

Unit 1: General Research Methodology

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Research Methodology and Biostatistics, subject code MRM301T, is the common theory subject of M.Pharm Semester 3, taken by every specialisation (Pharmaceutics, Pharmaceutical Chemistry, Pharmacology and all others) in the semester devoted to research work. It carries 4 credits and 60 hours of theory, taught at 4 hours per week, for 100 marks. This subject teaches the student how to do the research that Semester 3 and 4 demand, and how to judge the research of others. Unit 1 covers general research methodology: what research is, how a study is designed, and the defensive machinery (controls, randomization, placebo, blinding) that keeps a study honest. Unit 2 is the biostatistics core, and the reason this page is the M.Pharm Biostatistics notes page for every branch: sample size, the null hypothesis and P values, and the named parametric and non parametric tests, each taught with a fully worked numerical example whose arithmetic is shown step by step. Unit 3 turns to medical research ethics: the four values of autonomy, beneficence, non maleficence and justice in their classic form, informed consent, confidentiality, and the professional practice problems of conflicts of interest, referral and vendor relationships. Unit 4 sets out the CPCSEA guidelines for the laboratory animal facility, the rules under which the preclinical half of a pharmacy research project is housed and run. Unit 5 closes with the Declaration of Helsinki, the founding ethical document of modern medical research, its history and its two sets of principles. A student who masters this subject can plan a defensible project, analyse its data with the right test, and house, consent and report the work inside the rules.

1.1 What research is

Research is systematic, controlled and critical investigation carried out to discover new facts, to verify or revise accepted facts, or to build new theory from them. The word itself suggests searching again: knowledge is not collected once and finished, it is re-examined whenever a better instrument, a new drug or a sharper question appears. In pharmacy, research spans the bench (a new molecule, a new formulation), the animal facility (pharmacology and toxicology), the clinic (trials in patients) and the population (pharmacoepidemiology), and the method changes with the territory while the discipline stays the same.

Three characteristics separate research from casual inquiry. It is **systematic**: the steps are planned in advance and followed in order, so that another worker could repeat them. It is **controlled**: as far as possible, only the factor under study is allowed to vary, and everything else is held constant, matched or randomised away (sections 1.9 to 1.13 exist for this purpose). And it is **empirical**: conclusions rest on observations and measurements, not on authority or plausibility. A result that cannot, in principle, be tested against observation is not yet a research finding.

Research is also classified by purpose. **Basic (pure) research** pursues knowledge for its own sake, such as the mechanism of a receptor. **Applied research** aims at a practical problem, such as improving the dissolution of a poorly soluble drug. **Action and evaluative research** test whether an intervention or a programme works in its real setting. The M.Pharm project usually sits in applied research, but it borrows its rigour from the basic tradition.

1.2 Objectives of research and the research problem

Every study begins as a problem: a gap between what is known and what needs to be known, stated sharply enough to be answered. "Improve the tablet" is not a research problem; "does replacing lactose

with mannitol raise the 45 minute dissolution of drug X tablets from 75 percent to at least 85 percent" is one, because it names the intervention, the outcome and the size of change worth having. The **objective** of a study is the formal statement of what the study will establish. A primary objective names the single main question; secondary objectives list the supporting questions. Objectives must be specific, measurable, achievable with the available facilities, relevant and time bound.

From the objective flow the remaining planning decisions: what will be measured (the outcome variables), in whom or in what (the study units), with what comparison (the control), and how many (the sample size of Unit 2). A hypothesis, a testable prediction that the study will confirm or refute, is often written alongside the objective; its formal statistical twin, the null hypothesis, is the subject of section 2.8. A common failure of student projects is to collect data first and invent the objective afterwards; the objective is not decoration, it is the contract the analysis must fulfil.

