A Placebo – controlled Study of a New Medicine for Coronary Heart Disease (CHD)

In many ways, the design of a study is more important than the analysis. Applied statistics is not merely about conducting statistical tests using given data and specified tests; it is a discipline intending to, with the help of statistics, test the quantified confidence we have in making a conclusion or decision for a real world question, and most importantly design experiments that can yield statistically valid and easily verifiable results.

For example, one of the critical tasks professionals have in the field of evidence-based medication is to find out whether a new medication that treats patients with coronary heart disease (CHD) is more effective than placebo in considering approval for the new drug. This paper designed the clinical trial (also called interventional study) to be performed to assist statisticians concerned with evidence-based heart disease medication.

Performance Objectives

1. List three important factors to consider in designing heart disease medicine clinical trial.
2. List two possible experiment objectives for the heart disease medicine clinical trial.
3. Describe briefly various procedures to analyze data obtained from medication trials.
4. Analyze feasibility and compliance of sampling and data collection technique.
5. Differentiate between several experimental designs including but not limited to completely randomized design, randomized block design, matched pairs design, etc.
6. Analyze two types of hypotheses test, including an evaluation of the conditions necessary to run the test

0. Introduction

This clinical trial on the new medicine treatment to coronary heart disease (CHD) considers an input, which is the drug's medical intervention or 200 participants' exposure to the new drug, and an output, which is some measure of the heart's health that the intervention is supposed to affect.

In this clinical trial, the new drug we are testing and finding evidence of more efficiency than placebo is a kind of treatment to coronary heart disease specifically. Coronary heart disease is a disease in which a waxy substance called plaque builds up inside the coronary arteries. Over time, hardened plaque narrows the coronary arteries and reduced flow of oxygen-rich blood to heart muscle can cause heart attacks and lead to heart failures. Treatments for CHD include heart-healthy lifestyle changes, medicines, medical procedures and surgery, and cardiac rehabilitation. In this clinical trial, all the treatments excluding medicine (the drug of interest) are control variables. The output of the experiments will be in quantitative form of levels of proteins tested through blood tests. During a heart attack, heart muscle cells die and release proteins into the bloodstream. High levels of these proteins are a sign of a recent heart attack and therefore a good measurement of the efficiency of the drug of interest.

The long-term nature of trials involving human subject and varying objectives and expectations of this CHD medicine trial demand that adequate caution be exercised in its design. Three important issues worth noting include:

- submit application to Institutional Research Board (IRB) for review of this study involving human subjects
- restrictions on blood testing measurement as an indicator of heart health
- Levels of obedience and cooperation of 200 participants over a long span of time of six months

1. Statistical methods

I summarized seven steps for the clinical trial on a new drug for CHD. Proper execution of each of the seven steps is critical to the usefulness of statistical methods.

1.1 Define and state the problem
1.2 Identify objectives and develop hypothesis
1.3 Design and collect data using certain technique
1.4 Conduct experiments to test the hypothesis
1.5 Evaluation of chosen data collection method and hypothesis test

1.1 Define and state the problem

Since the levels of proteins are indicators of chances of heart attacks and thus the drug's efficiency, the lower the levels of proteins detected through blood tests are, the more efficient the drug is. We can have two problems of interest.

1.1.1 We are interested in testing the drug's efficiency for each of the two genders respectively.
1.1.2 We are interested in testing the drug's efficiency in general.

1.2 Develop hypothesis

For problem 1.1.1:

1.2.1 Null hypothesis: the drug is not efficient for the male/ female participants (the difference in the mean level of proteins of participants receiving placebo and the mean level of proteins of participants receiving the drug is zero);
Alternative hypothesis: the drug is efficient for the male/ female participants (the difference in mean level of proteins is not zero).

For problem 1.1.2:

1.2.2 Null hypothesis: Having the medicine for 3 months does not change the participants' level of proteins (the mean protein level difference is zero);
Alternative hypothesis: Having the medicine for 3 months decreases participants' level of proteins (the mean protein level difference is not zero).

1.3 Design and conduct hypothesis tests

We have a total of 200 participants with 100 females and 100 males. We assume that the pool of subjects has approximately equal levels of protein and heart disease status before the start of the study. The clinical trial will last for a total of 6 months. We are also ruling out confounding effects of other factors, so during the 6-month experiment, the participants with CHD are not exposed to other treatments such as lifestyle changes and medical procedures and surgeries but only receiving the drug of interest or placebo as a treatment. The study should be double blinded - neither the investigator nor the subject being aware of what treatment the subject is undergoing.

1.3.1 Experiment design

Randomized Block Design

	Treatment	
Gender	Placebo	Medicine
Male	50	50
Female	50	50

For problem 1.1.1 and hypothesis 1.2.1 where it is considered that men and women are physiologically different and react differently to medication, we adopt randomized block design. We divide participants in subgroups called blocks, based on gender, such that the variability within blocks is less than the variability between blocks. For this experiment, 50

men get the placebo, 50 men get the medicine, 50 women get the placebo, and 50 women get the medicine.

Matched Pairs Design

	Treatment	
Pair	Placebo	Medicine
1	1	1
2	1	1
...	...	...
100	1	1

For problem 1.1.2 and hypothesis 1.2.2, we adopt the special case of the randomized block design, a special case of the randomized block design. This design is adoptable because we have only two treatment conditions, and participants can be grouped into pairs based on some blocking variable. Then within each pair, participants are randomly assigned to different treatments. In this clinical trial, 200 participants are grouped into 100 matched pairs.
Each pair is matched on age
and gender. For example, pair 1 might be two women, both age 21. Pair 2 might be two men, both 21, and so on.

