# PharmacoLearn

**MPP104T Clinical Research, M.Pharm Semester 1**

## Unit 2: Types and Designs Used in Clinical Research and the Trial Team

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### 2.1 Planning and execution of clinical trials

Planning and execution are the two halves of trial conduct, and the syllabus names them together because a trial is won or lost in the planning. Planning begins with the research question, in which population, which intervention, compared with what, changing which outcome, and fixes the design, eligibility, endpoints and statistical approach in advance in the protocol, with the operation built around the science: sites, product supply, data systems, monitoring and the regulatory and ethical approvals. A planning error cannot be repaired by excellent execution, because the data faithfully record the wrong experiment. Execution is the disciplined running of that plan: site activation, recruitment and consent, treatment and follow up exactly as the protocol prescribes, data captured as events happen, safety watched continuously, and deviations recognised, recorded and corrected rather than hidden.

### 2.2 Phases of clinical trials: the map

The phases of clinical trials are the conventional stages of human study, numbered I to IV, through which a new medicine passes as knowledge and confidence grow. The table below states the comparison qualitatively, without invented participant numbers.

| Phase | Governing question | Typical participants | What is principally learned | What it decides |
|---|---|---|---|---|
| Phase I | Is it tolerable, and how does the body handle it? | Small number of healthy volunteers, or patients where the product class requires it | Safety and tolerability, pharmacokinetics, dose range for study | Whether human study continues, and at what doses |
| Phase II | Does it show activity, and at what dose? | Patients with the target condition | Early efficacy signals, dose response, further safety | Whether proof is worth seeking, and in which dose and population |
| Phase III | Does it truly benefit patients? | Larger patient groups, often many centres and countries | Confirmatory efficacy against a comparator, fuller safety profile | Whether the evidence supports marketing approval |
| Phase IV | What happens in real use? | Patients in ordinary practice after approval | Longer term and rarer effects, use in wider populations, effectiveness in practice | Labelling refinement, risk management, place in therapy |

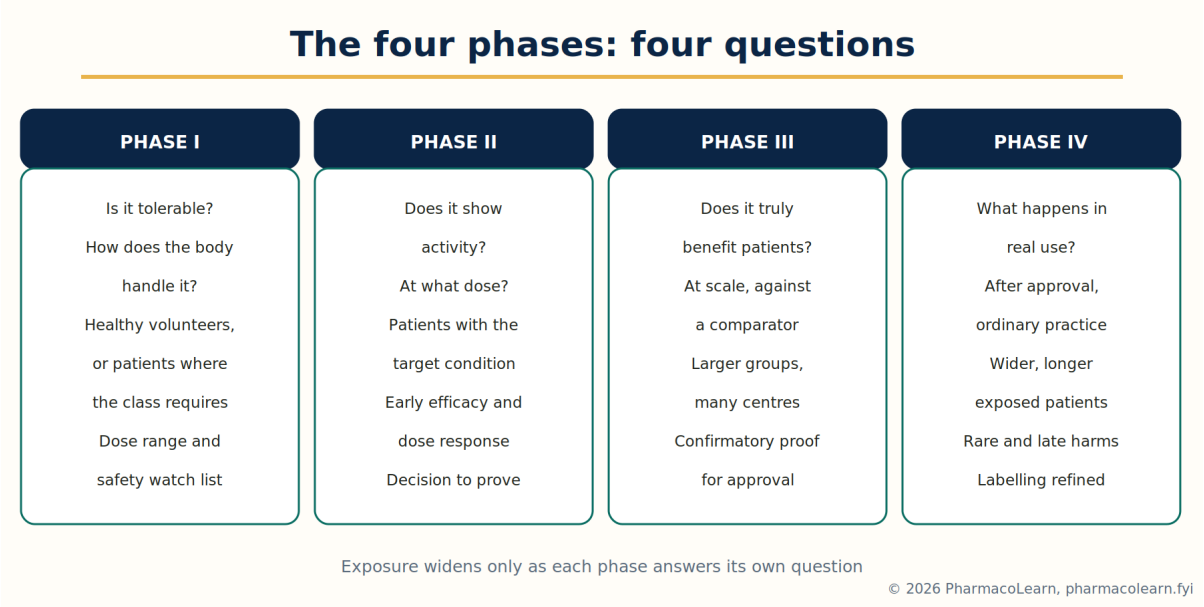


*Figure: The four phases as four questions. Each phase earns the right to the next by answering its own question honestly.*

