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

Oslo universitetssykehus

UiO : University of Oslo

Why: research question

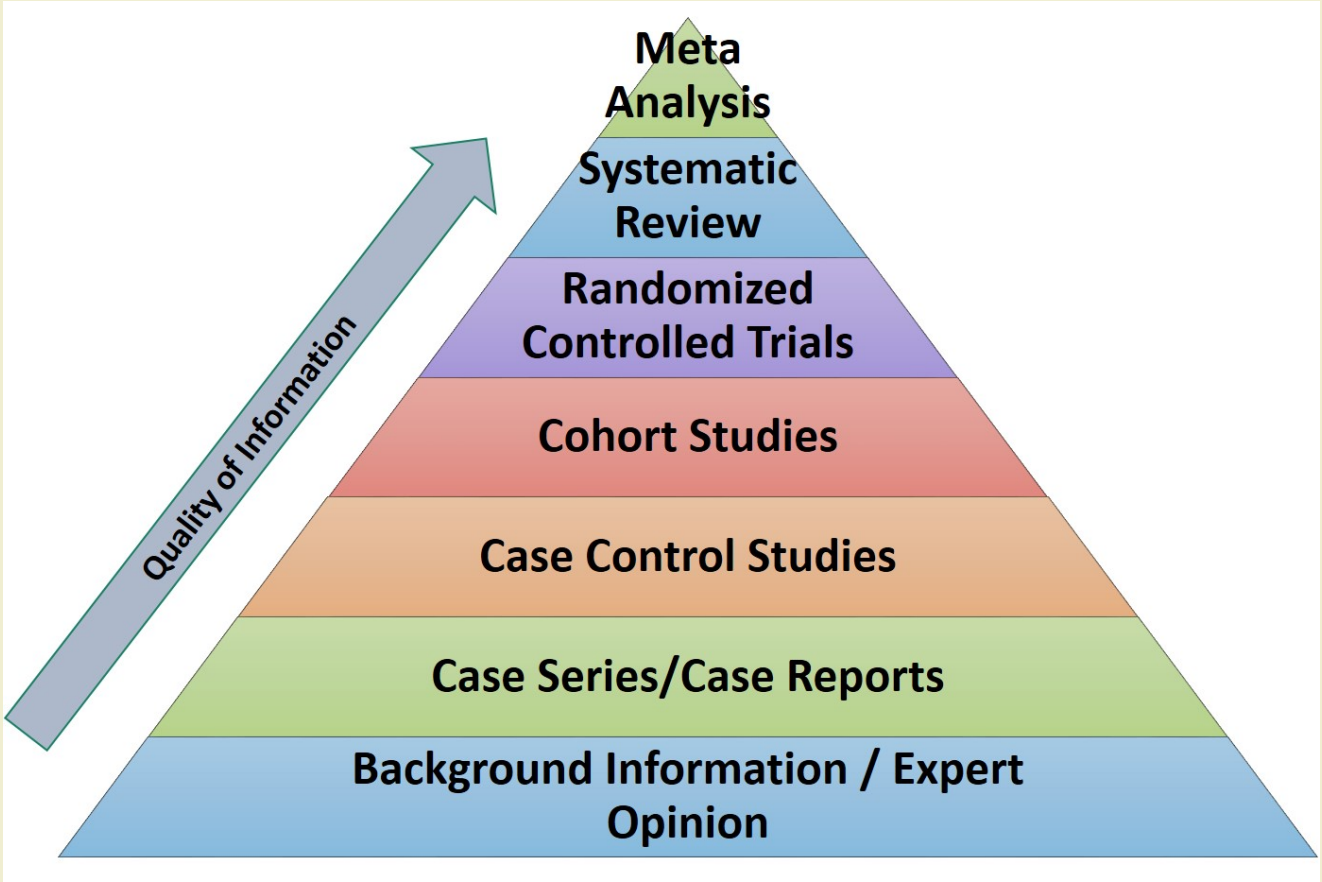
Experiments conducted to answer a clinical research question

