed or unexposed to the drug or factor of interest, and both are followed over time while the incidence of the outcome is counted in each; the comparison is a relative risk, incidence in exposed divided by incidence in unexposed. Run forward in calendar time it is prospective; reconstructed from records of exposure and outcome that already exist, it is retrospective, and no less a cohort study for that. Cohort designs suit rare exposures and multiple outcomes of one exposure, give true incidence, and establish that exposure preceded outcome. Their costs are time, size, and blindness to rare outcomes: a harm occurring in one user in ten thousand needs a cohort of hundreds of thousands to be seen at all, which is why drug safety leans so heavily on the next design.

2.6 Case control studies

A **case control study** reverses the direction of inquiry: it assembles groups by outcome and looks backward to exposure. Cases, people who have suffered the outcome, classically a suspected adverse reaction, are compared with controls, similar people who have not, and the history of exposure to the suspect drug is traced in each group; the comparison is an odds ratio, the odds of exposure among cases divided by the odds among controls. Because the study starts from the outcome, it is the efficient design for rare outcomes and long latencies, quick and comparatively cheap, and it can examine several exposures for one outcome. Its weaknesses are the mirror image: it cannot give incidence, it studies one outcome at a time, and it lives or dies by the quality of exposure history and the fairness of the controls chosen. The thalidomide and phocomelia story of Unit 4 is, methodologically, a case control insight drawn from case reports.

2.7 Cross sectional studies

A **cross sectional study** measures exposure and outcome at one point in time, a snapshot of a defined population: how many people are taking the drug, how many have the condition, and how the two overlap. It yields prevalence, not incidence, and because snapshot association cannot show which came first, it cannot by itself establish causation. Its proper work is descriptive and administrative: drug utilization patterns, prevalence of prescribing problems, the burden a safety programme must handle. In the vocabulary of Unit 5 it is the design of drug utilization studies and prescription event monitoring snapshots, the map on which the analytic designs then operate.

2.8 The designs compared

Feature	RCT	Non randomized experimental	Cohort	Case control	Cross sectional
Investigator assigns exposure	Yes, at random	Yes, by a non random rule	No	No	No
Direction of inquiry	Forward from intervention	Forward from intervention	Forward from exposure	Backward from outcome	Single point in time
Measure of comparison	Risk or outcome difference between arms	Risk or outcome difference, bias prone	Relative risk (incidence compared)	Odds ratio (exposure odds compared)	Prevalence
Strongest use	Efficacy and common safety outcomes	Feasibility, early phase questions	Rare exposures, incidence, multiple outcomes	Rare outcomes, long latency, several exposures	Prevalence, drug utilization
Chief weakness	Cost, size, artificial population	Allocation bias, confounding	Slow, huge for rare outcomes	No incidence, recall and selection bias	No time order, no causation

2.9 The clinical trial study team

A trial is executed by a defined cast, and GCP assigns each member duties that cannot be silently delegated. The four roles the syllabus names are the **investigator**, who leads at the site; the **study coordinator**, who makes the site's work happen day to day; the **sponsor**, who owns the trial as a whole; and the **contract research organization (CRO)**, to which the sponsor may transfer duties. Around them stand the ethics committee of Unit 1, the monitor of Unit 3, pharmacists, laboratory staff and data managers; the four named roles carry the examinable responsibilities, set out next.

2.10 The investigator

The **investigator** is the person responsible for the conduct of the trial at a site, and where a team works, its leader, the principal investigator. GCP's charge on the investigator is personal: to be qualified and experienced for the responsibility; to know the protocol and the investigator brochure thoroughly; to conduct the trial exactly as approved, documenting any deviation and its reason; to protect participants, obtaining informed consent properly, providing their medical care, and acting on adverse events; to control the investigational product at the site; to keep accurate source records and case report forms; to report serious adverse events to sponsor and ethics committee within the required timelines; and to communicate with the ethics committee throughout. The investigator's signature converts a protocol from paper into a promise.

2.11 The study coordinator

The **study coordinator** (clinical research coordinator) is the site's operating centre: scheduling and conducting study visits, preparing and maintaining documents and files, assisting with consent administration, completing case report forms from source data, coordinating laboratory samples and product accountability, and serving as the daily point of contact among investigator, monitor, sponsor and participants. The role is administrative in form and clinical in consequence: most protocol deviations and data queries in real trials are prevented or created at the coordinator's desk, which is why GCP training and delegation logs treat the coordinator as trial personnel under the investigator's supervision, with duties recorded in writing.

2.12 The sponsor

The **sponsor** is the individual, company, institution or organization that takes responsibility for the initiation, management and financing of the trial. Sponsorship is accountability, not merely funding. The sponsor designs the protocol with expert advice, selects qualified investigators and sites, supplies the investigational product and the investigator brochure, obtains regulatory and ethics approvals or ensures they are obtained, appoints monitors, arranges insurance and indemnity and compensation for trial related injury, manages safety information flowing in from all sites, and owns the final clinical study report. A sponsor may be the drug's manufacturer, or, in investigator initiated research, the institution or investigator, in which case sponsor and investigator duties unite in the sponsor investigator. What cannot happen under GCP is a trial with nobody answerable for it: that answerability is the sponsor's definition.

2.13 The contract research organization and its management

A **contract research organization (CRO)** is a company contracted by the sponsor to perform one or more of the sponsor's trial duties: protocol development, site selection and monitoring, data management, statistics, medical writing, safety processing, or the whole trial end to end. GCP's rule on transfer is precise: a sponsor may transfer duties to a CRO, in writing, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor, and any duty not specifically transferred is retained by the

sponsor. Managing a CRO is therefore a sponsor competence, not an abdication: selection by capability and inspection of quality systems, a contract specifying duties, deliverables and quality standards, oversight through reports, audits and key performance indicators, and audit certificates documenting that the work was checked. The growth of the CRO industry is the economic fact behind this syllabus item: most large trials are now executed by this sponsor, CRO, site triangle, and the pharmacovigilance processing of Unit 5 is commonly housed in the same arrangement.

CHOOSING A DESIGN: THE WORKING LOGIC

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Can the exposure be assigned ethically and practically?
|
+-- Yes --> Can it be assigned at random?
|           +-- Yes --> RANDOMIZED CONTROLLED TRIAL
|           +-- No  --> NON RANDOMIZED EXPERIMENTAL STUDY
|
+-- No --> Is the outcome rare or long delayed?
           +-- Yes --> CASE CONTROL STUDY
           +-- No --> Is incidence over time the question?
                   +-- Yes --> COHORT STUDY
                   +-- No  --> CROSS SECTIONAL STUDY
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