

Unit 1: Clinical Drug Development Process

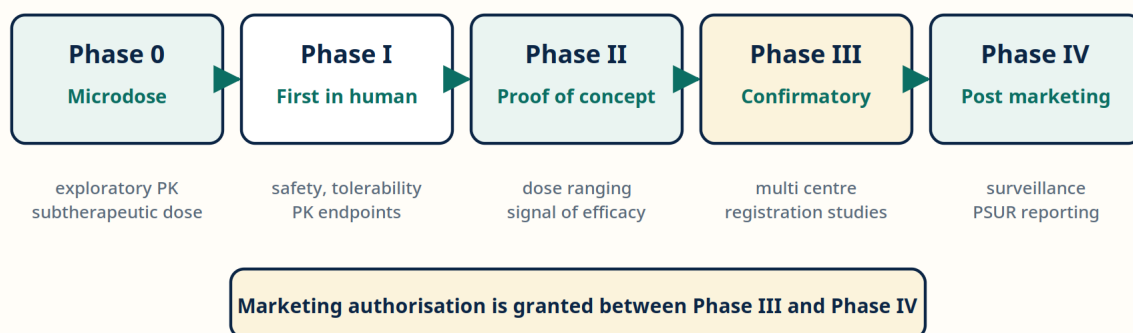
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Clinical Research Regulations, subject code MRA103T, is the third core subject of M.Pharm Regulatory Affairs, Semester 1. It carries 4 credits and 60 hours of theory, taught at 4 hours per week, for 100 marks. MRA101T taught the good practices of manufacture and the laboratory, and MRA102T the documents that carry a product to a regulator; this subject teaches the one experiment in pharmaceutical development that is performed on people. A clinical trial is at once a scientific study, an ethical undertaking and a regulated legal act, and it cannot begin, in any serious jurisdiction, until a regulator and an ethics committee have both said yes. This subject explains how that permission system is built: how a drug travels from first in human testing to post marketing surveillance, what history forced the rules into existence, who guards the rights of the participants, and which laws, rules and guidelines a regulatory affairs professional must command in India, the United States and the European Union. The course is designed to impart fundamental knowledge on the clinical development process of drugs, pharmaceuticals and medical devices, the phases and conduct of clinical trials and research, and the regulations and guidance governing clinical research in India, the USA and the EU. Its objectives run in the order of the units: the history, origin and ethics of clinical and biomedical research and evaluation; the development process and the types and phases of trials; and the regulatory requirements and guidance for the conduct of clinical trials and research. Unit 1 walks the development process itself, phase by phase, ending with the special case of medical devices and IVDs. Unit 2 is the ethical foundation: the historical abuses that wrote the rules, the committees that guard participants, and the informed consent on which everything rests. Unit 3 states the governing regulations of the three regions, including India's New Drugs and Clinical Trials Rules 2019. Unit 4 collects the working guidelines, from ICH GCP to the ICH efficacy series. Unit 5 reads the two great foreign rulebooks in detail: the United States Code of Federal Regulations, part by part, and the European Union's directives, EudraLex volumes and device framework.

1.1 The clinical development process: a regulated experiment on people

A new drug reaches the clinic only after discovery and preclinical work (pharmacology, toxicology, formulation) have produced a candidate with enough evidence of possible benefit and acceptable risk to justify human exposure. From that moment the development is **clinical**: a planned sequence of studies in human participants, each designed to answer a defined question, each gated by regulatory permission and ethics approval, and each more expensive and less forgiving than the last. The regulatory affairs function exists inside this process because the gates are documentary: an application to test, a protocol to approve, reports to file, safety data to submit on fixed clocks. Three ideas organise the whole unit. The development is **phased**, because questions must be answered in order: is it safe enough, does it work at all, does it work well enough against the standard, and does it stay safe in real use. It is **comparative**, because from Phase II onward the drug is judged against a control, not against hope. And it is **cumulative**, because each phase's dossier becomes the evidence base the next phase's application stands on: the clinical trial application of Unit 3 is only ever as strong as the preclinical and earlier clinical data behind it.

The Clinical Development Pipeline: Phases 0 to IV



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Figure: The clinical development pipeline: each phase answers one governing question, and marketing authorisation sits between the confirmatory and post marketing phases (Unit 1, section 1.1).

