

## Unit 5. Research Designs and Terminologies

### Unit 5: Research Designs and Terminologies

#### Learning Goals

By the end of this unit, you will be able to:

- Differentiate **case reports** and **case series** and recognise their role in signal generation.
- Classify studies as **cross-sectional** or **longitudinal**, and choose appropriate measures.
- Plan and appraise **cohort** and **case-control** studies, including control of confounding.
- Understand the architecture of **clinical trials (RCTs)** and their variants.
- Conduct **literary research and reviews** with transparent, reproducible methods.
- Distinguish **preclinical methods: in-silico, in-vitro, in-situ, in-vivo**.
- Correctly use core **terminologies**: randomisation, matching, blinding, and bias.

#### 1) Case Reports

**What it is:** A detailed description of an **individual patient** (or a few) highlighting unusual **presentation, diagnosis, management, outcome, or adverse event**.

**Why it matters:**

- Generates **hypotheses** and **early safety signals** (e.g., suspected herb-drug interaction).
- Teaches **diagnostic reasoning** and documentation quality.
- May describe **novel techniques** (e.g., a modification in *Nasya* administration for a specific anatomical variant).

**Key elements (CARE guideline mindset):**

- Clear timeline, baseline, differential diagnoses, intervention details (dose, route, *anupāna*), outcomes, follow-up, and informed consent for publication.
- Avoid **causal claims**; emphasise plausibility, not proof.

**Strengths/limits:** Quick, inexpensive, clinically rich / **no control group**, high risk of bias, cannot estimate frequency or effect size.

#### 2) Case Series

**What it is:** A **descriptive** summary of several similar cases treated or observed in a defined period/place **without a comparator**.

**Use:**

- Early evaluation of **feasibility**, typical responses, adverse events, procedural refinements.
- Documentation of **service models** (e.g., whole-system Ayurvedic package for osteoarthritis over 12 months).

**Cautions:**

- Susceptible to **selection** and **publication** bias.
- Do not over-interpret; at best, provides **denominators** and suggests variables for future analytical studies.

## 3) Cross-Sectional and Longitudinal Studies

### 3.1 Cross-Sectional

**Snapshot at one time;** measures **prevalence** and associations.

- **Questions:** “How common is *Agni* impairment among OPD attendees?” “Is *Prakṛti* associated with BMI category?”
- **Measures:** Prevalence, mean/median, **prevalence ratio** or **odds ratio** for associations.
- **Strengths:** Fast, economical; useful for planning services.
- **Limits:** **Temporal ambiguity**—exposure and outcome measured together; cannot estimate incidence.

### 3.2 Longitudinal

**Repeated observation over time;** includes **cohort** studies, **panel** studies, and **repeated measures**.

- **Questions:** “What is the **incidence** of dyspepsia after dietary change?” “How do pain scores evolve after *Virechana* across 12 weeks?”
- **Measures:** Incidence rate/risk, **risk ratio (RR)**, **hazard ratio (HR)**; trajectories.
- **Strengths:** Temporal ordering supports causal inference; can assess **change**.
- **Limits:** Cost, **loss to follow-up**, changing exposure definitions.

## 4) Cohort Studies

**Design logic:** Enrol participants **free of outcome**, classify them by **exposure** (e.g., received *Basti* vs not), and **follow forward** to measure outcome occurrence. Can also be **retrospective** if reliable records exist.

**Best for:**

- Estimating **incidence** and **relative risk**.
- Studying **multiple outcomes** of one exposure (e.g., benefits and harms of a formulation).

**Typical outputs:**

- **Risk Ratio (RR)** = risk in exposed / risk in unexposed.
- **Hazard Ratio (HR)** from survival models when time-to-event is key.
- **Absolute Risk Difference** and **Number Needed to Treat/Harm (NNT/NNH)**.

**Strengths:** Clear temporality, direct computation of risks, multiple outcomes.

**Limitations:** Confounding by indication, large sample/time for rare outcomes, losses to follow-up.

**Bias control:**

- **Design:** restriction, **matching**, random sampling, careful exposure definition.
- **Analysis:** multivariable regression, **propensity scores**, inverse-probability weighting, sensitivity analyses.
- **Data quality:** validated outcomes, blinded adjudication when feasible.