1.3 Requirements of a good research study

A defensible study must satisfy a short list of requirements before the first observation is made:

- **A written protocol or proposal** stating the problem, objectives, design, methods, sample size and analysis plan in advance.
- **A design matched to the question**, chosen from the families of section 1.7, strong enough for the claim the student wants to make.
- **Defined materials and methods**, so that the work is reproducible: identified drug source and purity, calibrated instruments, named animal strain, stated inclusion and exclusion criteria for subjects.
- **Bias control built in**, not argued afterwards: controls, randomization, blinding and a placebo where the design needs them.
- **Ethical clearance** before the work begins: institutional ethics committee approval for human work, Institutional Animal Ethics Committee approval under CPCSEA for animal work (Unit 4).
- **Adequate resources and time**: the requirements of research are practical as well as intellectual, and a study that runs out of animals, reagents or follow up time produces fragments, not findings.
- **An analysis plan**, including which statistical test will answer which objective, decided before the data arrive (Unit 2).

The research process then runs in a fixed order, each step feeding the next:

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    A[Problem identified and objectives stated] --> B[Review of literature (what is already known)]
    B --> C[Study design chosen, protocol written]
    C --> D[Ethics approval + sample size fixed]
    D --> E[Data collected as per protocol]
    E --> F[Data analysed with the planned tests]
    F --> G[Interpretation, conclusion, report and thesis]
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The Research Process



Evaluation feeds back: a finished study raises the next question.

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Figure: The research process. No later step can rescue a study whose earlier steps were skipped: a weak design is not repaired by a large sample or a clever test.

1.4 Practical difficulties in research

The syllabus names practical difficulties because real research meets them constantly, and examiners expect the student to know the standard ones and their remedies. **Finance and materials:** research costs money, and imported reagents, animals and instrument time strain a department budget; the remedies are realistic scoping, institutional and external grants, and designs that answer the question with fewer subjects (a crossover design, section 1.11, is one such economy). **Time:** a two semester project competes with coursework, and slow steps (animal acclimatization, stability studies, patient recruitment) cannot be hurried; the remedy is a work plan with margins. **Non availability and non cooperation of subjects:** patients refuse, drop out (section 2.7) or cannot be followed; animal supply fails. **Lack of standardised tools and techniques:** two laboratories measuring the same quantity differently cannot pool or compare results, which is why validated methods and calibrated instruments are a requirement, not a virtue. **Bias of the investigator:** the researcher's hope for a positive result is itself a source of error, answered by the machinery of sections 1.9 to 1.13. **Ethical and administrative constraints:** some questions cannot be asked experimentally in humans at all, and approval timelines are real. Naming the difficulties in the proposal, with the plan for each, is part of research competence.

1.5 Review of literature

The **review of literature** is the systematic survey of what has already been published on the problem. It does five jobs. It prevents duplication: rediscovering a published result wastes a year. It defines the gap the new study will fill, which sharpens the objective. It borrows and improves methods: the best published design for the same question is the starting point for the new protocol. It supplies the comparison values (expected effect size, expected variability) that the sample size calculation of Unit 2 needs. And it warns of difficulties others have met.

Sources are searched in a hierarchy of reliability. Primary sources (original research papers in peer reviewed journals) carry the evidence; secondary sources (reviews, textbooks) organise it; databases and

indexes (PubMed and MEDLINE, Scopus, Web of Science, Google Scholar, and the library's journal holdings) find it. A working review records for each paper the question, the design, the sample, the result and the limitation, not merely the conclusion. The review ends by stating, in a paragraph, what is known, what is disputed and what is missing: the missing part is the justification of the new study.

1.6 Study design: the plan of the investigation

A **study design** is the complete plan that specifies how subjects or materials are selected, how groups are formed, what is done to each group, what is measured, when, and how the results will be analysed. It is chosen before data collection and written into the protocol. The design decides in advance the strength of conclusion the study can support: a well designed small study outranks a large careless one, because size cannot repair a design flaw, it only estimates the wrong quantity more precisely.

