Choosing the Right Design and Methods

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Source: Microsoft 365, Stock Images

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  - Slides in this presentation heavily based on her original slides

Clinical Research Question

- Defining the main objective of a clinical trial
- Should be well-defined and specific
- Supported by data
- Driving key decisions and influencing the conduct of the trial
  - Study design
  - Statistical methods

Population, Intervention, Comparison, and Outcome (PICO)

- Framework used to formulate research questions
- PICO: Population
  - Patient group of interest
  - Defined according to eligibility criteria
- PICO: Intervention
  - Treatment being tested

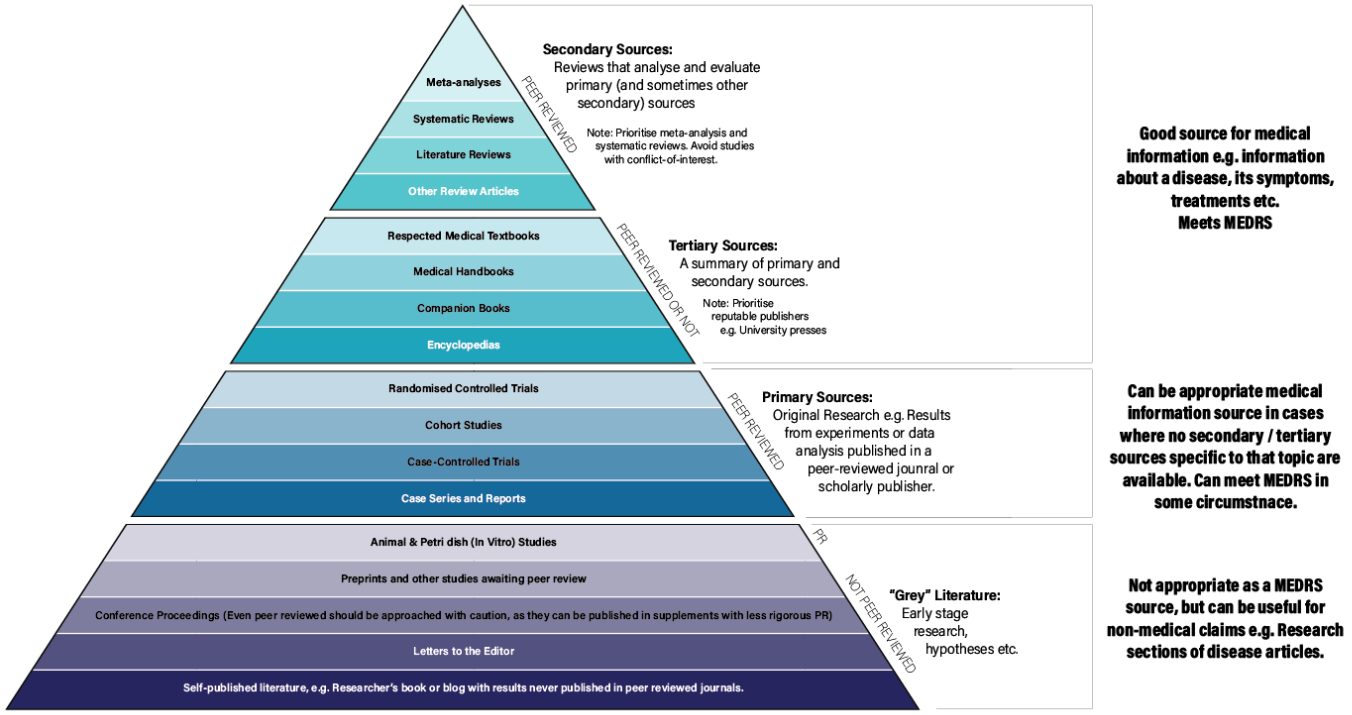
Population, Intervention, Comparison, and Outcome (PICO)

- PICO: Comparison
  - Treatment used as comparison
  - Necessary for detecting differences only due to the treatment
- PICO: Outcome
  - Primary outcome determining the result of the study
  - Secondary outcomes
  - How are outcomes measured?
  - Side effects and adverse events
  - Blinding to avoid assessment bias

Pyramid of Evidence

- Ranking study types by strength of evidence
  - Higher levels indicating higher methodological rigor and reliability
- Highest levels
  - Meta-analyses and systematic reviews
- Middle levels
  - Randomized controlled trials, cohort studies, and case-control studies
- Lowest levels
  - Case series, case reports, background information, and expert options