## 5) Case-Control Studies

**Design logic:** Start with **cases** (have outcome) and select **controls** (do not). Look **back** to compare exposure histories.

**Best for:**

- **Rare outcomes** (e.g., herb-induced liver injury), **long latency** diseases, early signal testing.

**Measure: Odds Ratio (OR)**  $\approx$  RR when outcome is rare.

- $OR = (\text{odds of exposure among cases}) / (\text{odds of exposure among controls})$ .

**Control selection:**

- Should represent the **same source population** as cases.
- **Matching** (age, sex, clinic) can improve efficiency but avoid **overmatching** (don't match on variables in causal pathway).

**Strengths:** Efficient for rare outcomes, quicker, lower cost.

**Limitations:** **Recall bias, selection bias**, cannot directly estimate incidence; temporal sequence may be uncertain.

**Good practices:**

- Pre-define exposure windows; use records where possible to reduce recall bias.
- Use multiple control groups if justified; analyse matched data with appropriate models (e.g., conditional logistic regression).

## 6) Clinical Trials (Randomised Controlled Trials)

**Essence:** Investigators **assign interventions** by **randomisation** to compare outcomes.

### 6.1 Trial Taxonomy

- **Explanatory (efficacy) RCTs:** strict eligibility, fixed protocol, intensive follow-up; **high internal validity**.
- **Pragmatic (effectiveness) RCTs:** broad eligibility, flexible delivery in routine care; **high external validity**.
- **Cluster RCTs:** randomise clinics/wards/districts; adjust sample size for **intra-cluster correlation (ICC)**.
- **Stepped-wedge trials:** staggered rollout; all clusters eventually receive intervention.
- **Adaptive/platform trials:** modify arms or add/drop interventions based on interim data under pre-specified rules.

### 6.2 Core Architecture

- **Prospective registration;** pre-specified **primary outcome** and **analysis plan**.
- **Sample size** based on **MCID**, variance, alpha, and power.
- **Randomisation** (simple, block, stratified, minimisation) with **allocation concealment** (e.g., central randomisation, opaque sequentially numbered envelopes).
- **Blinding** of participants/personnel/outcome assessors where feasible.
- **Intention-to-treat (ITT)** analysis; sensitivity **per-protocol** analysis.
- **Data Safety Monitoring Board (DSMB)** for moderate-to-high-risk trials.
- **CONSORT**-aligned reporting of flow diagram, baseline, outcomes, harms.

### 6.3 Integrative/Ayurveda-Specific Notes

- **Describe whole-system care:** diagnostic framework (*doṣa, dūṣya, srotas, agni*), components (diet, lifestyle, *Pañcakarma*, formulations with botanical identity, dose, *anupāna*), and fidelity monitoring.
- Use **patient-important outcomes** (pain, function, quality of life) alongside validated **Ayurvedic constructs** (e.g., *Agni* scale), and monitor **herb-drug interactions**.

## 7) Literary Research and Reviews

**Purpose:** Synthesize **existing knowledge** or critically analyse **classical texts** and modern literature to answer a focused question.

## 7.1 Types

- **Narrative review:** broad overview; may be selective—useful for orientation but prone to bias.
- **Scoping review:** maps **what evidence exists**, concepts, and gaps; useful when questions are broad or heterogeneous.
- **Systematic review (with/without meta-analysis):** predefined protocol, **comprehensive search, risk-of-bias assessment**, and transparent synthesis.
- **Umbrella review:** review of systematic reviews.

## 7.2 Method (Systematic Mindset)

- Frame a **PICO/PEO** question; register a protocol where applicable.
- Search multiple sources (databases, theses, registries); document strategies.
- Use appropriate **risk-of-bias tools** (e.g., RoB 2 for RCTs, ROBINS-I for non-randomised, QUADAS-2 for diagnostic).
- If meta-analysis is possible, address **heterogeneity** ( $I^2$ ), use **random/fixed effects** as justified, assess **publication bias** (funnel plots, Egger test).
- Grade certainty (e.g., **GRADE** framework) and present **summary of findings tables**.

## 7.3 Classical (Ayurveda) Literary Research

- Compare **manuscript variants**, commentaries (e.g., **Dalhana, Cakrapāṇi**), and **pariyāya (synonyms)** consistently.
- Trace **term evolution** (e.g., *Grahani, Pāṇḍu*) across *Samhitā* to later *Nighaṇṭu* literature; ensure accurate **botanical mapping** for dravyas.
- Maintain a **citation trail**; avoid selective quoting; document translation decisions.