Designing a study means deciding four things. First, the **study units** and how they are sampled. Second, the **comparison structure**: is there a control group, and of what kind (section 1.9)? Third, the **allocation**: who or what receives which intervention, and is it randomised (section 1.10)? Fourth, the **measurement plan**: outcomes, instruments, time points, and the safeguards of placebo and blinding where perception can distort measurement. The next section names the standard families these choices produce.

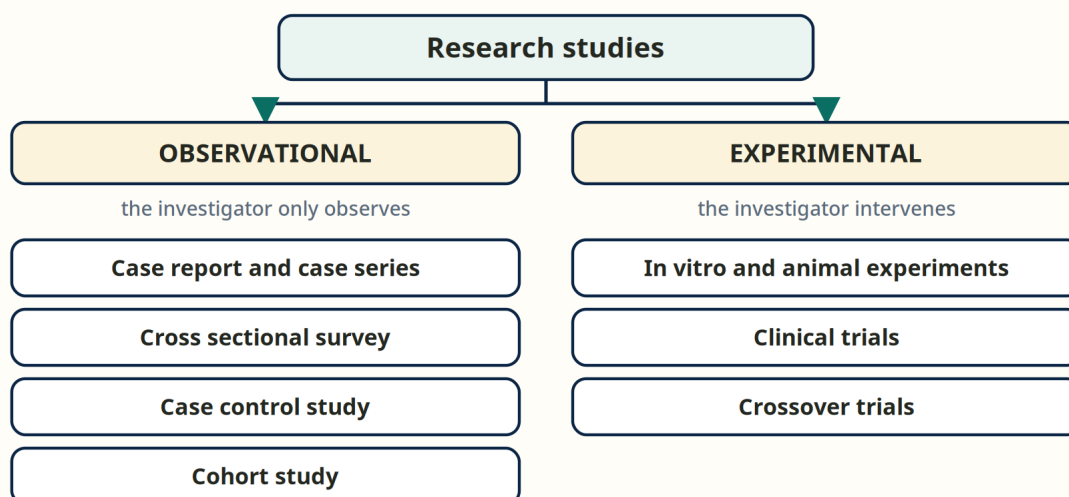
1.7 Types of studies

Studies are classified first by whether the investigator assigns the exposure or merely observes it.

Family	What the investigator does	Standard members	Typical pharmacy use
Descriptive	Observes and reports, no comparison group	Case report, case series, cross sectional survey	ADR case reports, drug utilisation surveys
Analytical observational	Observes exposures and outcomes, no assignment	Cohort, case control, cross sectional analytical	Pharmacoepidemiology, risk factor studies
Experimental (interventional)	Assigns the intervention	Randomised controlled trial, crossover trial, preclinical experiments	Clinical trials, animal pharmacology
Review based	Works on published studies, not new subjects	Narrative review, systematic review, meta analysis	Evidence synthesis for a thesis introduction

In a **cohort study** exposed and unexposed groups are followed forward to compare outcome rates; it can estimate incidence but is slow and costly. In a **case control study** cases (with the outcome) and controls (without) are compared backward for past exposure; it is fast and the classic design for rare outcomes such as rare adverse reactions, but it cannot estimate incidence and leans on records and memory. A **cross sectional study** measures exposure and outcome at one point in time, a snapshot suited to prevalence. **Experimental studies** assign the intervention and so support causal claims most strongly; in preclinical work the "subjects" are animals, cell lines or formulations, and the same design logic applies. The choice among them is dictated by the question, the rarity of the outcome, ethics and resources, in that order.

