

# Choice of design and methods

Forskerinitierte kliniske studier: fra idé til publikasjon

Erica Ponzi

Clinical Trial Unit, Oslo University Hospital (OUS)  
Oslo Center for Biostatistics and Epidemiology (OCBE),  
University of Oslo

[eripon@ous-hf.no](mailto:eripon@ous-hf.no)

## Why: research question

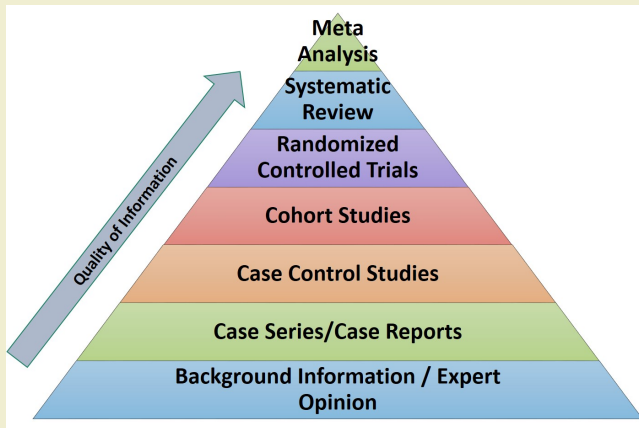
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# Why: research question

Experiments conducted to answer a **clinical research question**

- The objective of our work
- Well defined and specific
- Supported by data
- It affects all subsequent decisions and tasks

## RCTs in the context



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- RCTs are considered the **gold standard**
- Strongest evidence in establishing **causality**
- **IF the RCT is correctly planned and correctly analysed!**

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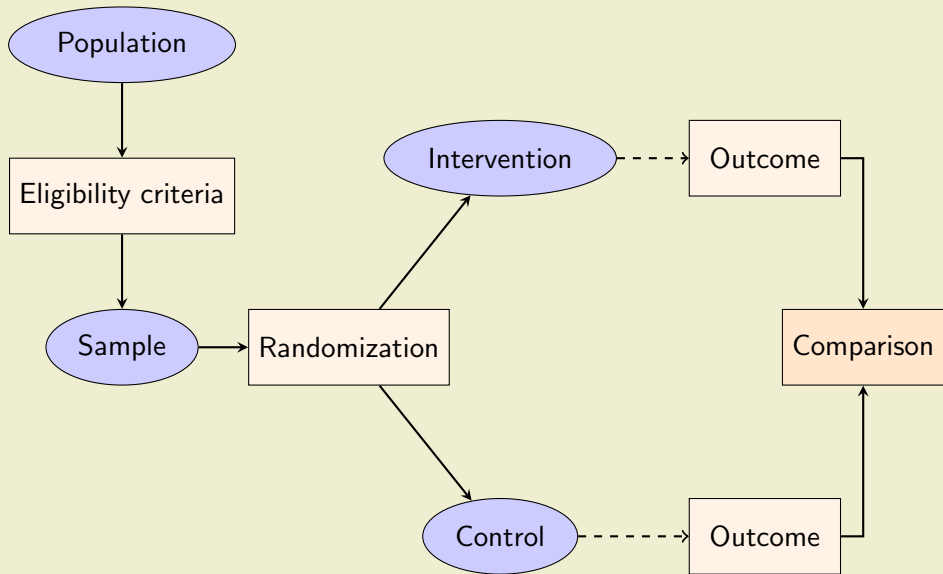
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## Randomized Controlled Trial

→ **Controlled**: the new treatment is given to the **treated** group, and another treatment is given to the **control** group

→ **Randomized**: Patients are allocated to one of the two groups **by** randomization

# Structure of an RCT



# Main ingredients: PICO

**P**opulation

**I**ntervention

**C**ontrols

**O**utcome

## P I C O: Population

A sample of **eligible** patients

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→ To generalize results to all patients who are similar

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- Intervention = treatment being tested  
drug, practice, surgical intervention, diagnostic tool, ...



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→ Allocation at random!

# Randomization techniques

- Simple randomization
- Random permuted blocks ("block randomization") to avoid size imbalance across groups
- Stratified randomization to avoid imbalance in prognostic factors
  - ▶ Choose 2-3 factors at most
  - ▶ Important prognostic factors measured at baseline
  - ▶ Will have to be accounted for in the analysis

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- Side effects? Adverse events?
- Assessment bias: **Blinding!**



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} PICO

## Handling of intercurrent events

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- Can be related to disease or intervention, or completely unrelated
- Examples: patients who discontinued treatment or took rescue medication

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- Can be related to disease or intervention, or completely unrelated
- Examples: patients who discontinued treatment or took rescue medication
- Several possible strategies:
  - ▶ Treatment policy: event is irrelevant, the outcome is used regardless
  - ▶ Hypothetical: as if the event didn't occur
  - ▶ Composite: occurrence of event is part of the outcome definition
  - ▶ While on treatment: the treatment effect is of interest only before the occurrence of an intercurrent event
  - ▶ Principal stratum: target population is set where event did not occur

