Week 13

Study Designs and Sample Size Determination

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Learning Objectives

- Introduce the four different strategies in biomedical research data.
- Introduce some basic concepts about types of designs, clinical trial, etc.
- Determine the sample space in each phase of the study.

Types of Study Designs

- Biomedical research data may be collected based on four different strategies:
    1. **Retrospective studies** (of past events, commonly referred to as case–control studies).
    2. **Prospective studies** (of past events) not commonly used because they depend on the existence of records of high quality.
    3. **Cohort studies** is an epidemiological designs in which one enrolls a group of persons and follows them over certain periods of time. The cohort study design focuses on a particular exposure rather than a particular disease as in case–control studies.
    4. **Clinical trials** are experiments on human beings.
- **In biomedical research:**
    - the sample survey is not a common form of study, and prospective studies of past events and cohort studies are not often conducted because cohort studies are time and cost consuming.
    - Clinical trials and Clinical trials are the most popular of all study designs.

Clinical Studies

- **Clinical studies** form a class of all scientific approaches to evaluating medical disease prevention, diagnostic techniques, and treatments.
- **Clinical trials:** form a subset of those clinical studies that evaluate investigational drugs.
- **Trials, especially cancer trials, are classified into phases:**
- **Phase I trials:** Focus on safety of a new investigational medicine. These are the first human trials after successful animal trials.
- **Phase II trials:** Small trials to evaluate efficacy and focus more on a safety profile.
- **Phase III trials:** Well-controlled trials, the most rigorous demonstration of a drug's efficacy prior to governmental regulatory approval.
- **Phase IV trials:** often conducted after a medicine is marketed to provide additional details about the medicine's efficacy and a more complete safety profile.

Placebo Effect and Control Groups

- **Placebo** is known as a fake treatment (e.g. smoking an electronic cigarette with no nicotine or drinking fake bill to grow head hair) that is known to have no medical effect.
- Placebo may have psychological effects known as Placebo effects (feel better even it is fake).
- **Control group** receives the Placebo (but not always) as a treatment.
- If the experiment units are not human or animals (perceive things psychologically), e.g. plants, then we don't really need a placebo. In this case:
  - The experimental group of plants receives the treatment.
  - The control group gets absolutely nothing.
  - Hence, we compare the results from the experiment group with the results from the control group without placebo effect.
- **Randomized experiments** are considered the "gold standard in scientific investigations.
- **Randomization** is a technique to ensure that the two groups, the one receiving the real drug and the one receiving the placebo, are more comparable, more similar with respect to known as well as unknown factors (so that the conclusion is more valid).

Experiment: The Need for Control Groups

Table 1.2.4 Number of colds in cold-vaccine experiment

	Vaccine	Placebo
n	201	203
Average number of colds		
Previous year (from memory)	5.6	5.2
Current year	1.7	1.6
% reduction	70%	69%

Blind and Double Blind Experiments

- Treatment assignment is kept blind (secret) from the experimental subject.
- The purpose of blinding the subject is to minimize the extent to which his or her expectations influence the results of the experiment.
  - For instance: Mice are fed one of three diets; the effects on their liver are assayed (examined) by a research assistant (or evaluating physicians) who does not know which diet each mouse received.

Trials in phases III and IV are often conducted as a double blind.

- **Double Blind** Experiment In order to prevent bias and manipulation of results, experimental group is compared to control group where neither group knows if they got the placebo or if they got the actual treatment. Should also not know which group is which.

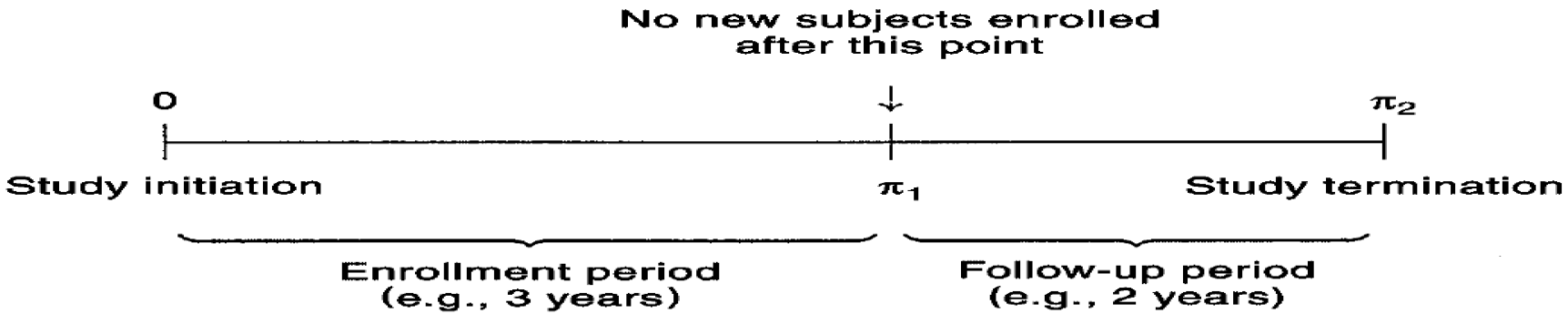

Figure 12.1 Phase III or IV clinical trial.