Types of Research Studies



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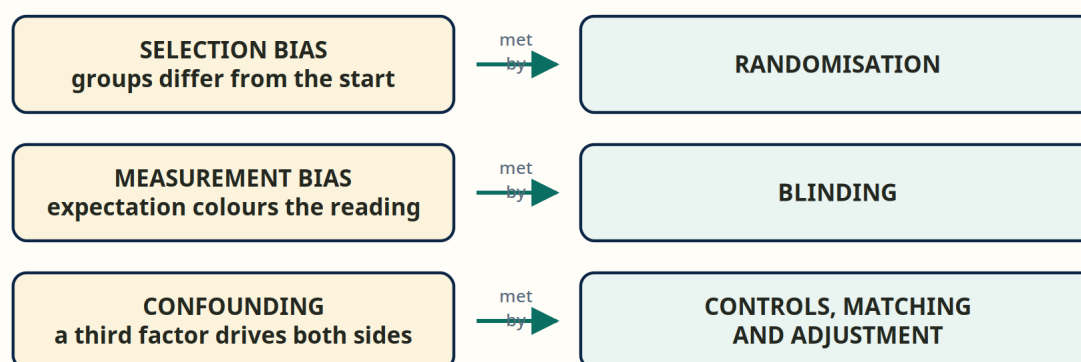
Figure: The families of study designs. Moving right, the investigator controls more of the conditions and the design supports stronger causal claims, at greater cost and ethical weight.

1.8 Errors and bias, and the strategies against them

Two kinds of error threaten a study. **Random error** is chance variation: it scatters individual results around the truth, shrinks as sample size grows, and is quantified by the confidence intervals and P values of Unit 2. **Systematic error, or bias**, pushes results consistently away from the truth in one direction; no sample size cures it, because a biased method applied to a million subjects is precisely wrong. Bias enters at every stage: **selection bias** when the groups differ from the start (healthier patients channelled to the new drug), **information or measurement bias** when outcomes are measured differently between groups (an unblinded assessor scoring the favoured group generously), and **confounding** when a third factor linked to both exposure and outcome imitates an effect (age confounding a comparison between a drug given to the young and one given to the old).

The strategies to eliminate errors and bias are the armoury of the next five sections, and they divide by target. Against selection bias and confounding: randomization (section 1.10), supported by restriction and matching at the design stage and adjustment at analysis. Against measurement bias: blinding (section 1.13), standardised instruments and objective endpoints. Against the expectation effects of subjects and the natural course of disease: controls and placebo (sections 1.9 and 1.12). A protocol should name, for each foreseeable bias, the strategy that answers it.

Bias and Its Controls



The P value prices random error only: it cannot rescue a biased design.

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Figure: The bias control toolkit. Each tool answers a named family of bias; a protocol should pair every foreseeable bias with its tool.

1.9 Controls

A **control** is the comparison condition against which the test condition is judged. Without a control, a change observed after treatment cannot be attributed to the treatment: patients improve spontaneously, measurements drift, seasons change, and disease fluctuates. The control group experiences everything the test group experiences except the active intervention, so the difference between groups isolates the intervention's effect.

Controls are classified by time and by content. A **concurrent control** runs alongside the test group in the same period and is the standard; a **historical control** is taken from past records and is weaker, because everything else (care standards, diagnostics, population) has also changed. By content, the control may receive **no treatment** (acceptable only where no effective treatment exists or withholding is harmless), a **placebo** (section 1.12), the **standard treatment** (active control, the usual choice once an effective therapy exists), or a **different dose** of the same drug. In preclinical work the equivalents are the vehicle control (the solvent or base without drug), the untreated control and the positive control (a standard drug of known effect, proving the assay could have detected an effect). The choice of control is an ethical as well as a scientific decision, and Unit 5 states the governing rule: participants must not be denied the best proven intervention without strong justification.

1.10 Randomization

Randomization is the allocation of subjects to groups by chance alone, using a random process (random number tables or a computer generator) rather than the investigator's judgement, alternation or record number. It does two things no other device does. It removes **selection bias** at allocation, because nobody, consciously or not, can steer the promising subjects into the favoured group. And it distributes **all other factors, known and unknown**, between the groups in proportion, so that on average the groups differ only in the intervention: age, severity, habits and confounders nobody has thought of are balanced by the same throw of the dice. This second property is why the randomised controlled trial sits at the top of the design hierarchy.