1.3.2 Data collection and hypothesis tests

For problem 1.1.1: Comparing means

Two-sample t-test for the difference between two means
For problem 1.1.1 and hypothesis 1.2.1, since we are interested in the drug's efficiency within each blocking variable (male and female), we will conduct a two-sample t-test with 199 degrees of freedom for the difference between two means of the amount of protein from participants in placebo group and medicine group. We need the following parameters: sample size of each group (both are 100), sample means (average of all the level of proteins within each group), sample standard deviation for each group.

Data collection

For all the male participants, we will have 50 of them randomly assigned to receiving placebo (a pill containing only sugar) as a control group and another 50 assigned to the group receiving the medicine to be evaluated. The same for the female participants. All subjects do not know whether they are receiving real or placebo treatment and they will start taking pills assigned to them on Jan 1st 2016 for a total of six months until June 1st 2016. We will conduct blood tests on all participants twice, the first time on March 1st 2016 and the second time on June 1st 2016 when we record the amount of proteins for each subject as an indicator of recent heart attacks. We will take the average of the twice evaluated amount of protein for each participant as output for the trial and round all the quantitative variables to 2 decimal digits.

Checking conditions and assumptions

- Randomization condition: it is justified for us to assume the pool of subjects are selected at random and is a reasonably representative random sample.
- Independence assumption: it is justified for us to assume that all the participants are independent of each other.
- Independent group assumption: The two groups of participants, one with placebo and another with the medicine are two different groups of subjects and must be independent of each other.
- Nearly normal condition: the samples are of medium size, but we plot out the sampling distributions of both groups and the histograms look unimodal and symmetric.

The conditions are met so I will use a Student's t-model to perform a two-sample t-test.

For problem 1.1.2: Paired samples and blocks

Paired t-test

For problem 1.1.2 and hypothesis 1.2.2, since we are interested in whether the medicine to be evaluated has changed the amount of protein for each pair of participants after the clinical trial, in other word, we are interested in the mean protein level difference within each pair, we will conduct a paired t-test with 199 degrees of freedom. We need the following parameters: sample size of each group (both are 100), sample mean of difference (average of all the 100 pairs' differences of level of protein), sample standard deviation of the differences.

Data collection

We will assign the 200 participants to 100 pairs based on their age and gender. Subjects of similar/ same age and same gender are more likely to have similar amount of protein before the start of the study and are more comparable. Within each pair, two subjects are randomly assigned to placebo group or medicine group. All subjects do not know whether they are receiving real or placebo treatment and they will start taking pills assigned to them on Jan. 1st 2016 for a total of six months until June. 1st 2016. We will conduct blood tests on all participants twice, for the first time on March. 1st 2016 and the second time on June. 1st 2016 when we record the amount of proteins for each subject as an indicator of recent heart attacks. We will take the average of the twice evaluated amount of protein for each participant as output for the trial and round all the quantitative variables to 2 decimal digits. Then we will take the difference between two subjects' amount of protein within each pair.

Checking conditions and assumptions

- Independence assumption: each outcome of level of protein

is independent of the others, so the differences are mutually independent

- Paired data assumption: the data are paired because participants are put in pairs based on age and gender.
- Randomization condition: within each group, subjects are assigned to treatment at random. Repeating the experiment with different treatments would give randomly different values.
- Nearly normal condition: The histogram of the differences is unimodal and symmetric.

The conditions are met, so I'll use a Student's t-model with 199 degrees of freedom and perform a paired t-test.

2. Evaluation of sampling techniques and experiment designs

Sample size

In this clinical trial, a sample from the real CHD population is obtained before the start of the study. The merit of any data will depend on their representativeness of the underlying population and their capacity for assessment and minimization of the various errors. If possible, we should aim for larger size of sampling units than 200 so that the the plot size and/or frequency should be large enough to include a good representation of the CHD population.

Random assignment

In this clinical trials, random assignments are required for several times. The key to the randomized controlled trials lies in the random allocation process. When done correctly in a large enough sample, random allocation is an effective measure in reducing bias. We should pay close attention to the two steps of the random allocation process: firstly, generating an unpredictable random sequence, and then implementing the sequence in a way that conceals the treatments

until patients have been formally assigned to their groups. We should ensure concealment otherwise a biased estimate of the treatment effect can be up to 40% or larger.

Data collection

In this clinical trial, the output of each participant is calculated as the average of the amount of protein tested on both March 1st 2016 and June 1st 2016. If possible, we should conduct blood tests on all participants every month from March to June, and then take average of all months' data as final output. We should do this because the medicine is expected to decrease the overall amount of protein after two consecutive months' intake, and in order to get most representative amount of protein in each participant's blood we should collect data as frequent as possible from March to June.

Blood testing as a measurement

We adopt blood tests on the amount of protein as a quantitative measurement of heart health of CHD patients. Two concerns worth notice are that the amount of protein is one of many indicators of heart health of CHD patients but not the only one, and amount of protein can be factitiously changed/ increased by protein-rich diet. As we know, there are other tests that more comprehensively demonstrate heart health than blood test alone, such as EKG (Electrocardiogram), Stress Testing, and etc. If possible, we should combine these tests together to come up with a direct but also quantitative measurement of heart health instead of relying on a single indicator - the amount of protein.