1.2 Types of clinical studies

The syllabus opens with the types, because the regulatory weight of a study depends on what kind it is. The first division is between **interventional studies**, in which the investigator assigns an intervention (a drug, a device, a procedure) by protocol, and **observational studies**, in which exposure happens in ordinary care and the investigator only records outcomes: cohort, case control and cross sectional designs, familiar from the biostatistics teaching, belong to the second family and generally need ethics approval and registration discipline but not a trial licence. Within interventional studies the working vocabulary of design is examinable in itself:

Design feature	Principal forms	Regulatory significance
Allocation	Randomised, non randomised	Randomisation is the standard defence against selection bias; departures must be justified in the protocol
Control	Placebo, active comparator, dose comparison, historical, no treatment	The choice of control is an ethical and scientific decision governed by ICH E10 (Unit 4)
Blinding	Open label, single blind, double blind	Blinding protects endpoints from expectation; unblinding rules belong in the protocol
Structure	Parallel group, crossover, factorial	Crossover suits stable chronic conditions and small populations; carryover must be excluded
Purpose	Exploratory, confirmatory	Confirmatory trials carry the registration claim and are run to the strictest evidentiary standard

A study is also classified by its relation to marketing: a **pivotal** or registration study is one designed to support an approval claim, and the same study run after approval changes regulatory character even where its science is identical. The type of study decides the type of permission: that sentence is the bridge from this unit to Unit 3.

1.3 The clinical trial protocol: the study's constitution

Every item in this subject returns to one document. The **clinical trial protocol** is the written plan that states what the study is, why it is justified, how it will be conducted, analysed and reported, and how participants will be protected. Its standard contents, set by ICH GCP (Unit 4), run: background and rationale; objectives; design; the participant population with inclusion and exclusion criteria; treatments and dosing; assessments

and endpoints; safety reporting and stopping rules; statistical methods and sample size; data handling and quality management; ethics, consent and compensation arrangements; and the publication policy. The protocol is approved twice before a single participant is enrolled: by the **ethics committee** (Unit 2), which judges the ethics and the science that carries ethical weight, and, where the rules require it, by the **regulatory authority**, which judges the product and the plan together. Changes after approval travel as **protocol amendments**, classified and approved in the same order of importance, and departures in conduct are recorded as deviations and violations, because the approved protocol is the benchmark against which the whole study will one day be inspected. Beside the protocol stands the **investigator's brochure**, the compiled preclinical and clinical evidence about the product that lets investigators and committees judge risk; the protocol says what will be done, the brochure says what is already known.

1.4 Phase 0 studies: the exploratory first step

Phase 0 is the syllabus's most modern item: exploratory, first in human studies conducted before the traditional Phase I, under an exploratory investigational framework, with very limited human exposure and no therapeutic intent. The defining technique is **microdosing**: a subtherapeutic dose, conventionally not more than 100 micrograms and not more than one hundredth of the dose expected to produce a pharmacological effect, given to a small number of subjects so that sensitive analytical methods (accelerator mass spectrometry, positron emission tomography) can answer an early pharmacokinetic question: is the molecule absorbed, how is it distributed, which candidate of several deserves full development. Because exposure is so small, the preclinical package required is reduced, and the study cannot establish safety or tolerability in the ordinary sense and must never be sold to participants as treatment. Phase 0 is a development economics tool: it spends a little to avoid spending a fortune on the wrong molecule, and a regulator reading a microdose study reads it for exactly that limited purpose.

1.5 Phase I studies: safety, tolerability and pharmacokinetics

Phase I is the first systematic administration of the drug to humans, normally in **healthy volunteers**, and normally in small numbers at a single centre, with the exceptions a student must know: where the drug is expected to be too toxic for healthy people, classically cytotoxic anticancer agents, Phase I is run in patients. The objectives are safety and tolerability above all: the maximum tolerated dose or the highest safe exposure, the pattern of adverse effects, and the pharmacokinetic profile (absorption, distribution, metabolism, excretion) that every later phase will use. Phase I is not designed to show efficacy, and a Phase I report that claims efficacy misdescribes its own design. The phase is also the home of the special studies of the next section, which is why the syllabus lists Phase I together with its subtypes: the subtypes are not decorations, they are the standard building blocks from which a Phase I programme is assembled.