## 2.3 Phase I: first study in humans

Phase I is the first administration of the investigational product to human beings, and its governing concerns are safety, tolerability and pharmacokinetics, not proof of benefit. Participants are usually healthy volunteers, because the object is to learn how a human body handles the product without the confusion of disease; where the product is expected to be markedly toxic, as with many anticancer agents, the first studies are done in patients instead. The design features all serve caution: a conservative starting dose from the preclinical margins of Section 1.4, single doses before repeated doses, small groups dosed in sequence with review before the next begins, gradual escalation under predefined stopping rules, and intensive monitoring in a setting equipped for emergencies.

## 2.4 Phase II: activity, dose and the decision to prove

Phase II moves the product into patients with the target condition and asks the first therapeutic questions: is there evidence of the intended activity, what dose and schedule produce it, and does the safety profile in patients, who are ill and usually taking other medicines, still leave a usable margin. Early Phase II work is commonly exploratory, comparing doses and refining the population and the endpoints. Later Phase II work firms those choices into the design Phase III will test. Small, short studies can show an effect is plausible and worth proving, or that a programme should stop, but they cannot establish benefit: chance, selection and the natural course of disease all imitate treatment effects at this scale.

## 2.5 Phase III and Phase IV: proof at scale, and learning after approval

Phase III is the confirmatory stage: large, controlled trials, commonly randomized against the standard treatment or another accepted comparator, in the population for which approval will be sought, measuring endpoints that represent real clinical benefit, over periods long enough for that benefit and the common harms to declare themselves. Its scale is set by statistics, the need to detect a difference of the size claimed with acceptable certainty, and its conduct is commonly multicentre and multinational, which is why the full machinery of this subject, monitoring, data management, central systems, exists at its most developed here. Phase IV is study after approval, in wider, older and more medicated populations than any trial enrolled, through further trials, observational studies and registries, and continuing safety surveillance, detecting the rare and long latency harms no pre approval programme can exclude and feeding labelling and risk management.

## 2.6 Bioavailability and bioequivalence studies

Bioavailability is the rate and extent to which the active substance is absorbed from a product and becomes available at the site of action, measured in practice by the concentration time profile in the blood: how much in total, and how fast it peaks. A bioavailability study characterises that profile for a product, absolutely against an intravenous reference or relatively against another product, and answers the formulation and handling questions behind it. Bioequivalence is the comparative judgement built on that measurement: two products are bioequivalent when their bioavailabilities are so similar, in rate and extent, that their effects can be expected to be essentially the same, so that one may be substituted for the other on the strength of the comparison rather than a fresh clinical programme. The characteristic bioequivalence design follows from the precision the judgement needs: a crossover study in healthy volunteers, in which each participant receives both products in randomly assigned order separated by a washout period, so that every person serves as their own control and the comparison is made within, not between, individuals; concentrations are measured through the profile; and the products are compared on the standard summary measures of extent and rate under the acceptance framework the applicable rules prescribe. In India these studies sit inside the New Drugs and Clinical Trials Rules, 2019, with their own approval, ethics and conduct requirements.

