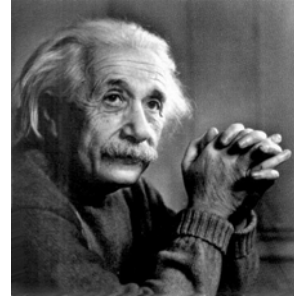


Study Design

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**Imagination is more important
than knowledge.**

**“... a poor design
cannot be salvaged
be good statistics.”**

Good Work Team Work

- Choose mentor wisely
- Get an epidemiologist / statistician on board at start



Designs

- Retrospective Case-Control
 - Rare events
 - Resident research projects
- Prospective Cohort
 - Defining incidence
- Randomized Controlled Trial (RCT)
 - Eliminates bias & confounding
 - The best for establishing cause & effect
- Crossover
 - Efficient but watch out for that carry-over effect

Bias

- Any process which tends to produce results or conclusions that differ systematically from the truth.

Murphy. In: The Logic of Medicine (1976)

Bias

- Systematic error
- Unlike random error it leads to results which are consistently wrong in one direction

David Sackett

- Categorized 56 different types of biases:
 - Selection or sampling
 - Measurement
 - Analytical



J Chron Dis 32:51-63 (1979)

3 Players

- Clinical Investigator
 - Selection bias
 - Expectation bias
- Study subject
 - Volunteer bias
 - Recall bias
- Statistician
 - Data dredging bias

There is a natural tendency of human beings to see what they expect or want to see.

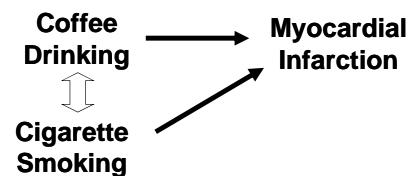
Study design largely determines the potential for and type of bias.

Confounding Factor

- A variable that differs between study and control groups
- Affects outcome

Example

- Cigarette smoking ... confounder
- Apparent association between coffee drinking and MI



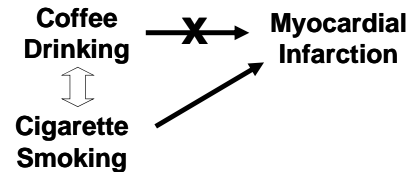
Coffee, Caffeine & Cardiovascular Disease in Men
DE Grobbee, M Stampfer et al.

- **Methods**
 - Prospective cohort of 45,589 US men
- **Results**
 - Total coffee consumption not associated with heart disease
- **Comment**
 - Coffee drinkers twice as likely to smoke
 - Confounding may have been a problem in previous studies

NEJM 323:1027 (1990)

Confounding

- Multivariate RR = 1.01 for more than 4 cups of coffee a day



Decaffeinated Coffee

- Associated with increased risk in MI (RR = 1.58)

Decaffeinated Coffee

- Associated with increased risk in MI (RR = 1.58)
- *“Chemicals used in the caffeine extraction process?”*

Cause & Effect

- Does Factor A cause Disorder B?
- Established empirically.

Cause & Effect

Bradford Hill Criteria:

- **Temporal relationship**
 - Cause precedes effect
- **Specificity**
 - Altering only the cause must be shown to alter the effect
- **Biologic gradient**
 - Dose response
- **Biologically plausible**
 - Does it make sense

Incidence

- Number of new cases over time
- Used to calculate relative risk

Prevalence

- Number of existing cases divided by the number of people at risk
- Used in the context of diagnostic testing
- Cross-sectional studies

3 Basic Designs

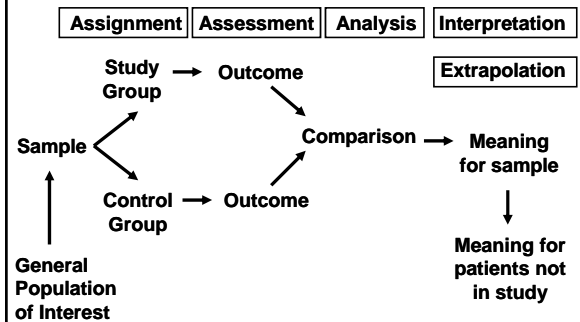
- Case-Control
- Cohort
- Clinical Trial

Example

- Relationship between unopposed estrogen exposure and uterine cancer

Unopposed Estrogen \Rightarrow 2 to 8 times increased risk Endometrial Cancer

Framework for Studying a Study



Random sample

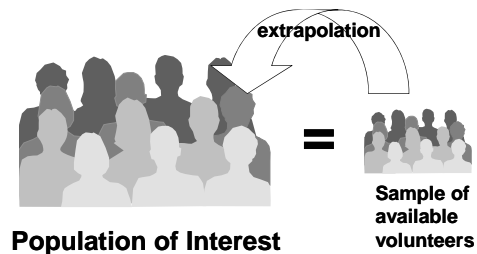
- Each subject in the population of interest has an equal chance of being chosen for the study
- Maximizes the likelihood that the results of the study can be generalized or extrapolated to the entire population of interest

Do we use random samples in clinical research?