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
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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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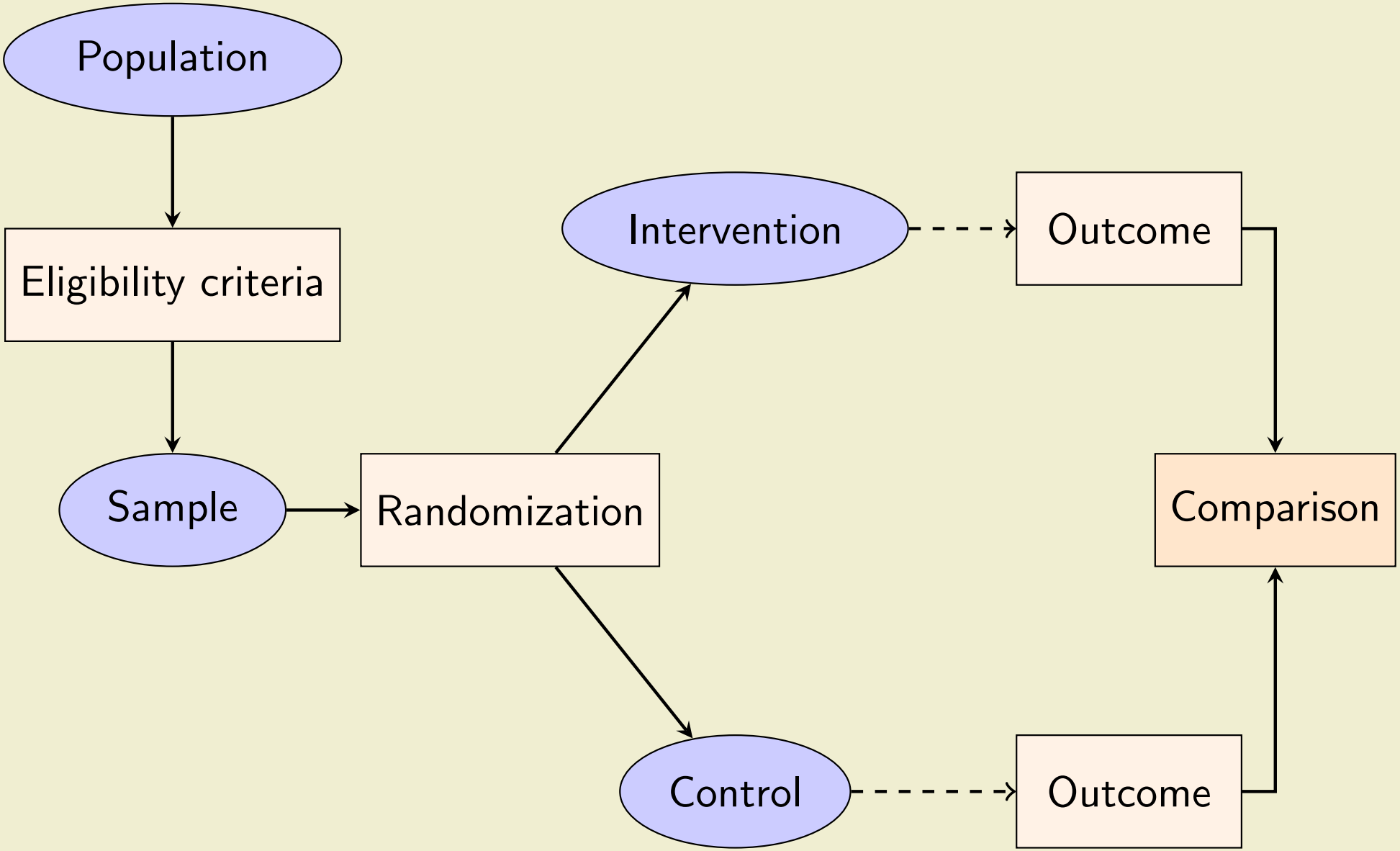
Randomized Controlled Trial

→ 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

Population

Intervention

Controls

Outcome

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A sample of eligible patients

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- Type and stage of the disease
- Age
- Gender
- Type of surgery/intervention received before
- ...

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$\rightarrow$ To generalize results to all patients who are similar

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  drug, practice, surgical intervention, diagnostic tool, ...

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$\rightarrow$ 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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  - Outcome variable
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Handling of intercurrent events

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- Can be related to disease or intervention, or completely unrelated
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- 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 occurr
  - 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 occurr

Population level summary measure for outcome

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

$$\rightarrow d$$

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

$$\rightarrow \sigma$$

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

$$\rightarrow 1 - \beta$$

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

$$\rightarrow \alpha$$

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?

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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