## 2.7 Randomization: why allocation must be left to chance

Randomization is the allocation of participants to the treatment groups of a trial by a chance process, and it is the single most important design device in the confirmatory trial. Random allocation, honestly executed and concealed until the moment of assignment, distributes known and unknown prognostic factors between the groups by chance alone, so that systematic bias has no route in, and remaining differences can be quantified by the statistics of chance. Three disciplines make randomization real rather than nominal: the sequence is generated before the trial and held independently of enrolling staff; allocation is concealed, so the enroller cannot foresee the next assignment; and allocation is implemented exactly as generated, with the record preserved for audit.

## 2.8 Randomization techniques: simple, restricted, blocking and stratification

The syllabus names the randomization techniques in a family that runs from the simplest to the more controlled. Simple randomization allocates each participant independently by the chance process, like the toss of a coin for two groups. It is pure and unpredictable, and its weakness appears in small and moderate trials: chance alone can leave the groups uneven in number and, occasionally, uneven on an important prognostic factor. Restricted randomization is the family of methods that keep the purity of chance while restraining that imbalance, and its two named members are the standard examination pair. Blocking, in permuted block randomization, generates the sequence in small blocks within which the groups are exactly balanced, the order inside each block being random, so that at every stage of recruitment, and at any early stopping point, the numbers per group are close; block sizes are varied and kept undisclosed, because a fixed known block size would let an observant enroller predict the last assignment of each block and break allocation concealment. Stratification generates separate randomization sequences within strata defined by a strong prognostic factor, such as centre, disease severity or age band, so that balance is guaranteed not only overall but within each level of that factor.

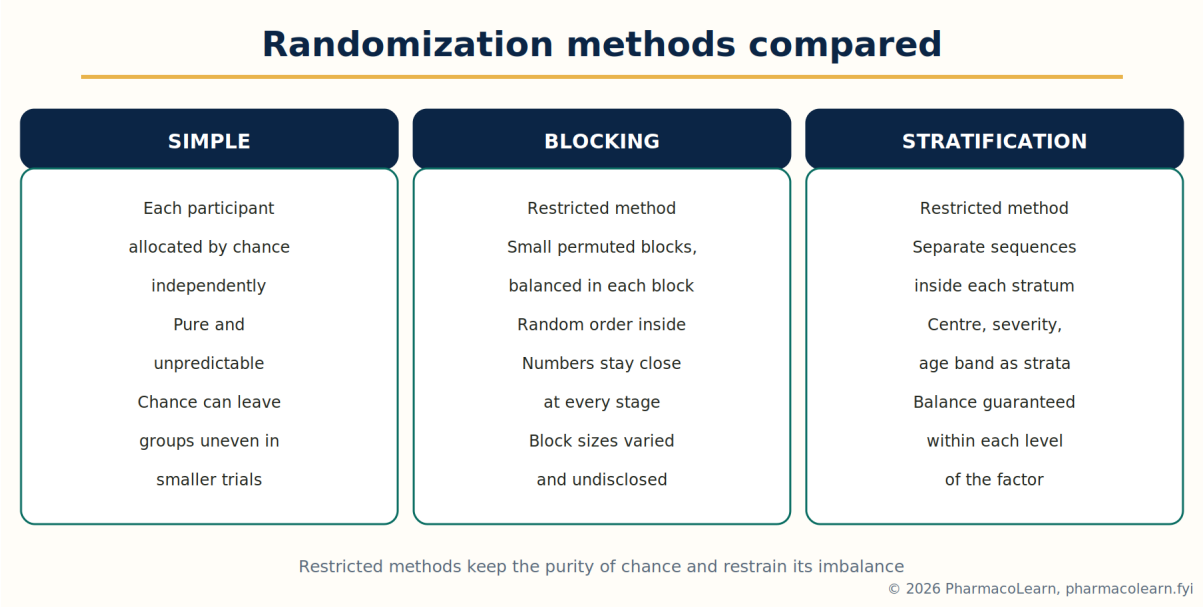


*Figure: Three ways to let chance decide. The methods differ in how much imbalance they permit chance to leave behind.*