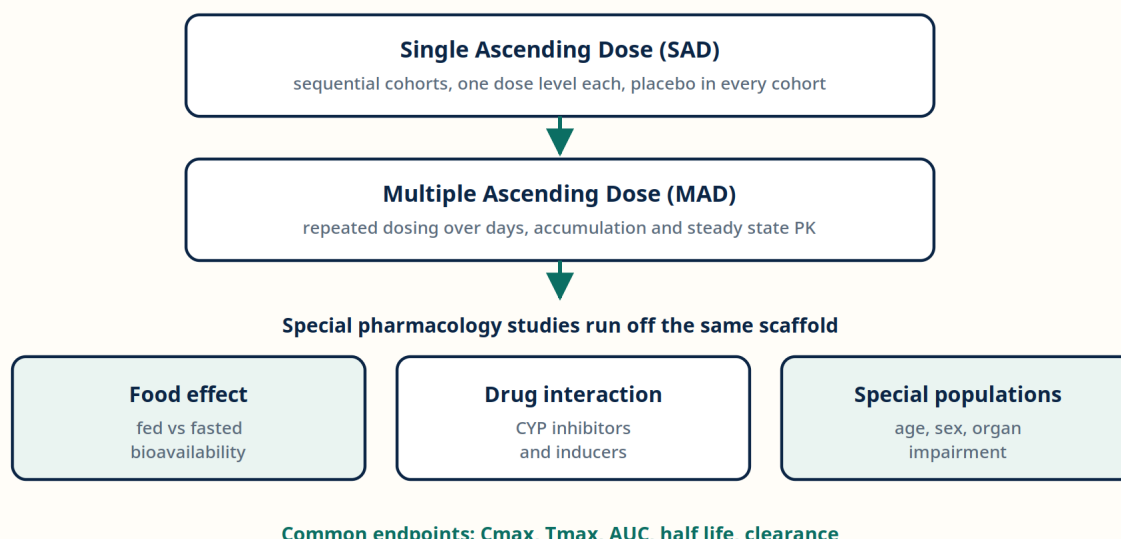
1.6 Phase I subtype studies

The subtypes each isolate one question:

- **Single ascending dose (SAD) studies** give one dose to successive cohorts, each cohort higher than the last, with sentinel dosing and predefined stopping rules, to map tolerability and pharmacokinetics across the dose range.
- **Multiple ascending dose (MAD) studies** give repeated doses over days to weeks, revealing accumulation, time dependent kinetics and tolerability at steady state.

- **Dose escalation methods** are the logic that orders the cohorts: the classical rule based schemes (the 3+3 design borrowed from oncology, the modified Fibonacci escalation of older practice) and model based approaches all answer the same ethical problem, how to climb toward an informative dose while exposing the fewest subjects to the highest risk, and the protocol must state the method and the criteria for stopping the climb.
- **Food effect studies** compare exposure fasted and after a standard high fat meal, because food can change bioavailability enough to dictate the dosing instruction on the label.
- **Drug-drug interaction studies** test the candidate against known inhibitors, inducers or substrates of the enzymes and transporters it uses, so that the label can state what must not be co-prescribed.
- **PK end points** are the measured quantities these studies exist to produce: maximum concentration (C_{max}), time to that maximum (T_{max}), area under the concentration time curve (AUC), half life, clearance and volume of distribution, the numbers that convert a molecule into a dosable medicine.

Phase I: The Study Designs of the First Human Exposure



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Figure: Phase I subtype studies: single and multiple ascending dose designs, with the food effect, drug interaction and special population studies that complete the first human characterisation (Unit 1, section 1.6).

1.7 Phase II studies: proof of concept

Phase II is the first administration to patients with the target condition, and its governing idea is the syllabus's own phrase, **proof of concept**: does the drug, at tolerable doses, move the biology or the clinical measure it was designed to move. Phase II work is typically divided in teaching into an early exploratory stage (signal finding, dose ranging across several doses, choice of endpoint) and a later stage in which the dose and population for Phase III are fixed. The outputs are decisions, not approvals: the dose range worth carrying forward, the endpoint that responds, the population that benefits, and the safety profile in patients rather than volunteers. A failed proof of concept ends most programmes, which is the point: Phase II is where money is deliberately risked in small studies so that the enormous Phase III spend is reserved for candidates that have already shown a pulse.

1.8 Phase III studies: the registration evidence

Phase III is the large, confirmatory, usually multicentre and randomised stage that produces the principal evidence of efficacy and the broader safety database on which a marketing application stands. Three of the

syllabus's qualifiers each carry a lesson. **Multi ethnicity**: a programme intended for global registration must justify that its results travel across populations, because intrinsic factors (genetics, body size, metabolism) and extrinsic factors (diet, medical practice) can shift exposure and response; the bridging logic that handles foreign data returns in Unit 3. **Global clinical trials**, run simultaneously across countries (the multiregional trial), replace the old pattern of repeating studies country by country, and they place India inside world programmes rather than after them, with the regulatory consequences Unit 3 describes.

