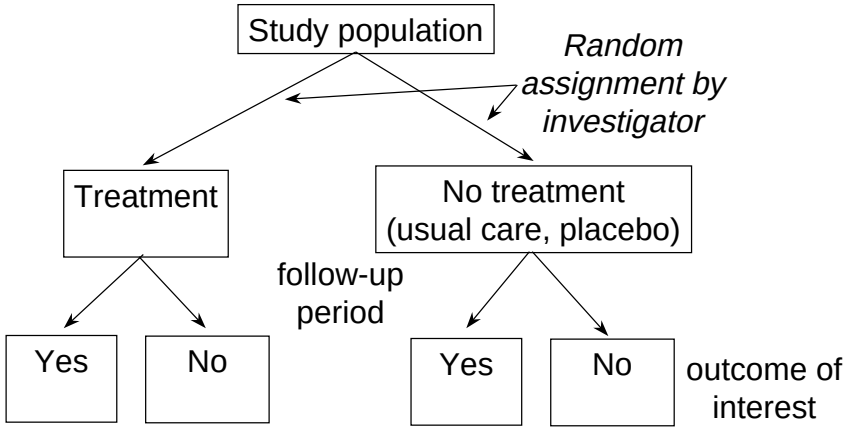
Clinical trial

- 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

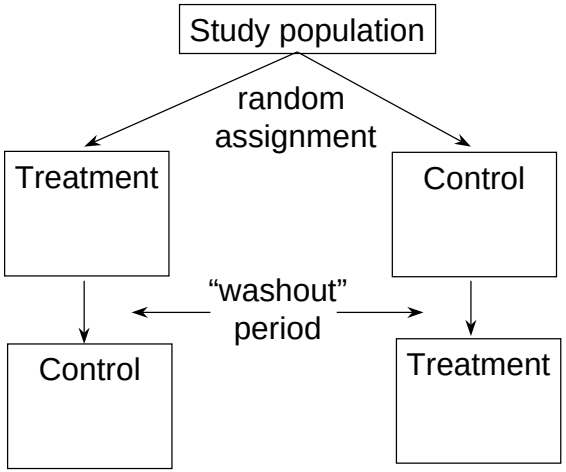
- Conducted to evaluate specific intervention (treatment group) vs. either alternative or no intervention (control group)
- Crucial comparison: outcomes in treatment group vs. control group
- Groups treated *identically* except for intervention
  - enrollment
  - randomization
  - data collection
  -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

Basic clinical trial design



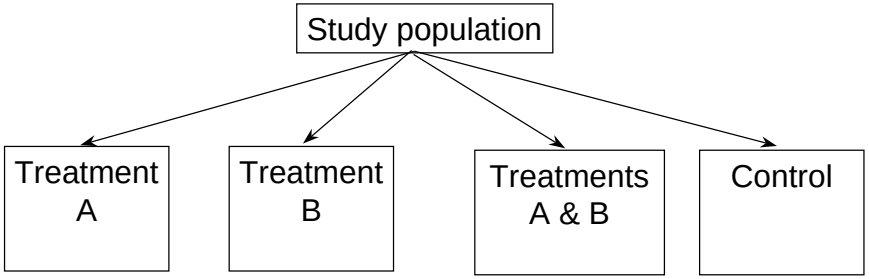
Estimate of effect is rate (risk) in exposed vs. unexposed

