Clinical trial

- Patients/participants allocated randomly to either receive or not receive a specific intervention
- a.k.a.
  - randomized controlled trial
  - randomized clinical trial
  - experiment
- Widely regarded as most rigorous study design

- Conducted to evaluate specific intervention (treatment group) vs. either alternative or no intervention (control group)
- Crucial comparison: outcomes in treatment group vs. control group
- Groups treated *identically* except for intervention
  - enrollment
  - randomization
  - data collection
  - follow-up
  - ascertainment of outcomes

Basic clinical trial design

- Study population
- Random assignment by investigator
- Treatment
- No treatment (usual care, placebo)
- follow-up period
- Yes/No
- outcome of interest

Estimate of effect is rate (risk) in exposed vs. unexposed

Other designs: crossover

- Study population
- Random assignment
- Treatment
- Control
- “washout” period
- Yes/No

Note: this design is powerful but inappropriate if effects are sufficiently persistent to contaminate the crossover conditions
Other designs: factorial

Study population

<table>
<thead>
<tr>
<th>Treatment A</th>
<th>Treatment B</th>
<th>Treatments A &amp; B</th>
<th>Control</th>
</tr>
</thead>
</table>

Note: this design is appropriate if synergy (interaction) among treatments is expected

A & B | B
A | None/usual care

Relative merits of clinical trials

Advantages
- strong claims for causality
- control of most bias, confounding
- tight control on exposure/treatment
- high internal validity
- possible to examine multiple outcomes

Disadvantages
- time consuming
- expensive, resource intensive
- compliance, drop-out
- sometimes severe ethical constraints
- may not mirror practice
- generalizability may be limited (i.e. selection bias)

Cohort study

- a.k.a.
  - prospective or concurrent study
  - follow-up study
  - longitudinal study
- Patients/participants classified as “exposed” to a given risk factor/predictor (or level of risk) or unexposed and followed to determine whether exposure status predicts outcome
- Widely regarded as most rigorous observational (i.e. non-randomized) design

- Design, analysis parallels RCTs but without random assignment to exposure
- Crucial comparison: outcomes in exposed vs. unexposed
- Unlike RCT, exposed and unexposed groups may be substantially different
- Crucial task: accounting for all differences except exposure status
Basic cohort design

Study population

Exposed

Unexposed

follow-up period

Yes

No

Yes

No

outcome of interest

Estimate of effect is rates in exposed vs. unexposed (usually relative risk: risk in exposed/ risk in unexposed)

Relative merits of cohort studies

Advantages

• Clear temporal relationship
• Least susceptible to some forms of bias
• Can examine multiple predictors of outcome
• Useful when RCT infeasible, unethical

Disadvantages

• No control over exposure (vs. RCT)
• Inefficient for rare or long-latent diseases
• Loss to follow-up threatens validity
• More expensive than other observational designs

Case-control study

• a.k.a.:
  – retrospective study
  – case referent study
  – case comparison study

• Patients/participants identified on the basis of outcomes, with prior exposure status determined after outcome status
  – cases=those with outcome of interest
  – controls=those without outcome of interest

• Basic approach
  – identify cases
  – identify suitable controls
  – determine prior exposure in cases and controls
  – calculate relative odds of exposure, adjusting for important covariates

• Crucial comparison: rates of exposure (or levels) in cases vs. controls
• Case and control groups may be substantially different (see cohort slides)
• Crucial task: accounting for all differences except exposure status
Basic case-control design: A “backwards” cohort study

Comparison of exposure rates between cases and controls provides estimate of effect (usually odds ratio [OR])

Thinking of case-control studies as part of a hypothetical prospective study

Relative merits of case-control studies

**Advantages**
- Efficient use of time, resources
- Efficient for rare outcomes
- Efficient for outcomes with long latency
- Can assess multiple exposures
- Best when cohort study infeasible, RCT unethical (e.g. harm)

**Disadvantages**
- Inefficient for rare exposures
- Difficult to identify appropriate controls
- Ascertaining historic exposure often difficult
- More prone to some forms of bias
- Must be able to assess confounding, bias