Unit 5. Research Designs and Terminologies

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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.

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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.

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

OR = (odds of exposure among cases) / (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).

WHERE CLASSICAL WISDOM MEETS INTELLIGENT LEARNING

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.

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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** (I²), 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, Cakrapāni), and paryāya (synonyms) consistently.
- Trace **term evolution** (e.g., *Grahani*, *Pāṇḍu*) across *Saṃhitā* 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
In-silico	Computer-based modelling (QSAR, docking, ADMET, network pharmacology)	Prioritise leads, predict toxicity/interactions	Fast screening; needs experimental validation
In-vitro	Experiments in controlled environment outside a living organism (cell lines, organoids, enzyme assays)	Mechanisms, potency, preliminary toxicity	Standardise extract; ensure assay reproducibility
In-situ	Studies within natural tissue/site (e.g., tissue sections, localised measurements)	Localisation of molecules, receptor distribution	Preserves micro-environment; interpret with care
In-vivo	Experiments in living organisms (animal models)	Efficacy, safety, PK/PD, dose finding	Follow 3Rs and ARRIVE reporting; justify species/model

Translational flow: in-silico \rightarrow in-vitro \rightarrow in-vivo \rightarrow early clinical \rightarrow trials \rightarrow 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.

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- 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? Case report/series (signal)

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Question Prefer

How common at a point in time? Cross-sectional

What is the incidence or prognosis? **Cohort**

What caused a rare outcome? Case-control

Does an intervention work? **RCT** (pragmatic/explanatory/cluster as suited)

What does literature collectively show? **Systematic review/meta-analysis**Mechanism/toxicity before human use? **Preclinical** (in-silico → in-vitro → in-vivo)

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.

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 guestion to conclusion.

C. Long-Answer Questions (LAQs)

- 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).

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- 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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