Pyramid of Evidence

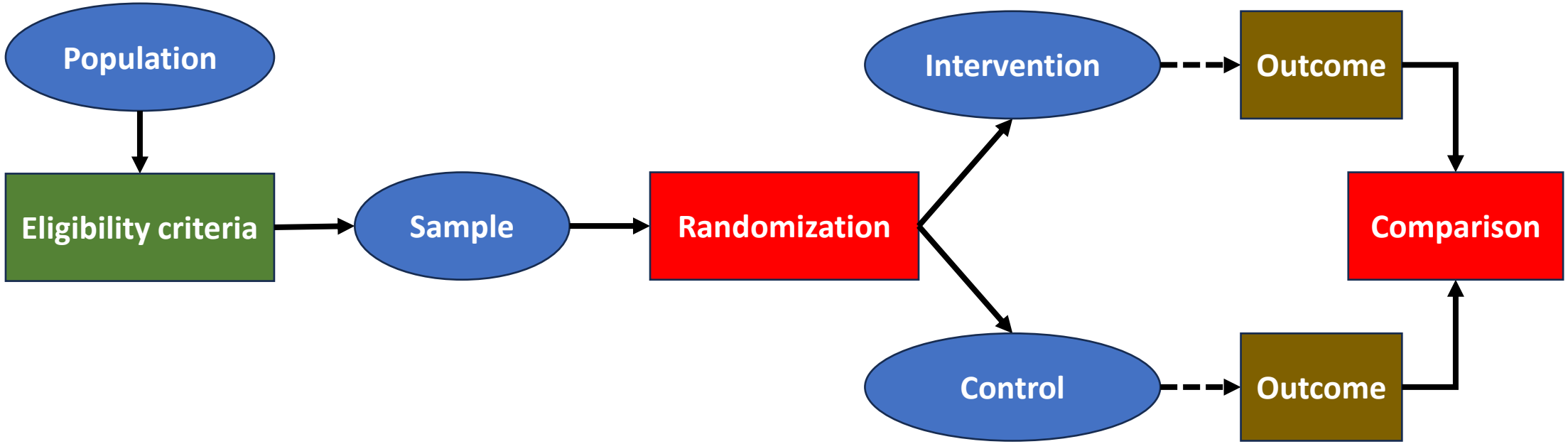


Daphne Morrow, 2025 (https://commons.wikimedia.org/wiki/File:MEDRS_Pyramid_of_evidence_2.png)

Randomized Controlled Trial (RCT)

- Assessing the efficacy of an experimental treatment
- RCT: Randomized
  - Subjects randomly allocated to one treatment group
- RCT: Controlled
  - Including a comparison group (e.g., standard treatment or placebo)
- Considered the gold standard among study types
  - Strongest evidence in establishing causality when properly planned and analyzed

RCT Structure



Randomization Techniques

- Simple randomization
- Block randomization
  - Random permuted blocks, usually with variable block sizes
  - Helps preventing large imbalances in sample size across treatment groups
- Stratified randomization
  - Important prognostic factors (2–3 at the most) measured at baseline
  - Must be accounted for in the final statistical analysis
- Minimization (dynamic randomization)

Estimand

- Precise description of the treatment effect
  - Directly linked to the research question
  - What do you want to estimate?
- Bundling several pieces of information
  - Population, treatment conditions, and outcome (PICO)
  - Handling of intercurrent events
  - Population-level summary measure of the outcome

Estimand

- ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials
  - https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-and-sensitivity-analysis-clinical-trials-guideline-statistical-principles-clinical-trials-step-5_en.pdf

Intercurrent Events

- Events occurring after the intervention
- Potentially precluding observation of the outcome or affecting its measurement
  - Discontinuation of treatment
  - Rescue medication
- May be related to the disease or the intervention – or not

Handling of Intercurrent Events

- Treatment policy
  - Event irrelevant
  - Outcome used regardless
- Hypothetical
  - As if the event did not occur
- Composite outcome
  - Event part of the outcome definition

Handling of Intercurrent Events

- While on treatment
  - Treatment effect only of interest before the event
- Principal stratum
  - Target population where the event would not have occurred

Population-Level Summary Measure of the Outcome

- Showing the difference between treatments
- Depending on the type of outcome
  - Dichotomous outcome → risk difference, risk ratio, odds ratio
  - Categorical outcome → relative risk ratio
  - Continuous outcome → mean difference, median difference
  - Count or rate outcome → incidence rate ratio
  - Survival (time-to-event) outcome → hazard ratio

