Clinical Research Design

Sources of Error
Types of Clinical Research
Randomized Trials

Daniel I. Sessler, M.D.
Professor and Chair
Department of OUTCOMES RESEARCH
The Cleveland Clinic
Sources of Error

There is no perfect study
• All are limited by practical and ethical considerations
• It is impossible to control all potential confounders
• Multiple studies required to prove a hypothesis

Good design limits risk of false results
• Statistics at best partially compensate for systematic error

Major types of error
• Selection bias
• Measurement bias
• Confounding
• Reverse causation
• Chance
Statistical Association

- Chance
- Causal
  - A → B
- Selection Bias
- Measurement Bias
- Confounding Bias
- Causal
  - B → A
Selection Bias

Non-random selection for inclusion / treatment

- Or selective loss

Subtle forms of disease may be missed

When treatment is non-random:

- Newer treatments assigned to patients most likely to benefit
- "Better" patients seek out latest treatments
- "Nice" patients may be given the preferred treatment

Compliance may vary as a function of treatment

- Patients drop out for lack of efficacy or because of side effects

Largely prevented by randomization
Confounding

Association between two factors caused by third factor

For example:

• Transfusions are associated with high mortality
• But larger, longer operations require more blood
• Increased mortality consequent to larger operations

Another example:

• Mortality greater in Florida than Alaska
• But average age is much higher in Florida
• Increased mortality from age, rather than geography of FL

Largely prevented by randomization
Measurement Bias

Quality of measurement varies *non-randomly*

Quality of records generally poor
- Not necessarily randomly so

Patients given new treatments watched more closely

Subjects with disease may better remember exposures

When treatment is unblinded
- Benefit may be over-estimated
- Complications may be under-estimated

Largely prevented by blinding
## Example of Measurement Bias

<table>
<thead>
<tr>
<th>Reported parental history</th>
<th>Arthritis (%)</th>
<th>No arthritis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neither parent</td>
<td>27</td>
<td>50</td>
</tr>
<tr>
<td>One parent</td>
<td>58</td>
<td>42</td>
</tr>
<tr>
<td>Both parents</td>
<td>15</td>
<td>8</td>
</tr>
</tbody>
</table>

$P = 0.003$

From Schull & Cobb, J Chronic Dis, 1969
Types of Clinical Research

Observational

- Case series
  - Implicit historical control
  - “The pleural of anecdote is not data”
- Single cohort (natural history)
- Retrospective cohort
- Case-control

Retrospective versus prospective

- Prospective data usually of higher quality

Randomized clinical trial

- Strongest design; gold standard
- First major example: use of streptomycin for TB in 1948
Case-Control Studies

Identify cases & matched controls

Look back in time and compare on exposure

Exposure

Time

Case Group

Control Group
Cohort Studies

Identify exposed & matched unexposed patients

Look \textit{forward} in time and compare on \textit{disease}

Exposed

Unexposed

\textbf{Disease}

\textbf{Time}
Randomized Clinical Trials (RCTs)

A type of prospective cohort study

Best protection against bias and confounding

- Randomization: reduces selection bias & confounding
- Blinding: reduces measurement error
- Not subject to reverse causation

RCTs often “correct” observational results

Types

- Parallel group
- Cross-over
- Factorial
- Cluster
Factorial Trials

Simultaneously test 2 or more interventions

Clonidine vs. Placebo

Clonidine + ASA

Clonidine + Placebo

Placebo + ASA

Placebo + Placebo

ASA vs. Placebo

Clonidine + ASA

Clonidine + Placebo

Placebo + ASA

Placebo + Placebo
Pros & Cons

Advantages
• More efficient than separate trials
• Can test for interactions

Disadvantages
• Complexity, potential for reduced compliance
• Reduces fraction of eligible subjects and enrollment
• Rarely powered for interactions
  – But interactions influence sample size requirements
Randomization and Allocation

Only reliable protection against
• Selection bias
• Confounding

Concealed allocation
• Independent of investigators
• Unpredictable

Methods
• Computer-controlled
• Random-block
• Envelopes, web-accessed, telephone

Stratification
• Rarely necessary
Blinding / Masking

Only reliable prevention for measurement bias
- Essential for subjective responses
  - Use for objective responses whenever possible
- Careful design required to maintain blinding

Potential groups to blind
- Patients
- Providers
- Investigators, including data collection & adjudicators

Maintain blinding throughout data analysis
- Even data-entry errors can be non-random
- Statisticians are not immune to bias!

Placebo effect can be enormous
Selection of Outcomes

Surrogate or intermediate
- May not actually relate to outcomes of interest
  - Bone density for fractures
  - Intraoperative hypotension for stroke
- Usually continuous: implies smaller sample size
- Rarely powered for complications

Major outcomes
- Severe events (i.e., myocardial infarction, stroke)
- Usual dichotomous: implies larger sample size
- Mortality

Cost effectiveness / cost utility

Quality-of-life
Composite Outcomes

Any of $\geq 2$ component outcomes, for example:
- Cardiac death, myocardial infarction, or non-fatal arrest
- Wound infection, anastomotic leak, abscess, or sepsis

Usually permits a smaller sample size

Incidence of each should be comparable
- Otherwise common outcome(s) dominate composite

Severity of each should be comparable
- Unreasonable to lump minor and major events
- Death often included to prevent survivor bias

Beware of heterogeneous results
Interim Analyses & Stopping Rules

Reasons trials are stopped early
- Ethics
- Money
- Regulatory issues
- Drug expiration
- Personnel
- Other opportunities

Pre-defined interim analyses
- Spend alpha and beta power
- Avoid “convenience sample”
- Avoid “looking” between scheduled analyses

Pre-defined stopping rules
- Efficacy versus futility
Conclusion: Good Clinical Trials…

Test a specific *a priori* hypothesis
  • Evaluate clinically important outcomes

Are well designed, with
  • *A priori* and adequate sample size
  • Defined stopping rules

Are randomized and blinded when possible

Use appropriate statistical analysis

Make conclusions that follow from the data
  • And acknowledged substantive limitations