## 8) Preclinical Methods

Method	Meaning	Typical Uses	Notes
<b>In-silico</b>	Computer-based modelling (QSAR, docking, ADMET, network pharmacology)	Prioritise leads, predict toxicity/interactions	Fast screening; needs experimental validation
<b>In-vitro</b>	Experiments in controlled environment outside a living organism (cell lines, organoids, enzyme assays)	Mechanisms, potency, preliminary toxicity	Standardise extract; ensure assay reproducibility
<b>In-situ</b>	Studies <b>within</b> natural tissue/site (e.g., tissue sections, localised measurements)	Localisation of molecules, receptor distribution	Preserves micro-environment; interpret with care
<b>In-vivo</b>	Experiments in <b>living organisms</b> (animal models)	Efficacy, safety, PK/PD, dose finding	Follow <b>3Rs</b> and <b>ARRIVE</b> reporting; justify species/model

**Translational flow:** in-silico → in-vitro → in-vivo → early clinical → trials → implementation. At each step, ensure **quality assurance** and **replicability** (materials, dose, processing).

## 9) Terminologies: Randomisation, Matching, Blinding, Bias

### 9.1 Randomisation

**Definition:** A process that uses **chance** to allocate participants to study arms, ensuring **comparable groups** on both measured and unmeasured factors.

**Types:**

- **Simple:** like repeated coin toss; risk of imbalance in small samples.
- **Block:** preserves balance within blocks (e.g., size 4/6); keep block size concealed.

- **Stratified:** separate randomisation lists within strata (e.g., site, severity).
- **Minimisation:** dynamic allocation balancing on multiple covariates.
- **Cluster randomisation:** units are clusters (clinics/schools).
- **Adaptive randomisation:** probabilities change using accruing data (pre-specified rules).

**Allocation concealment vs blinding:** concealment prevents **predicting** the next assignment **before** enrolment; blinding prevents **knowing** the assignment **after** allocation.

## 9.2 Matching

**Definition:** Selecting controls (or designing cohorts) so that groups are **similar** on potential confounders.

**Types:**

- **Individual matching:** one-to-one or many-to-one on variables like age, sex.
- **Frequency matching:** ensure similar **distribution** of a variable across groups.

**Cautions:**

- Avoid **overmatching** (matching on mediators or strong correlates of exposure that block causal pathways).
- Use **appropriate analysis** (e.g., conditional logistic regression for individually matched case-control studies).

## 9.3 Blinding (Masking)

**Definition:** Keeping participants, caregivers, outcome assessors, and/or analysts **unaware** of allocated intervention.

**Levels:**

- **Single-blind:** usually participant or assessor.
- **Double-blind:** participant **and** key trial personnel.
- **Triple-blind:** extends to data analysts/DSMB (with safeguards).

**When blinding is difficult:** use **objective outcomes, sham controls** where ethical, **central blinded assessment**, or **PROs** with validated instruments.

## 9.4 Bias

**Definition:** **Systematic error** that distorts the estimate away from the truth.

**Major families:**

- **Selection bias:** differences in who enters/retains in the study (e.g., volunteer bias, loss to follow-up).
- **Information (measurement) bias:** misclassification of exposure/outcome (recall bias, interviewer bias).
- **Confounding:** distortion by a third variable related to both exposure and outcome.

**Mitigation:**

- **Design:** randomisation, restriction, matching, standardised protocols, pilot testing, allocation concealment, blinding.
- **Analysis:** multivariable adjustment, propensity methods, instrumental variables, sensitivity analyses.
- **Reporting:** pre-registration, adherence to guidelines (CONSORT/STROBE/PRISMA), transparency about deviations.