# Population level summary measure for outcome

- How to present the results
- How to show difference between treatments
- Depends on the outcome definition:
  - ▶ Binary outcome → risk difference, risk ratio, odds ratio, 1-risk ratio, ...
  - ▶ Continuous outcome → mean difference, median difference, mean difference in AUCs, median ratio, ...
  - ▶ Count/rate outcome → incidence rate ratio
  - ▶ Survival/time-to-event outcome → hazard ratio, 1-risk ratio

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- Not too few: we want to detect something
- Not too many: ethical reasons and waste of resources
- Power calculations: formulas and software
- Needs to be done beforehand and can not be changed
- Relies on choices and assumptions you have to make

# What do I need for sample size calculation?

- **Research question**: clear idea of what we want to estimate and how, including the design of the study
- Choice of **endpoint**: binary, continuous, time to event,...
- Idea of statistical **method** you will use: t-test, comparing proportions, regression,...

## But I also need some numbers...

- **Effect size**: effect of the treatment, we need a size of the effect that is clinically relevant to detect
- **Variation in the data**: estimate of standard deviation in the outcome variable
- **Power**: how strongly we avoid false negatives, ability to detect a difference if there is one.
- **Significance level**: how strongly we avoid false positives, do not detect a difference if there is none.

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- **Effect size:** effect of the treatment, we need a size of the effect that is clinically relevant to detect

→  $d$

- **Variation in the data:** estimate of standard deviation in the outcome variable

→  $\sigma$

- **Power:** how strongly we avoid false negatives, ability to detect a difference if there is one.

→  $1 - \beta$

- **Significance level:** how strongly we avoid false positives, do not detect a difference if there is none.

→  $\alpha$

## Formula for sample size calculation

$$n = \frac{(Z_{\alpha} + Z_{\beta})^2 \cdot \sigma^2}{d^2}$$

- Higher effect size fewer patients needed
- Higher variation more patients needed

## Where do I find these numbers?

- Good news: power and significance are often set to standard levels
- Power set to 80% or 90%
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- Power set to 80% or 90%
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- Bad news: effect size and standard deviation are difficult to find
- Some options: literature, pilot studies, ...

## When does it get more complicated?

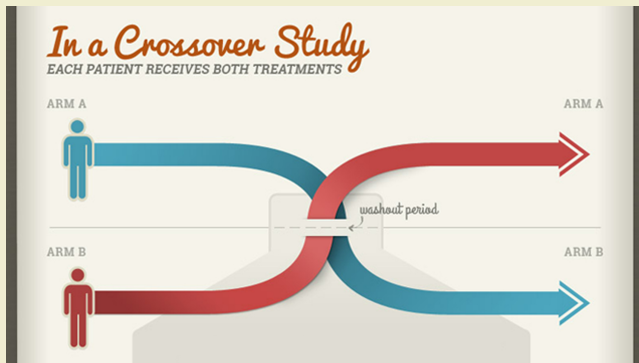
- More than one primary outcome
- More than one look at the results: interim analysis
- More than one arm
- Superiority vs non-inferiority
- More complex designs

## Choice of design

## Some designs

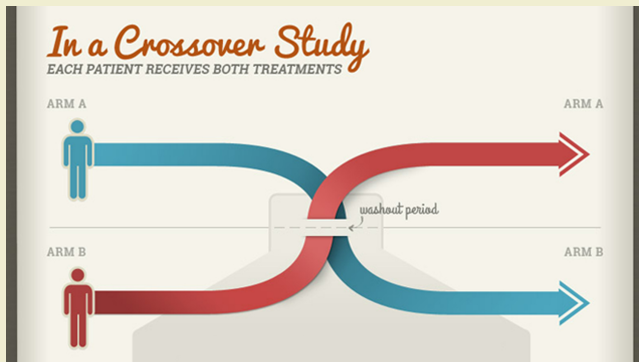
- Parallel arms
- Crossover trials
- Cluster randomized trials
- Factorial design
- Platform trials
- ...

# Crossover design



**Figure:** <https://blog.lillytrialguide.com/clinical-trial-design-parallel-crossover-studies/>

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- Carry-over effects: wash-out period
- Time effect: chronic, stable conditions
- Efficient
- Strong assumptions

# Cluster-randomized design

- Randomize groups (clusters) instead of individuals
- Examples: schools, hospitals, regions,...



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- Examples: schools, hospitals, regions,...
- Needs high sample size
- Heterogeneity vs within cluster interactions
- Pragmatic, quick to recruit
- Good for non- drug interventions

## Factorial design

	Control	Treatment 1
Control	Control	Treatment 1
Treatment 2	Treatment 2	Treatment 1 + Treatment 2

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- One control, two interventions
- Possible to assess interaction
- Efficient if no interaction
- Difficult to interpret if there is an interaction

# Summary

- Clear research question
- Estimand (PICO + intercurrent events + summary measure for outcome)
- Type of outcome
- Type of test (superiority vs non-inferiority vs ...)
- Number of patients
- Design: is parallel enough or do we need some other structure?

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→ Come and talk to us!