## 2.9 Designs by controlling method: experimental, quasi experimental and observational

The syllabus classifies research designs first by the controlling method, by how much control the investigator exercises over the exposure being studied. In experimental designs, the investigator assigns the intervention: the clinical trial is the type case, with its protocol, its eligibility criteria, its assigned treatments and, at its strongest, randomization and blinding. Control is maximal, and with it the ability to attribute an observed difference to the intervention, which is why experimental evidence stands highest for questions of treatment effect. In quasi experimental designs, an intervention is delivered and its effects measured, but a defining element of the true experiment is missing, commonly random assignment: before and after studies, studies with a non randomized comparison group, and interrupted time series in which an outcome is tracked across the introduction of a policy or treatment. In observational designs, the investigator assigns nothing: exposure and outcome are observed as they occur in ordinary life and care, and the design families of Section 2.10, cohort, case control and cross sectional, are its members. Observational work studies what trials cannot, rare harms, long latencies, real world use, exposures that cannot be assigned, at the price of confounding, the entanglement of the exposure with the characteristics of the people who receive it, which the analysis must measure and adjust for and can never wholly remove.

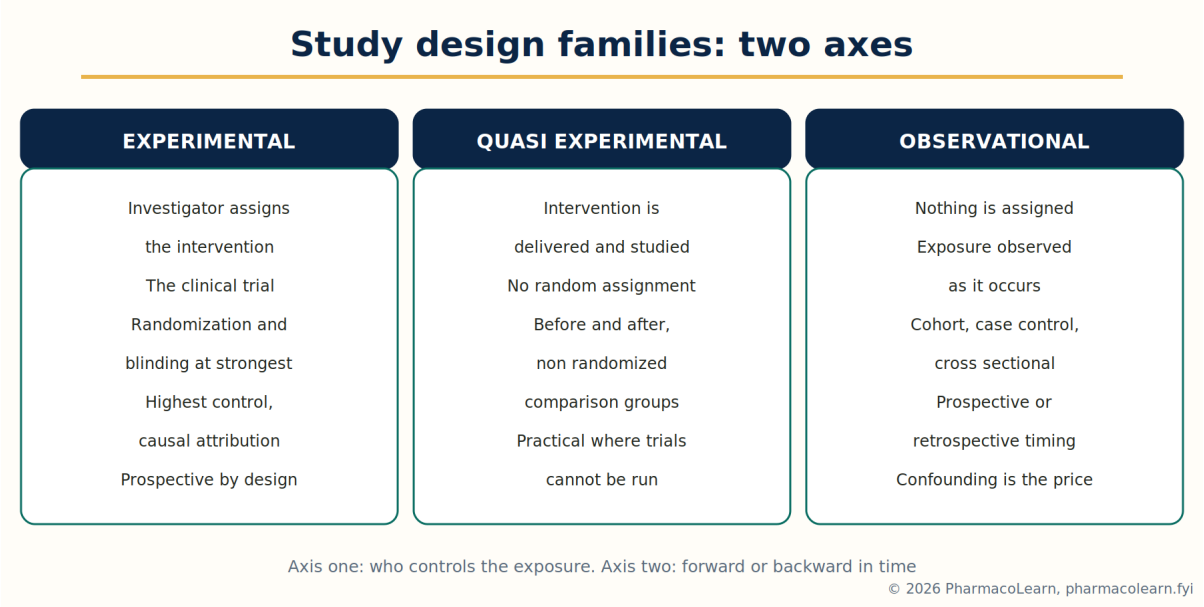


*Figure: Two axes classify every design: who controls the exposure, and whether the study looks forward or back from it.*

## 2.10 Designs by time sequence, and sampling designs: cohort, case control and cross sectional

The second classification of the syllabus is by time sequence. A prospective study looks forward: participants are identified by their present characteristics or exposure, and followed into the future for the outcomes to occur, as in a trial or a cohort study; its data are collected for the research question, at the price of time. The syllabus then names its three sampling designs, the observational families. A retrospective study, by contrast, looks backward from outcomes that have already occurred, reconstructing exposure from records and history. A cohort study assembles groups defined by exposure, exposed and unexposed, and follows them forward to compare the incidence of the outcome in each. A case control study assembles participants by outcome, cases with the condition and controls without it, and looks back to compare the frequency of past exposure in each, answering: given this outcome, how much more common was the exposure; it is the efficient design for rare diseases and long latencies, since the investigator starts from the cases rather than waiting for them. A cross sectional study measures exposure and outcome at one point in time in a defined population, a snapshot that yields prevalence and association but cannot by itself establish which came first.

