Clinical Trials

Zuber D. Mulla

1. **Systematic reviews, meta-analyses**
2. **Randomized controlled trials with definitive results**
3. **Randomized controlled trials with non-definitive results**
4. **Cohort studies**
5. **Case-control studies**
6. **Cross sectional surveys**
7. **Case reports**

What is an experiment?

What is an experiment?

- **A study in which the investigator manipulates the exposure. The investigator assigns the experimental units to 2 or more interventions (which could be treatments, educational programs, diets, etc.).**

Clinical Trial

- **An experiment in which the experimental units are humans.**

- **Randomized controlled trial (RCT)**

Assigning the experimental units to the interventions

- **Ideally this would be at random**
- **Randomization**

Randomization

- **Random allocation to groups by chance.**
- **R.A. Fisher**
- **Coin toss: equal chance**
- **Controls for confounding**

Sir Ronald Aylmer Fisher

- **Born February 17, 1890 (London, England)**
- **Died July 29, 1962 (Adelaide, Australia)**
- **"British statistician and geneticist who pioneered the application of statistical procedures to the design of scientific experiments."**
- **Fisher introduced the principle of randomization to avoid "…biased selection of experimental materials, which results in inaccurate or misleading experimental data."**

- **From http://www.britannica.com/EBchecked/topic/208658/Sir-Ronald-Aylmer-Fisher**

Sir Ronald Aylmer Fisher

- ***Statistical Methods for Research Workers*** **(1925) was in print for more than 50 years.**

- **Fisher also key in developing analysis of variance (ANOVA)**

- **Knighted in 1952**

- **From http://www.britannica.com/EBchecked/topic/208658/Sir-Ronald-Aylmer-Fisher**

Justification for randomized controlled trials

"The concept of random allocation when comparing different treatments has been an important aspect of the design of scientific experiments ever since the pioneering work of Fisher (1935). The first randomized experiments were in agriculture where the experimental units were plots of land to which the treatments, various crops and fertilizers, were assigned in a random arrangement."

- **From Pocock (1983)**

The purposes of randomization:

1. **To protect against any use of judgment leading to one treatment getting plots with poorer soil, that is, to avoid bias.**

2. **To provide a basis for the methods of statistical analysis (tests of statistical significance)**

- **From Pocock (1983)**

Randomization

- **Balances out known and unknown confounders**
- **Produce similar groups**
- **If the intervention groups are similar, then confounding is not possible**

Confounder

- **A variable that is related to the exposure and**
- **Independent of the exposure is a risk factor for the outcome**

- **Not in the causal pathway**

Association Between Hair Color & Death in a Fictitious Cohort Study

	Died	Survived
Black	3	97
White	10	90

Association Between Hair Color & Death

	Died	Survived
Black	3	97
White	10	90

RR for Death for B vs. W Hair Color = 3% / 10% = 0.30

Association Between Hair Color & Death

	Died	Survived
Black	3	97
White	10	90

Average age of exposed = 30 years

Average age of nonexposed = 62 years

Association Between Hair Color & Age

	≥ 60 y	< 60 y
Black		
White		

RR (black hair vs. white hair) for older age

Association Between Age & Death

	Died	Survived
Age ≥60 y		
Age <60 y		

RR (older age group vs. younger) for death

Confounder

- **A variable that is related to the exposure and**
- **Independent of the exposure is a risk factor for the outcome**
- **Not in the causal pathway**

Age is Not in Causal Pathway

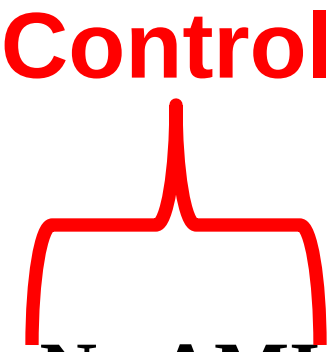
A warning about nomenclature:

The term “control” has more than one meaning in research

Association Between Breast Cancer Treatment Regimens and 90-Day Mortality in an RCT of 200 Breast Cancer Patients

	Died	Survived	
Tx A	6	94	100
Control — Tx B	1	99	100

Association Between Coffee Consumption and Acute Myocardial Infarction (AMI) in a Case-Control Study (fake data)



	AMI	No AMI	
Drinker	6	94	100
Nondrinker	1	99	100

Clinical Trial

- **Back to randomization**
- **What is the big deal about it?**
- **Reduces the chance of confounding by balancing out prognostic factors.**

Imbalances in possible confounders

- **Use your eyes**

- **Avoid using tests of statistical significance (avoid using *P* values in this situation)**

RCT of 200 Breast CA Patients

Variable	Tx A	Tx B
Average age	55 y	54.4 y
Proportion with distant metastases	30%	7%
Proportion diabetic	15%	17%

Why do you need a control group?

- Natural history of the disease
- Hawthorne effect
- Regression to the mean
- Placebo effect

When is a trial called for?

Equipoise

- **A trial is warranted when there is equipoise.**

Equipoise: from *A Dictionary of Epidemiology Fifth Edition* (Porta 2008)

- **A state of genuine uncertainty about the benefits or harms that may result from different exposures or interventions. A state of equipoise is an indication for randomized controlled trial, because there are no ethical concerns about one regimen being better for a particular patient.**

Types of Trials

- **Treatment**
- **Preventive**
- **Field**
- **Crossover**

Statistical Analysis

- **Cohort studies and clinical trials tend to have similar data analysis issues (time to event, losses to follow up, etc.)**

Statistical Analysis

- **The next several slides could also apply to a retrospective cohort study or prospective cohort study. Simply substitute "Exposed" for "Tx (treatment)" and "Unexposed" for "Placebo."**

2 x 2 Table for a Clinical Trial with Equal Lengths of Follow Up for All Subjects

	Improved	Did not improve
Tx	A	B
Placebo	C	D

$$\text{Risk} = \frac{\text{Number of new cases of a disease during a given period of time}}{\text{Total population at risk}}$$

Synonyms for Risk

- **Cumulative incidence**
- **Incidence proportion**

Relative Risk (RR)

$$RR = \frac{\text{Incidence in the Tx arm}}{\text{Incidence in the Placebo arm}}$$

2 x 2 Table

	Improved	Did not Improve	
Tx	A	B	A + B
Placebo	C	D	C + D

Relative Risk

Incidence in the Tx arm = A / (A + B)

Incidence in the Placebo arm = C / (C + D)

Relative Risk

$$= \frac{\frac{A}{A+B}}{\frac{C}{C+D}}$$

Possible Values of RR

Interpretation

RR = 1.25

The treated group was 1.25 times as likely or 25% more likely to improve than the untreated group.

Interpretation

RR = 0.80

The treated group had 80% of the probability of improving than the untreated, or was 20% less likely than the untreated group to improve.