Answer is No

- Clinical research uses “convenience samples”
 - Individuals coming to your hospital and attending your clinic.
 - Individuals that are available.
 - Volunteers Bias

Convenience sample

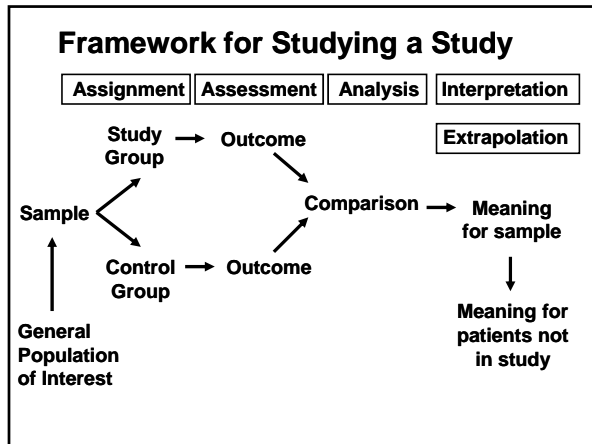


Where do we use random samples?

Survey Research

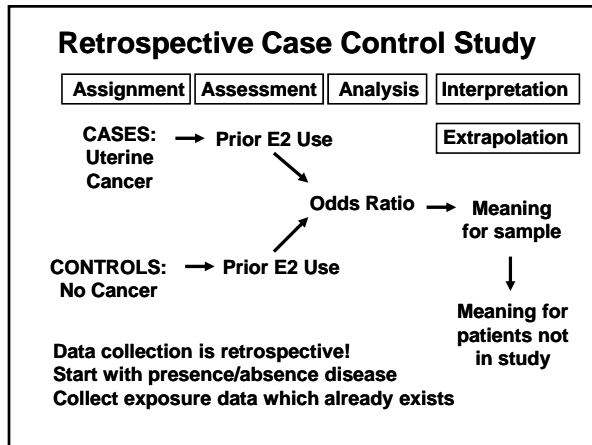
- Samples drawn at random
- Today most people have telephones
- Easy to draw a random sample from telephone directory or from random digit dialing
- Gallup Polls





Retrospective Case-Control Study

“House Red” on the research design wine list: more modest and a little bit riskier than the other selections, but much less expensive and sometimes surprisingly good.



Retrospective Case Control Study

Advantages

- Efficient for rare events
- Less time & money
- Examine many predictor variables at once:
 - # of sexual partners
 - Family history of Endometrial Ca

Retrospective Case Control Study

Disadvantages

- Inaccurate data collection
 - patient’s recall or charts
- Difficult to establish cause & effect
 - Temporal relationship is backwards
- No way to calculate incidence
 - “number of new cases over time”
- Only one outcome (Endometrial Cancer) can be studied

Retrospective Case Control Study

Recall Bias

- Persons with disease are more likely than those without disease to recall exposures that they consider related to their disease
- Persons with disease have vested interest

Retrospective Case Control Study

Recall Bias

- Women with endometrial cancer may be more likely than women without cancer to recall their prior usage of estrogen
- Inflate the estimated risk attributed to estrogen exposure

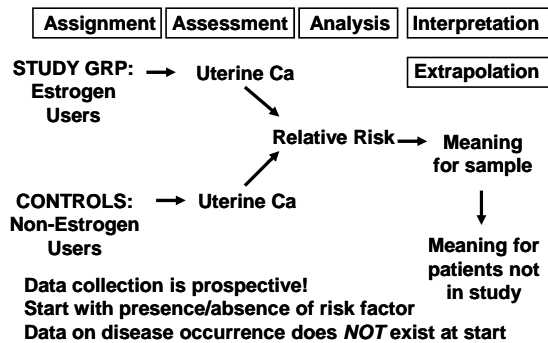
Prospective Cohort Study

Cohort is an ancient Roman military unit of 300-600 men

A group of soldiers marching forward in battle



Prospective Cohort Study



Prospective Cohort Study

Advantages

- Accurate data collection
- Easier to establish cause & effect
- Good for defining incidence
- >1 outcome can be studied
 - Breast cancer
 - Hot flushes

Prospective Cohort Study

Disadvantages

- More costly & time consuming
- Must collect data prospectively
- Not feasible for outcomes that are rare or have long lag times
- Potential for bias & confounding

Prospective Cohort Study

- Bias
 - Everyone is in the know
 - Subjects know whether they're taking active treatment
 - Investigators know who's on what
- Confounding
 - Study and control groups may differ in a way that affects the outcome

What's the solution to bias and confounding?

