EXPERIMENTAL EPIDEMIOLOGICAL STUDIES

Epidemiologic studies are either **observational** or **experimental**. Observational studies, including ecologic, cross-sectional, cohort, and case-control designs, are considered “natural” experiments, but experimental studies are considered true experiments. We will spend the next 2 modules discussing these designs.

Before we begin to discuss study designs, we need a brief introduction to a concept that we will spend more time discussing in later modules -- **bias**. The definition of bias is:

“Deviation of results or inferences from the truth, or processes leading to such deviation. Any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that are systematically different from the truth.” (Last, J.M., A Dictionary of Epidemiology, 4th ed.)

Epidemiologists are naturally concerned whether the results of an epidemiologic study are biased, since many important public health decisions are often drawn from epidemiologic research. The severity of the bias, that is - how much it influences or distorts the results, is related to the study design as well as how information is analyzed.

**Experimental Studies**

The defining feature of experimental studies is that the investigator assigns exposure to the study subjects. Experimental studies most closely resemble controlled laboratory experiments and serve as models for the conduct of observational studies, thus they are the “gold standard” of epidemiologic research. Experimental studies have high validity (i.e., less bias), and can identify even very small effects. The most well known type of experimental study is a **randomized trial (sometimes referred to as a randomized controlled trial)**, where the investigator randomly assigns exposure to the study subjects. In this type of study, the only expected difference between the experimental and control groups is the outcome variable being studied.

Experimental designs like the randomized trial can assess both **preventive interventions**, where a prophylactic agent is given to healthy or high-risk individual to prevent disease, or can assess effects of **therapeutic treatment**, such as those given to diseased individuals to reduce their risk of disease recurrence, or to improve their survival or quality of life.

**Preventive intervention**: Does tamoxifen lower the incidence of breast cancer in women with high risk profile compared to high risk women not given tamoxifen?

**Therapeutic intervention**: Do combinations of two or three antiretroviral drugs prolong survival of AIDS patients as well as regimens of single drugs?

The investigator can assign exposures (or allocate interventions) to either **individuals** or to an entire **community**.

**Individual-level assignment**: Do women with stage I breast cancer given a lumpectomy alone survive as long without recurrence of disease as women given a lumpectomy plus radiation?

**Community-level assignment**: Does fluoride in the water supply decrease the frequency of dental caries in a community compared to a similar community without such water treatment?
An experimental study is conducted in a few basic steps:
- First, a hypothesis is formed
- Study subjects are then recruited based on specific eligibility criteria and their informed consent to participate is sought
- Eligible and willing subjects are randomly allocated to receive one of the two or more interventions being compared
- Study groups are then monitored for the outcome under study (e.g., recurrence of disease, first occurrence of disease, getting better, side effects)
- Rates of the outcome in the various groups are compared

The defining feature of an experimental study such as a randomized trial is that participants are randomly assigned to their exposure status by the investigator. They do not have the health outcome of interest at the start of the study. For example, in a drug trial, many participants have disease, but the outcome of interest is a reduction in symptoms or prevention of disease recurrence. Participants are assigned exposure (exposed/not exposed) and followed to see if they get the outcome. The investigator is interested in the moment a person goes from outcome-free to having the outcome.

**Important Concepts in Experimental Study Design**

*Eligibility criteria* include restrictions on who is eligible to participate. If examining a preventive therapy, we may insist that participants be outcome-free at the study start. However, if the goal is to evaluate a treatment aimed to reduce symptoms or even cure disease, the investigator may require that participants have the disease of interest to be eligible. With regard to eligibility, the investigator must think about: 1) what group of individuals is of interest, 2) logistically, what group is accessible to the researcher, will comply with the study protocol, and can be most completely followed, and 3) how the study population differs from the reference population to which study findings will be generalized. This reference population is the general group to whom results of a trial should be applicable (such as all humans, or only HIV-positive individuals, or only menopausal women).
Treatment allocation should be randomly assigned. Random assignment means that each individual has the same chance of receiving each possible treatment (the intervention or the placebo). Random allocation can be assigned in several ways, such as via random number table, or even a coin toss. A non-random treatment assignment, such as alternately assigning treatment or placebo as participants enroll, can lead to bias and potential imbalances between the study groups with respect to important risk factors.