Other designs: crossover



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

Other designs: factorial



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

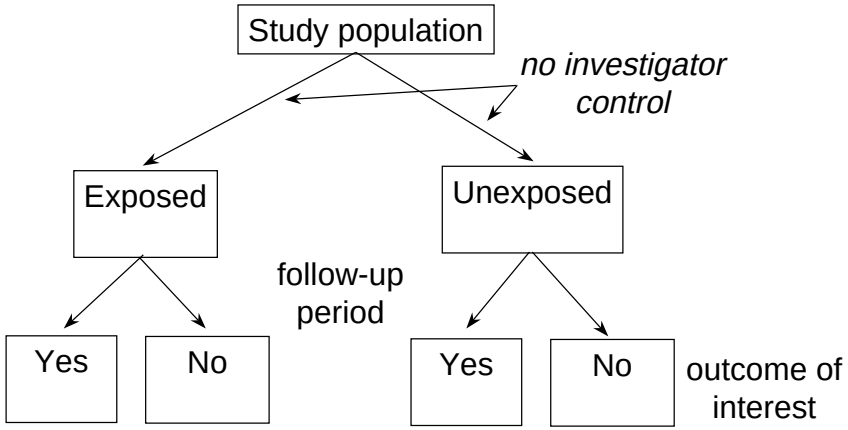
- time consuming
- expensive, resource intensive
- compliance, drop-out
- sometimes severe ethical constraints
- may not mirror practice
- generalizability may be limited (i.e. selection bias)

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



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

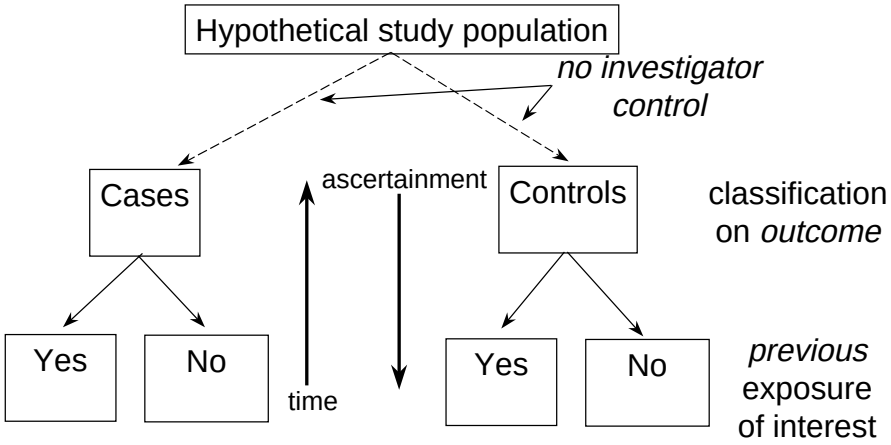
- No control over exposure (vs. RCT)
- Inefficient for rare or long-latent diseases
- Loss to follow-up threatens validity
- More expensive than other observational designs

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

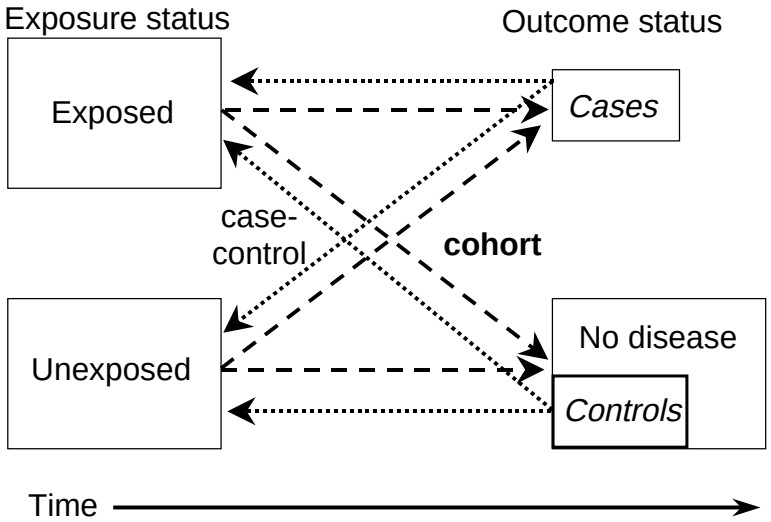
- Basic approach
  - identify cases
  - identify suitable controls
  - determine *prior* exposure in cases and controls
  - calculate relative odds of exposure, adjusting for important covariates
- Crucial comparison: rates of exposure (or levels) in cases vs. controls
- Case and control groups may be 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

<u>Advantages</u>

- 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)

<u>Disadvantages</u>

- 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