The Clinical Trial

■ Blinding

- Eliminates unintentional prejudices by those involved... honest answers

■ Random Assignment

- Comparable groups

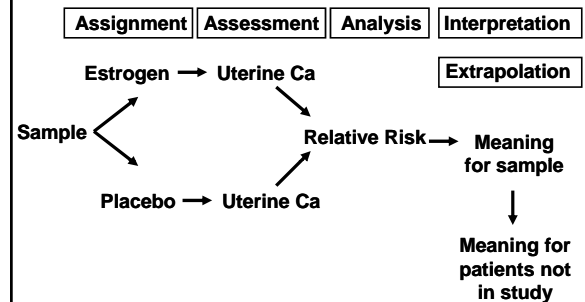


The Clinical Trial

Random Assignment

- The most important aspect of a RCT
- Leads to "intention-to-treat" analysis

Randomized Controlled Trial (RCT)



RCT

Advantages

- Potential for bias & confounding is theoretically eliminated
- Best design to establish cause & effect



Champagne on the Research Design Wine List

RCT \$\$\$

Disadvantages

- Most costly & time consuming
 - Randomization, blinding, placebos...
- Not feasible for outcomes that are rare or have long lag times
- Sample may be very restrictive making extrapolation difficult

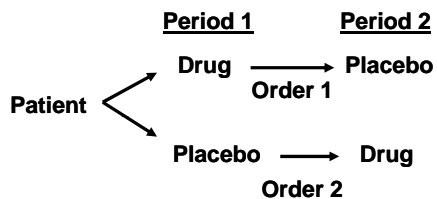
Crossover Clinical Trial

Pros & Cons

Crossover Trial

- Each patient receives both treatments (drug / placebo)
- Order of treatment is randomized
- Comparison is “within” patients not “between” patients

Crossover Trial



Crossover Design

Conditions

- Patient must complete both arms
- Drug must be short acting
- Outcome must be reversible

Crossover Design

Advantages

- Sample size reduced
- Allows a preference question

“Did you prefer treatment during 1st period or 2nd period”

Crossover Design

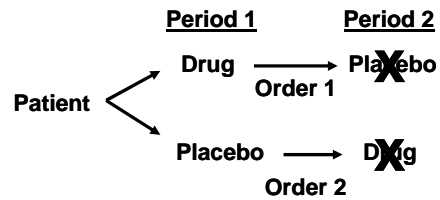
Disadvantages

- Possible carry-over effect (drug)
Drug → Placebo
- Possible period effect (time)
 - Unstable disease process
 - Cancer patients deteriorate over time
 - PMS patients get better with time
 - Effect is balanced by randomization

Significant Carry-over Effect

- The results are confounded
- Resort to comparison of 1st period only
- Reduce your power to detect a significant difference

Crossover Trial



Fertility Studies

- Pregnancy is the desired outcome
- Pregnancy (before crossover) concludes a subject's participation
- Subject would not have an opportunity to conceive by each treatment
- Does not meet conditions for crossover design

A RCT of clomiphene citrate and intrauterine insemination in couples with unexplained infertility.

Study Design

"If no pregnancy occurred during the first four cycles (treatment or control) then the couple automatically crossed over to the other arm of the study."

Fertility & Sterility 54:1083 (1990)



Possible role of pure human follicle-stimulating hormone in the treatment of male factor infertility: preliminary report.

Abstract

Design: Retrospective clinical evaluation

Main outcome measures: Pregnancy rates

Conclusions: A multicenter randomized, double-blind trial with crossover is needed.

Fertility & Sterility 55:1150 (1991)



Is there a place for the crossover design in infertility trials?

Salim Daya

.... the crossover design should be avoided

Fertility & Sterility, Volume 59 (1993)



Evaluation of clomiphene citrate and hCG treatment: a prospective randomized, crossover study during intrauterine insemination cycles.

A Arici et al.

Fertility & Sterility, Volume 61 (1994)



To the Editor:

... the (crossover) design is problematic in this setting. The event of pregnancy concludes the subject's participation in the study.

Fertility and Sterility, Volume 62 (1994)

Reply of the Authors:

We do not agree that a parallel design would be more appropriate than a crossover design because of difficulties in finding exact matched pairs in control groups.

In addition it would have been unfair to our patients to tie them down to a given treatment group without having definite proof of its efficacy.

Fertility and Sterility, Volume 62 (1994)

Editorial Comment:

Good letters like quarks come in pairs.

This exchange of letters illustrates the importance of the process of critical analysis.

Fertility and Sterility, Volume 62 (1994)

Closing Comment:

This exchange of letters illustrates the failure of the peer review / editorial process to recognize and filter out papers with inappropriate research designs.