## Quick Selection Guide

Question	Prefer
Unusual clinical phenomenon?	<b>Case report/series</b> (signal)



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Question	Prefer
How common at a point in time?	<b>Cross-sectional</b>
What is the incidence or prognosis?	<b>Cohort</b>
What caused a rare outcome?	<b>Case-control</b>
Does an intervention work?	<b>RCT</b> (pragmatic/explanatory/cluster as suited)
What does literature collectively show?	<b>Systematic review/meta-analysis</b>
Mechanism/toxicity before human use?	<b>Preclinical</b> (in-silico → in-vitro → in-vivo)

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## Take-Home Messages

- **Descriptive designs** (case report/series, cross-sectional) generate hypotheses; **analytical designs** (cohort, case-control, trials) test them.
  - Choose designs by **question, feasibility, ethics, and risk of bias**, not by habit.
  - In trials, **allocation concealment + blinding + ITT** protect validity.
  - Literary research demands the same rigour as primary studies: **protocol, comprehensive search, risk-of-bias assessment, transparent synthesis**.
  - Preclinical methods are complementary; always plan with **3Rs** and reporting standards.
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## Assessment

### A. Multiple-Choice Questions (MCQs)

1. The most appropriate design to study **risk factors for a rare adverse hepatic event** after a proprietary formulation is:  
A) Cross-sectional  
B) Case-control  
C) Cohort  
D) Case series  
**Answer: B**
  2. In a **cohort** study you can directly estimate:  
A) Incidence and risk ratio  
B) Odds ratio only  
C) Prevalence only  
D) Positive predictive value only  
**Answer: A**
  3. **Allocation concealment** primarily prevents:  
A) Detection bias  
B) Selection bias at enrolment  
C) Recall bias  
D) Confounding  
**Answer: B**
  4. When **individual randomisation may cause contamination** across participants, an appropriate design is:  
A) Case-control  
B) Cluster RCT  
C) Cross-sectional survey  
D) Case series  
**Answer: B**
  5. **Overmatching** occurs when you match on:  
A) Age and sex  
B) A mediator on the causal pathway  
C) A confounder
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D) A baseline risk factor unrelated to exposure

**Answer: B**

6. The **primary measure** in a standard case-control study is:

- A) Risk ratio
- B) Mean difference
- C) Odds ratio
- D) Hazard ratio

**Answer: C**

7. **Pragmatic RCTs** are designed mainly to maximise:

- A) Internal validity only
- B) External validity and real-world applicability
- C) Blinding feasibility
- D) Surrogate outcomes

**Answer: B**

8. A **scoping review** is most useful when:

- A) There are many homogeneous RCTs
- B) The question is broad and evidence is heterogeneous
- C) Meta-analysis is straightforward
- D) Only one case report exists

**Answer: B**

9. **In-silico** methods are primarily used to:

- A) Validate outcomes clinically
- B) Model interactions and prioritise leads
- C) Estimate hazard ratios
- D) Replace all in-vivo work

**Answer: B**

10. **Blinding** is least feasible in which trial?

- A) Capsule vs capsule
- B) Sham-controlled procedure
- C) Whole-system lifestyle + Panchakarma package vs usual care
- D) Placebo-controlled analgesic

**Answer: C**

## B. Short-Answer Questions (SAQs)

1. Differentiate with one example each: **case report** vs **case series** vs **cross-sectional**.
2. Define **risk ratio**, **odds ratio**, and **hazard ratio**; state which design typically uses each.
3. List **three strategies** to handle **confounding** in observational studies.
4. Explain **allocation concealment** and **intention-to-treat** with one line each.
5. Outline the **minimum steps** of a **systematic review** from question to conclusion.

## C. Long-Answer Questions (LAQs)

1. You plan to evaluate a **whole-system Ayurvedic package** for knee osteoarthritis. Compare **pragmatic RCT**, **cluster RCT**, and **prospective cohort** in terms of validity, contamination, logistics, outcomes, and ethics. Conclude with a justified choice for a district-hospital network.
2. Design a **case-control study** to investigate **herb-drug interaction-related gastritis**. Define cases/controls, exposure window, matching plan, sample size concept, bias mitigation, and analysis outline.

## D. Case Vignette (Applied Design Choice)

A teaching hospital pilots an **Abhyanga-Svedana** service for chronic low back pain. Administrators want: (i) immediate description of users and baseline pain; (ii) medium-term comparison of outcomes with usual care; (iii) a literature summary to guide policy.

### Tasks:

- a) Choose appropriate designs for (i), (ii), (iii).



- b) List one key measure for each design.  
c) Name one major bias to guard against in (ii) and one method to mitigate it.

*End of Unit 5.*

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