Null Value: No Association

RR = 1

Some Examples of Strong Associations

RR = 5.00

RR = 0.20

Some Examples of Weak Associations

RR = 1.04

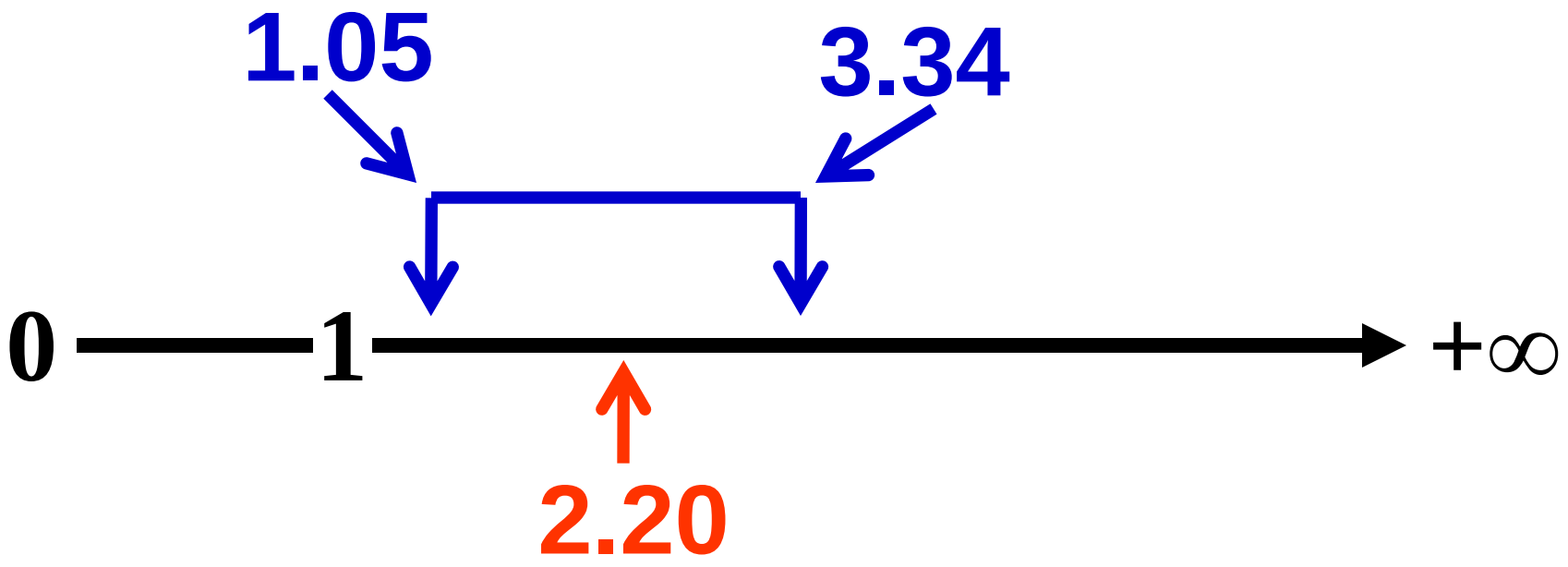
RR = 0.95

Statistical Significance: OR and RR

If P-value is 0.05 or less, then result is statistically significant

If the 95% CI excludes one (e.g., 1.05 – 3.34), then the result is statistically significant and the P-value will be 0.05 or less

Does the CI enclose 1?


1.05
3.34
0
1
+∞
2.20

Statistical Significance: OR and RR

If the 99% CI excludes one (e.g., 1.05 – 3.34), then the P-value will be 0.01 or less

Incidence Rate

- **Not a proportion so range is 0 to $+\infty$**

- **The momentary rate at which cases are occurring within a population**

Odds Ratios from a Cohort or RCT

	Had outcome	Didn't have outcome	
Exposed	A	B	A + B
Unexposed	C	D	C + D

Odds Ratios from a Cohort or RCT

$$OR = \frac{A \times D}{B \times C}$$

Same formula for an OR from a case-control study or cross-sectional prevalence study!

Blinding (Masking)

- **Single blind**
- **Double blind**
- **Triple blind**

- **To avoid bias when assessing the outcome (the endpoint), the evaluator should be blinded to the treatment assignment**

Analysis with Intention to Treat

- **At the time the researchers analyze the data, they proceed as if each subject had received the intervention that he/she was randomized to even if the subject did not receive that prescribed intervention.**