Registration studies is the plainest name for what Phase III is for: these are the pivotal trials named in the application, designed with the regulator's expectations in view, adequately powered, and conducted to the full GCP standard, because their reports will be read line by line by assessors and can be inspected to source. Phase III is also where the safety database reaches the size at which uncommon adverse effects begin to appear, which is why Phase III safety data, not Phase I, dominates the risk sections of the eventual label.

1.9 Phase IV studies and the PSUR: after the licence

Approval does not end the clinical process; it changes its centre of gravity. **Phase IV** covers studies conducted after marketing authorisation, in ordinary practice populations far larger and more varied than any trial: post marketing surveillance studies, registries, studies of long term and rare adverse effects, of use in populations the trials excluded, and of new indications pursued after the first approval. Many are conditions of approval or commitments made during assessment, and their results can change the label, restrict use or, at the limit, end the product's life. The syllabus pairs Phase IV with the **PSUR**, the Periodic Safety Update Report, the scheduled document in which the marketing authorisation holder assembles worldwide safety data for a period, evaluates the benefit risk balance afresh, and proposes label changes: in current practice the PSUR's successor format is the Periodic Benefit Risk Evaluation Report (PBRER) of ICH E2C. Post marketing study and post marketing reporting are one activity seen from two sides: generating safety knowledge, and formally accounting for it.

The clinical development staircase

Preclinical evidence (animal pharmacology, toxicology, formulation)

-> Phase 0: microdose exploration, candidate selection (no therapy intended)

-> Phase I: safety, tolerability, PK in humans (subtypes: SAD, MAD, food effect, interaction studies)

-> Phase II: proof of concept in patients, dose finding

-> Phase III: confirmatory registration studies, global and multi ethnic

-> Marketing authorisation on the assembled dossier

-> Phase IV: post marketing studies, PSUR cycle, label evolution

Every arrow is crossed only with ethics approval and, where required, regulatory permission: the subject of Units 2 and 3

1.10 Clinical investigation and evaluation of medical devices and IVDs

Devices break the drug pattern, and the syllabus closes the unit by making the student handle the break. A medical device acts physically rather than pharmacologically, its performance depends on the operator, its design iterates during study, and blinding and placebo control are often impossible (a sham procedure is an ethical problem, not a design option). In vitro diagnostics (IVDs) differ again: the "participant" contributes a sample, and the study measures diagnostic performance, sensitivity, specificity and agreement with a reference, rather than therapeutic effect. The regulatory system answers with two distinct activities, which the syllabus names as the unit's closing pair and which Indian law (the Medical Devices Rules 2017 of Unit 3) and ISO 14155 (Unit 5) both organise: **clinical evaluation**, the assessment of clinical data about a device, much of it from literature and equivalent devices, and **clinical investigation**, the prospective study in human subjects that generates new clinical data where evaluation alone cannot carry the claim. Confusing the two is a standard examination trap: evaluation is the wider, continuing process; investigation

is one source of evidence inside it.

1.11 Key concepts of medical device clinical evaluation

Clinical evaluation is a methodologically sound, ongoing process to collect, appraise and analyse clinical data about a device and to judge whether the evidence shows conformity with the essential principles of safety and performance when the device is used as intended. Its key concepts: it begins before marketing and continues across the product's life, fed by post market surveillance; it may rest on **equivalence**, a demonstrated sameness of clinical, technical and biological characteristics with a device whose data are already known, claimed rigorously and not by resemblance; it weighs the data for quality and relevance rather than merely counting papers; and it concludes in a clinical evaluation report that the regulator or notified body reads against the risk management file. Where the data are insufficient, the evaluation itself directs the remedy, a clinical investigation, which is the hinge to the final section.

1.12 Key concepts of clinical investigation

A clinical investigation is a systematic study in human subjects undertaken to assess the safety or performance of a device. Its key concepts adapt the drug trial machinery to the device world: a **clinical investigation plan** (the device counterpart of the protocol) stating objectives, design, endpoints and risk analysis; sponsor and investigator duties aligned to ISO 14155 rather than ICH GCP; ethics committee approval and regulatory notification or approval graded by the device's risk class and by whether the device already bears a mark; informed consent of the same ethical weight as in drug trials (Unit 2 governs both); and adverse event and device deficiency reporting that runs during and after the study. In India, clinical investigation of investigational medical devices requires the permission of the Central Licensing Authority under the Medical Devices Rules 2017, with ethics committee approval, and the investigation of an IVD is centred on performance evaluation against its intended use. With the process of both worlds now mapped, the subject turns to the question the process everywhere presupposes: what makes it permissible to experiment on a person at all.

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