The standard methods are **simple randomization** (each subject allocated by an independent random draw; simple, but can leave unequal group sizes in small trials), **block randomization** (allocation in small blocks, such as blocks of four containing two of each treatment in random order, keeping the groups

balanced throughout recruitment) and **stratified randomization** (randomization performed separately within strata of a strong prognostic factor, such as sex or disease severity, so that factor is balanced exactly). Two disciplines protect the device: the allocation sequence is **concealed** from the person enrolling subjects (sealed opaque envelopes or a central system), so the next allocation cannot be anticipated and gamed; and once randomised, subjects are analysed in their allocated group (the intention to treat principle), because moving them afterwards reintroduces the selection the dice removed.

1.11 Crossover design

In a **crossover design** each subject receives two (or more) treatments in sequence, in randomised order, separated by a **washout period** long enough for the first treatment's effect to disappear. Half the subjects take treatment A then B, the other half B then A, and each subject serves as his or her own control. Because the comparison is made within subjects, the large variation between people is removed from the error term, and the same precision is reached with far fewer subjects: the economy that makes the crossover the standard design of bioequivalence studies and of stable chronic condition trials (the two period, two sequence design of MPH202T is this design at work).

The design has strict conditions. The condition must be **chronic and stable**, returning to baseline when treatment stops; the treatments must have **reversible** effects, since a cure or a death in period one leaves nothing to cross over; washout must truly clear the first drug, or a **carryover effect** contaminates period two; and a **period effect** (the disease or the season changing between periods) must be checked in the analysis. Where the conditions hold, the crossover is the most efficient design in this unit; where they fail (acute curable infections, progressive fatal disease), it is unusable, and the parallel group design returns.

1.12 Placebo

A **placebo** is an inert preparation identical in appearance, taste and administration to the test treatment but without its active ingredient. Its scientific purpose is to separate the pharmacological effect of a drug from the **placebo effect**: the genuine improvement produced by the act of treatment itself, the expectation of benefit, the attention of the investigators and the natural course of the illness. In many symptomatic conditions (pain, anxiety, functional bowel complaints) a third or more of patients improve on placebo alone, so an uncontrolled "improvement" figure is meaningless until the placebo group's improvement is subtracted.

Placebo use is bounded by ethics. It is acceptable where no proven effective treatment exists, where the condition is minor and self limiting, or as an addition on top of standard therapy given to all groups. It is not acceptable to withhold a proven life saving or harm preventing treatment for the sake of a cleaner comparison; there the control must be the standard treatment (section 1.9), and the Declaration of Helsinki (Unit 5) states the exceptions narrowly. In preclinical and formulation work the placebo's cousins, the blank and the vehicle control, carry no such ethical weight and are routine.

1.13 Blinding techniques

Blinding (masking) keeps the identity of the allocated treatment unknown to the people whose knowledge could bend the result. In an **open label** study everyone knows; it is acceptable for objective endpoints (death, a laboratory value) and unavoidable for some interventions (surgery, devices), but it invites bias everywhere else. In **single blinding** the subject does not know which treatment he receives, answering expectation and reporting bias on the subject's side. In **double blinding** neither subject nor investigator or assessor knows, answering the assessor's measurement bias as well; it is the default standard for drug trials with subjective endpoints. **Triple blinding** adds the analyst or the data monitoring committee to the masked parties. Blinding is engineered, not declared: identical dosage forms, matched taste and

packaging, coded labels, sealed code breaks held by a third party, and a documented emergency unblinding procedure. Where two treatments cannot be made to look alike, the **double dummy** technique gives every subject two preparations, an active one and a dummy matching the other arm. A blind is only as good as its testing: side effects that reveal the drug (dry mouth, bradycardia) can unblind a trial in practice, which is one more reason objective endpoints are prized.

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