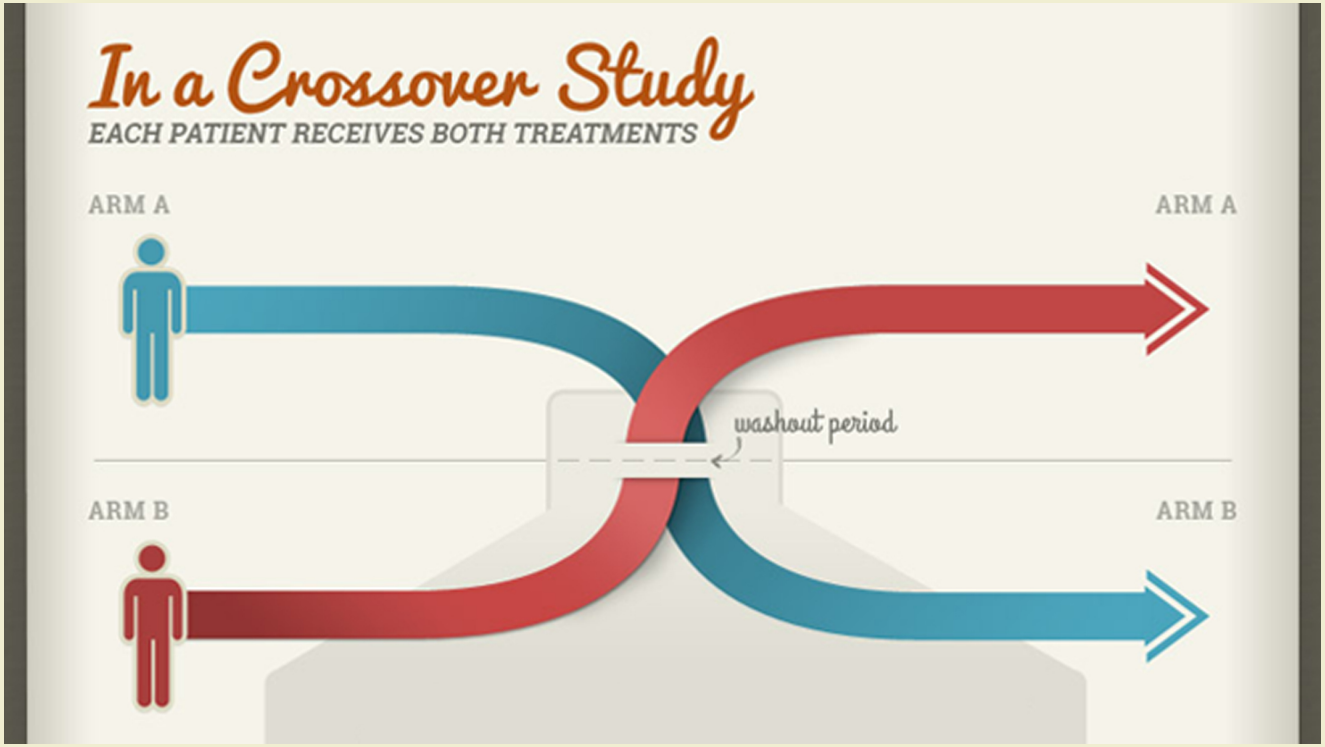
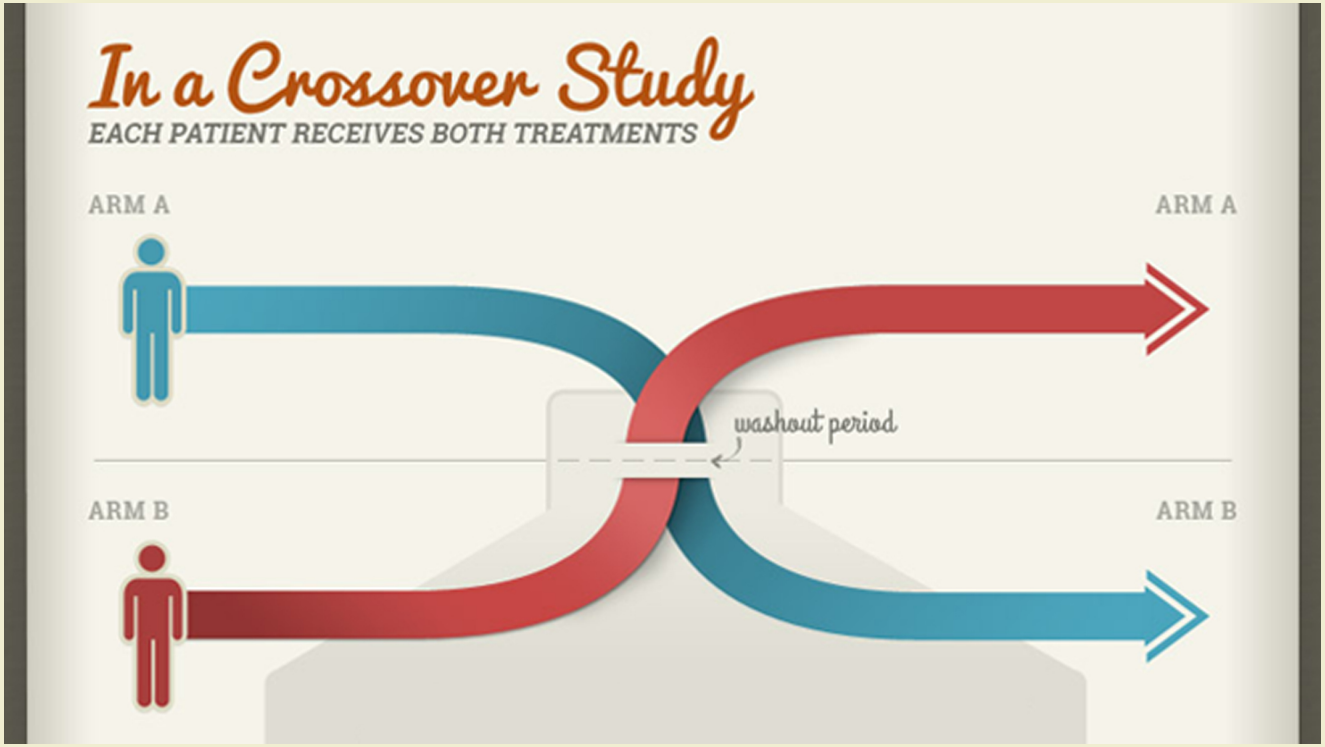


Figure: https://blog.lillytrialguide.com/clinical-trial-design-parallel-crossover-studies/

Crossover design



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

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- 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

Factorial design

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

- 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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$\rightarrow$ Come and talk to us!