**Randomization.** The goal of randomization is to achieve baseline comparability between compared groups on factors potentially related to outcome other than treatment. This is because the essence of good comparison between treatments is that the compared groups are the same except for the treatment. Any group of individuals will vary in response to a treatment based upon their sex, age, overall health, severity of illness, and other factors. The investigator may already know about some of these, but there are many unknown factors that are also relevant. The compared groups should have the same distribution of all of these characteristics. That is what randomization can accomplish: the equal distribution of known and unknown factors that are relevant to response to the treatment (these are called confounders, which will be discussed in more detail in future modules).

Randomization example: Distribution of age and race in a randomized trial of maternal-infant HIV transmission

<table>
<thead>
<tr>
<th></th>
<th>Zidovudine Group N = 239</th>
<th>Placebo Group N = 238</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median maternal age at entry</td>
<td>25 yrs</td>
<td>25 yrs</td>
</tr>
<tr>
<td>Percent White</td>
<td>42</td>
<td>38</td>
</tr>
<tr>
<td>Gestational age at entry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent 14-26 weeks</td>
<td>52</td>
<td>50</td>
</tr>
<tr>
<td>Percent &gt; 26 weeks</td>
<td>48</td>
<td>50</td>
</tr>
<tr>
<td>Mean CD4 count at entry</td>
<td>560</td>
<td>538</td>
</tr>
</tbody>
</table>

Sample size refers to both the number of people enrolled in the trial, as well as how many endpoints (outcomes under study) are expected. The larger the groups being compared, the better randomization works.

**Ethical considerations**

In order to conduct an experimental study in humans, there must be genuine doubt about efficacy of treatment yet sufficient belief that it may work, a concept called *equipoise*. Having predetermined stopping rules in place prior to the study’s conduction is also critical for ethical research. For example, what will the investigators do if it becomes apparent, before the trial is over, that the new treatment is beneficial (and should not be withheld from the placebo group)? Or alternatively, that the treatment is toxic and should be withdrawn?

Placebos and blinding are used to make the study groups as comparable as possible. The placebo is sham treatment designed to seem just like the real treatment (for example, a sugar pill or a saline injection instead of the actual therapy). Blinding is when subjects do not know if subjects are receiving treatment or placebo.
(single blind). When neither subjects nor investigators know who is receiving treatment or placebo, the study is called a double blind trial. The purpose of blinding is to avoid bias in ascertainment of outcome – if subjects know they are receiving placebo, for example, they may choose not to comply with their treatment.

**Maintenance and Assessment of Compliance**
A randomized trial requires active participation and cooperation of participants, but deviations from the protocol will occur related to side effects, illness, level of interest, and length of follow-up. Noncompliance makes the compared groups more alike, which reduces the ability of the investigator to detect a difference between the groups. Frequent contact with subjects and incentives to continue with the study (such as free health check-ups) may improve compliance, as will blinding treatment status.

**Ascertaining the Outcome of a Randomized Trial**
A primary goal of the investigator for an experimental study is to have high follow-up rates. This means to reduce the number of participants who are lost to follow up – such as when individuals drop out of the study for various reasons, or cannot be reached due to invalid contact information. Another goal is to have uniform follow-up for compared groups, so the investigator should strive to follow-up both groups with equal intensity. This is because non-uniform ascertainment of outcome may lead to bias in the results.

**Analysis of randomized trial data**

Data set up: the familiar 2 x 2 table

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>a</td>
<td>b</td>
<td>a+b</td>
</tr>
<tr>
<td>Placebo</td>
<td>c</td>
<td>d</td>
<td>c+d</td>
</tr>
<tr>
<td>Total</td>
<td>a+c</td>
<td>b+d</td>
<td>a+b+c+d</td>
</tr>
</tbody>
</table>

Measure of treatment effect: Relative Risk: \( \frac{a}{a+b} / \frac{c}{c+d} \) or Risk Difference: \( \frac{a}{a+b} - \frac{c}{c+d} \)

Planning for an informative result is important when analyzing experimental data. If the study finds no difference between compared treatments, does the investigator believe it - or was there a difference but the study was not large enough to detect it? Epidemiologists analyze by **intent-to-treat**: even though the study may not have 100% treatment compliance by participants, data are typically analyzed by the treatment assignment, regardless of whether it is known if the individual stops or continues treatment. The intent-to-treat principle is rationalized because less than 100% compliance may break the randomization that is designed to create comparable study groups.