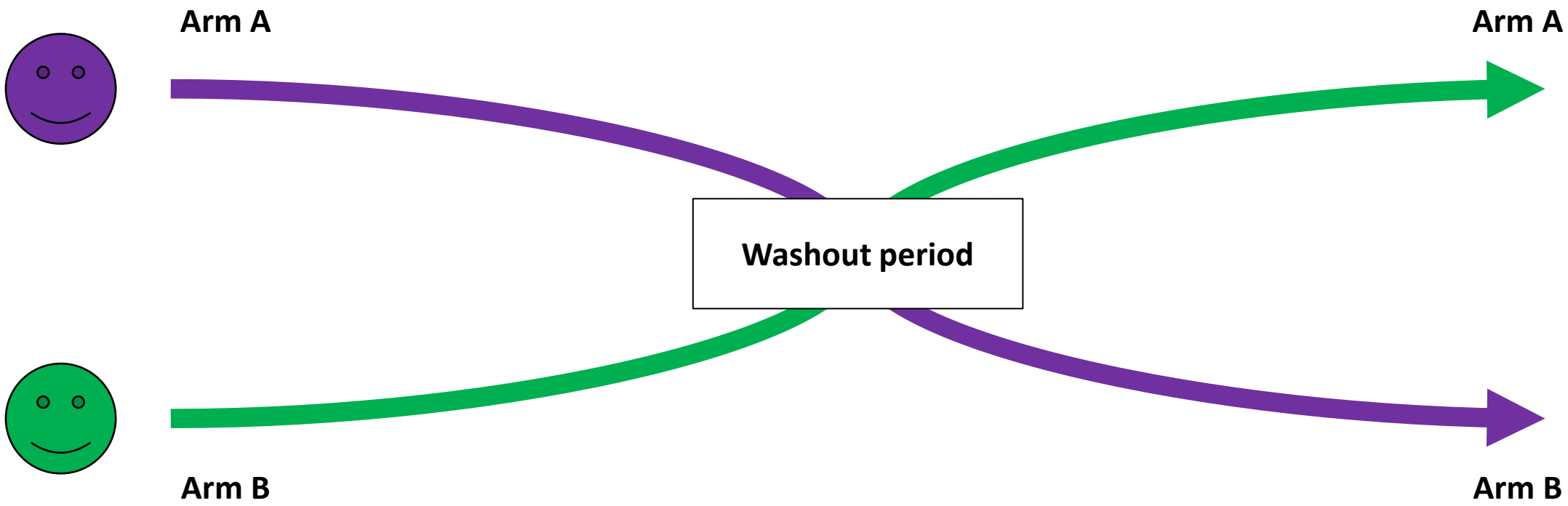
Study Design

- Parallel design
- Crossover design
- Cluster-randomized design
- Factorial design
- Platform design

Crossover Design

- Suitable for chronic, stable conditions
- Carryover effects
  - Must include a washout period
- Efficient
- Strong assumptions

Crossover Design



Cluster-Randomized Design

- Randomizing clusters instead of subjects
  - Hospitals, schools, regions, etc.
- Large sample size required
- Cluster heterogeneity and within-cluster correlation
- Pragmatic
  - Quick to recruit
- Well-suited for non-drug interventions

Factorial Design

- One control
- Two treatments
- Groups representing combinations of the treatments
- Possible to assess interaction (i.e., effect modification)
- Efficient when no interaction
- Difficult to interpret in the presence of interaction

Factorial Design

		Treatment B	
		No	Yes
Treatment A	No	Neither A nor B (control)	Only B
	Yes	Only A	Both A and B

Sample Size

- Not too small
  - Must be able to detect true a clinically important difference
- Not too large
  - Ethical considerations
  - Potential waste of resources
- Sample size and power calculations
  - Formulas and software (https://www.sealedenvelope.com/power/)
  - Relying on certain assumptions

Sample Size Considerations

- Research question
  - What to estimate and how to estimate it?
  - Study design
- Outcome
  - Dichotomous, categorical, continuous, time-to-event, count, etc.
- Statistical method
  - Two-sample test for proportions, *t* test, regression, etc.

Parameters for Sample Size Calculation

- Effect size: d
  - Treatment effect
  - Clinically important difference
- Standard deviation: σ
  - Variability in the outcome
  - Often difficult to determine
  - Based on previous literature and pilot studies

Parameters for Sample Size Calculation

- Significance level: α
  - Probability of false positives
  - Usually set to 5%
- Power: $1 - \beta$
  - Probability of true positives
  - Usually set to 80% or 90%

Sample Size Formulas

- Depending on the chosen statistical method
  - One population (one-sample mean): $n = \frac{\sigma^2 \times (Z_{1-\alpha/2} + Z_{1-\beta})^2}{d^2}$
  - Two populations (two-sample mean difference): $n = \frac{2\sigma^2 \times (Z_{1-\alpha/2} + Z_{1-\beta})^2}{d^2}$
- High effect size → fewer patients needed
- High variation → more patients needed

Factors Contributing to Complexity

- More than one primary outcome
  - Correction for multiple testing
- More than one treatment arm
- Interim analysis
  - Conducted before the planned end of the study
  - More than one look at the results
  - Alpha spending

Factors Contributing to Complexity

- Hypothesis testing objective
  - Superiority
  - Non-inferiority
  - Equivalence
- Complex study designs

Summary

- Clear research question
- Estimand
  - PICO
  - Handling of intercurrent events
  - Population-level summary measure of the outcome
- Study design
- Hypothesis testing objective
- Sample size

Clinical Trials Unit

Forskningsstøtte for kliniske studier – Clinical Trials Unit (CTU)

Planlegger du en klinisk studie? Avdeling forskningsstøtte for kliniske studier – Clinical Trials Unit (CTU) – er en del av den regionale forskningsstøtten i Helse Sør-Øst.

↓ Les mer om Forskningsstøtte for kliniske studier – Clinical Trials Unit (CTU)

Clinical Trials Unit

Slik finner du fram

Oppmøtested

Sogn Arena (Bertel O. Steen-bygget), hovedinngang, 3. etg., Klaus Torgårdsvei 3, 0372 Oslo.