Sample Size Determination for Phase II Trials (Aim to Estimate the Unknown Response Rate Measured on a Binary Scale)

Question: How large must the sample be to accomplish the goals of the study?

Answer: Depending on the study goals, the planning of sample size can be approached accordingly.

- If the goal of a study is to estimate an unknown response rate π by a 95% confidence interval. Then we will determine the sample size needed so that the margin of error must not exceed a d (set arbitrarily by the investigator). Therefore, our goal is find n such as

$$1.96\sqrt{\frac{p(1-p)}{n}} \leq d$$

where p is the sample proportion and d is the margin of error

leading to the required minimum sample size:

$$n = \frac{(1.96)^2 p(1-p)}{d^2}$$ rounded up to the next integer

The proportion p usually can be estimated from similar studies, past studies, or studies on similar populations. If no good prior knowledge about the proportion is available, we can replace $p(1-p)$by 0.25 and use a conservative sample size estimate:

$$n_{\max} = \frac{(1.96)^2 (0.25)}{d^2}$$

Example 12.1 If we set the maximum tolerated error d at 10%, the required minimum sample size is

$$n_{\max} = \frac{(1.96)^2(0.25)}{(0.1)^2}$$

or 97 patients, which is usually too high for a small phase II trial, especially in the field of cancer research, where very few patients are available. If we set the maximum tolerated error d at 15%, the required minimum sample size is

$$n_{\max} = \frac{(1.96)^2(0.25)}{(0.15)^2}$$

or 43 patients.

Example 12.2 Suppose that a study is to be conducted to estimate the smoking rate among N.O.W. (National Organization for Women) members. Suppose also that we want to estimate this proportion to within 3% (i.e., $d = 0.03$) with 95% confidence.

(a) Since the current smoking rate among women in general is about 27% (0.27), we can use this figure in calculating the required sample size. This results in

$$n = \frac{(1.96)^2(0.27)(0.73)}{(0.03)^2}$$
$$= 841.3$$

or a sample of size 842 is needed.

(b) If we do not want or have the figure of 27%, we still can conservatively take

$$n_{\max} = \frac{(1.96)^2(0.25)}{(0.03)^2}$$
$$= 1067.1$$

(i.e., we can sample 1068 members of N.O.W.). Note that this conservative sample size is adequate regardless of the true value π of the unknown population proportion; values of n and $n_{\max}$ are closer when π is near 0.5.

Sample Size Determination for Phase II Trials (Aim to Estimate the Unknown Mean Measured on a Continuous Scale)

- The sample size determination is similar to the case when the focus is the response rate.
- In this case, we may decide to have an estimate error not exceeding d, an upper bound for the margin of error. With a given level of the maximum tolerated error d, the minimum required sample size is given by

$$n = \frac{(1.96)^2 s^2}{d^2}$$ rounded up to the next integer

This required sample size is also affected by three factors:

1. The coefficient 1.96. As mentioned previously, a different coefficient is used for a different degree of confidence, which is set arbitrarily by the investigator; 95% is a conventional choice.
2. The maximum tolerated error d, which is also set arbitrarily by the investigator.
3. The variability of the population measurements, the variance. This seems like a circular problem. We want to find the size of a sample so as to estimate the mean accurately, and to do that, we need to know the variance before we have the data! Of course, the exact value of the variance is also unknown. However, we can use information from similar studies, past studies, or some reasonable upper bound. If nothing else is available, we may need to run a preliminary or pilot study. One-fourth of the range may serve as a rough estimate for the standard deviation.

Example 12.4

- Suppose that a study is to be conducted to estimate the average birth weight of babies born to mothers addicted to cocaine.
- Suppose also that we want to estimate this average to within 0.5 lb with 95% confidence.
- This goal specifies two quantities:

$$d = 0.5 \text{ and coefficient} = 1.96$$

- What value should be used for the variance?

Answer

- Information from normal babies may be used to estimate s.
- Suppose that the estimate from normal babies is $\sigma = 2.5$ lb, then the required sample size is

$$n = \frac{(1.96)^2(2.5)^2}{(0.5)^2} = 97 \text{ approximately}$$