## 2.11 Health outcome measures: clinical and physiological, humanistic and economic

A trial is its outcome measures: the endpoints chosen decide what the study can claim, and the syllabus classifies health outcome measures in three families. Clinical and physiological outcomes are the measures of disease and body function: the events a patient fears, death, relapse, major complications, and the clinical signs and laboratory and physiological measurements that track the disease. Humanistic outcomes measure the person's experience of health: symptoms as the patient reports them, functioning in daily life, and health related quality of life, captured by validated patient reported instruments. Economic outcomes measure the resources the treatment consumes and saves: the costs of the product, its administration and monitoring, and the hospital and community care it uses or averts, set against its effects in the economic evaluations that the sister subject MPP204T teaches in full. A well designed trial names one primary outcome, a small set of secondary outcomes, and safety outcomes watched throughout, and fixes all of them in the protocol before enrolment begins, because outcomes chosen after the data are seen can always be found to favour somebody.

## 2.12 The clinical trial study team: roles in overview

A clinical trial is conducted by a team whose roles the syllabus names individually. The sponsor owns the trial as a whole: its design, its quality, its regulatory standing and its data. The investigator owns the conduct at one site: the participants enrolled there, the protocol as actually followed, and the records made. Between and around them, the study coordinator makes the site's work happen day by day, the monitor verifies on the sponsor's behalf that the site's work is what the records claim, and the Contract Research Organization performs, under contract, whatever sponsor duties have been formally transferred to it.

## 2.13 Investigator and study coordinator

The investigator is the qualified person responsible for the conduct of the trial at a site, and, where a team works under them, the leader answerable for the team's trial work. Their GCP duties are to hold the approvals before enrolling anyone, follow the approved protocol and document deviations, obtain informed consent properly, ensure protocol compliant product handling and complete source data, make records available to monitors, auditors and inspectors, report adverse events as required, give participants proper medical care for trial related events, and report progress and completion to sponsor and ethics committee. The study coordinator, often a nurse or a pharmacist by training, is the operational centre of the site: scheduling visits, maintaining files and logs, tracking documents and samples, entering and correcting data, and coordinating between investigator, participants, pharmacy, laboratory and sponsor. The coordinator's work is delegated task by task by the investigator and recorded on the delegation log; the investigator's accountability for the site is not delegated with the tasks.

## 2.14 Sponsor, monitor and Contract Research Organization

The sponsor is the individual, company, institution or organisation that takes responsibility for the initiation, management and financing of the trial. Its duties include the trial's quality systems, selection of qualified investigators and sites, provision of the product made and labelled for trial use, the protocol, brochure and agreements, safety evaluation across the programme, monitoring and audit, and management of the data and the final report. The monitor, appointed by the sponsor, verifies that the site follows the protocol and GCP, that consent was properly obtained, that reported data agree with source records and that the product is accounted for; the monitor verifies and reports, and does not conduct the site's trial for it. The Contract Research Organization, or CRO, is an organisation contracted by the sponsor to perform one or more of the sponsor's trial duties, commonly monitoring, data management, statistics, pharmacovigilance or full trial management. The transfer is valid only as far as it is specified in writing: the sponsor retains ultimate responsibility for the quality and integrity of the trial and its data however much work the CRO performs. That sentence, sponsor accountability survives outsourcing, is the examination heart of the CRO topic.

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