Clinical Trials

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Clinical trials can be controlled or uncontrolled. A clinical trial without a control group is somewhat akin to a cases-series study in that it is hypothesis generating but not confirmatory.

The optimal design for a clinical trial is to include a concurrent control group because the intervention group and the control group are subject to the same conditions and study eligibility criteria.
Clinical Trials – Control Groups

Baseline

Response

Study end

Treatment

Control
Some trials use an external or historical control group for comparison.

Nonrandomized clinical trials, especially those with historical controls, tend to be biased toward showing positive results.

A clinical trial with a concurrent control group, and with randomization to the study groups, is considered the gold standard of evidence for investigating the efficacy of an intervention.
Some trials may invoke a crossover design in which patients serve as their own controls. For example, subjects may undergo an experimental therapy for six weeks and then “cross over” to the control therapy for another six weeks.

Crossover designs are appealing because the patients serve as their own controls. A crossover design typically will require a much smaller sample size than a “parallel” design.
Crossover designs should be invoked only for chronic diseases. For example, consider an acute condition such as the common cold. The condition may resolve itself within a short period of time, so there is nothing that the second treatment can do.

A disadvantage of a crossover design is the potential for “carryover” effects, i.e., the treatment administered during the first period may carry over into the second treatment period.
Suppose patients are randomized to the treatment sequences AB and BA in a crossover design:

<table>
<thead>
<tr>
<th>Period #1</th>
<th>Period #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment A</td>
<td>Treatment B</td>
</tr>
<tr>
<td>Treatment B</td>
<td>Treatment A</td>
</tr>
</tbody>
</table>

If Treatment A is pharmacological, then it is possible that it can carry over into the treatment B period for those patients randomized to the AB sequence.
Clinical Trials – Selecting Participants

- Define the inclusion/exclusion criteria carefully.

- Criteria that are more restrictive will yield a homogeneous sample of patients, so that variability will be lower.

- This will require a smaller target sample size, but recruitment will be difficult.

- Another drawback is that the results of the study may not be generalizable to other types of patients with the disease (lack of external validity).
Clinical Trials – Selecting Participants

- Criteria that are less restrictive will yield a heterogeneous sample of patients, so that variability will be higher.

- This will require a larger target sample size, but recruitment will be easier.

- More importantly, the results of the study should have some external validity.
Clinical Trials – Selecting Participants

- Consider an asthma trial with eligibility criteria during a two-week baseline period that includes:
  - 21-45 years of age
  - 70-90% predicted FEV$_1$
  - 2-3 nighttime awakenings due to cough per week
  - no more than 2 puffs of rescue albuterol per day

- These very restrictive criteria probably describe less than 10% of the adult asthma population.
Clinical Trials – Randomization

- Random allocation of participants to the study groups is ethical in the presence of equipoise, i.e., there is uncertainty prior to study conduct as to which study groups will perform best.

- Random allocation eliminates procedure selection bias, which occurs when the investigator assigns treatments based on prognosis.

- In a nonrandomized setting, the investigator could assign (consciously or subconsciously) the healthier patients to his/her favored treatment.
Clinical Trials – Randomization

- In order to be effective, the randomization scheme should not be “discoverable” to the investigator. In other words, the investigator should not know the identity of the next treatment assignment prior to assessing the eligibility of the patient (otherwise, it could bias his/her judgment).

- Modern randomization processes involve computer/web-based schemes or automated telephone systems.
Randomization also
- establishes the basis for statistical hypothesis testing among the groups
- tends to balance the study groups with respect to prognostic variables (variables that are predictive of outcome)
In a stratified randomization, the investigator actually forms a distinct randomization plan for each stratum.

For example, suppose patients are categorized at baseline as having mild, moderate, or severe disease.

To avoid imbalance between A and B within each disease severity, the investigator uses a distinct randomization plan for each stratum of disease severity.
Example:

<table>
<thead>
<tr>
<th>Severity</th>
<th>Treatment A</th>
<th>Treatment B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Moderate</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Severe</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>
Clinical Trials – Blinding (Masking)

- Blinding (masking) refers to the situation in which the patients do not know the treatment identity.

- A double-blinded study means that the investigators also are blinded to treatment identity, which eliminates assessment bias.

- It is not possible to design a masked trial in some situations, e.g., surgical trials. In such situations, the researchers who administer the treatments should be distinct from those who collect the data.
Clinical Trials – Choice of Control Group

- Placebo-controlled trials (superiority trials) typically provide an unambiguous statement of the research hypothesis, namely, demonstrate superiority of the treatment over placebo.

- A placebo control may not be ethical if the disease is life-threatening and/or an effective therapy already exists.
Clinical Trials – Choice of Control Group

- If standard-of-care is a different modality than the active treatment, then consider the following two treatment regimens:
  - standard-of-care + active treatment
  - standard-of-care + placebo treatment

- Sometimes this is called an “add-on” study design.
Clinical Trials – Choice of Control Group

- Suppose that the standard-of-care actually is an accepted pharmaceutical therapy. Then it may not be appropriate to combine the pharmaceutical therapy with the experimental therapy if it also is a pharmaceutical therapy.

- Another possibility is a non-inferiority trial design, in which the objective is to establish that the new therapy is not inferior to a standard therapy (active control).
Clinical Trials – Non-Inferiority Trial

- Unlike a placebo-controlled trial, a non-inferiority trial does not provide a natural check for internal validity.

- Non-inferiority of the experimental therapy to the active control does not necessarily imply that either of them is effective. It is possible that the experimental therapy is not inferior to the active control because the active control is ineffective.

- Thus, the selection of an effective active control is vital to the study design.
Clinical Trials – Examples


- Pfeffer et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *NEJM* 2002; 349:1893-1906.