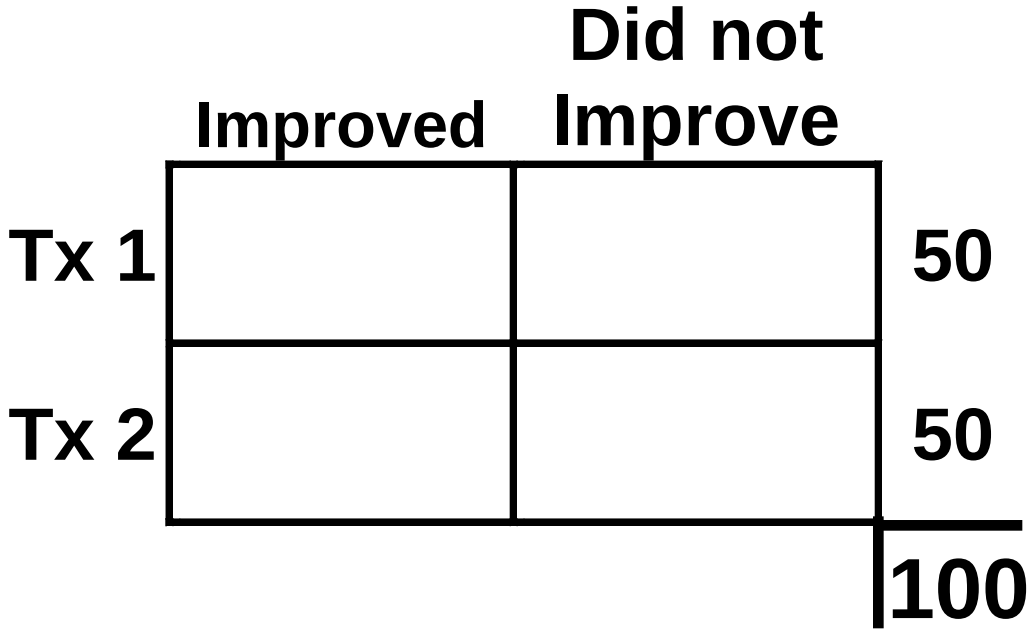
- **See Hennekens & Buring (1987) and Porta (2008)**

Analysis with Intention to Treat

- **Say a patient (John Doe) was randomized to treatment 1 but accidentally got treatment 2.**

- **When you analyze the data, you classify Mr. Doe as someone who received treatment 1**

100 patients with a serious bacterial infection randomized to one of two treatments (tx)



Analysis with intention to treat

- **Avoid the temptation to re-classify or delete these subjects who did not comply with the treatment protocol or for whatever reason didn't receive what they were randomized to**

- **"Once randomized, always analyzed."**

From Hennekens & Buring (1987)

Efficacy vs. Effectiveness

- **Efficacy:** **"The extent to which a specific intervention, procedure, regimen, or service produces a beneficial result under ideal conditions; the benefit or UTILITY to the individual or the population of the service, treatment regimen, or intervention. Ideally the determination of efficacy is based on the results of a RANDOMIZED CONTROLLED TRIAL."**

- **From Porta (2008)**

Efficacy vs. Effectiveness

- **Effectiveness: "…a measure of the extent to which a specific intervention, procedure, regimen, or service, when deployed in the field in the usual circumstances, does what it is intended to do for a specified population…To be distinguished from EFFICACY and EFFICIENCY."**

- **From Porta (2008)**

Advantages of Experiments (RCTs)

- **Causality can be inferred**
- **Considered to yield high-quality results if conducted properly**

Disadvantages

- **Can be very expensive and time consuming.**
- **Validity can be affected by losses to follow-up.**

Final Thought on Clinical Trials

- **Can every research question be addressed with a randomized intervention study?**

- **Smoking and lung cancer? Ethically, one can't randomize subjects to smoke or not smoke.**

Cited References

- **Hennekens CH, Buring JE. *Epidemiology in Medicine*. Little, Brown and Company, Boston; 1987.**

- **Pocock SJ. *Clinical Trials: A Practical Approach*. John Wiley & Sons, Chichester; 1983.**

- **Porta M. *A Dictionary of Epidemiology* Fifth Edition. Oxford University Press, New York; 2008.**