***Randomization*.** Creating a randomization list for assigning subjects to treatment groups is an important task in clinical trials. Use the following two methods introduced in class to **generate a randomization list** for assigning n=20 subjects to t=2 treatment groups. **Compare and discuss the resulting sample sizes** between the two groups. Note. Similar problems can be found in Homework 2.2 and 2.3 of [T2].

**Method 1.** Simple randomization where each subject is assigned to a treatment group based on a uniform random number.

A screenshot of a computer program

Description automatically generated

A screenshot of a number grid

Description automatically generated

A screenshot of a computer screen

Description automatically generated

The treatment Group 1 (trt = 1) has 9 units (45% of the sample), while the treatment Group 2 (trt = 2) has 11 units (55% of the sample). The 2 groups are not equal in size but the difference is small (45% vs 55%).

**Method 2.** Permuted-block randomization where each block contains s=2 replicates of each treatment.

A screenshot of a computer

Description automatically generated

A screenshot of a computer screen

Description automatically generated

A close-up of a computer code

Description automatically generated

A screenshot of a calendar

Description automatically generated

A white background with black and blue text

Description automatically generated

A screenshot of a computer screen

Description automatically generated

Each group has 15 observations with that each group accounts for 50% of the total observations. This randomization methods produce a perfect balance between 2 groups with an equal number of observations in each group.

***2. Treatment Comparison with continuous response.*** The file **DBP.csv** contains the data of diastolic blood pressure (DBP). As mentioned in Sec. 3.1.1 of [T1], “this dataset is typical of diastolic blood pressure data measured in small clinical trials in hypertension from the mid-to-late 1960s and for approximately a decade thereafter. During this time, hypertension was more severe, the number of effective treatments was relatively small, and the definition (DBP > 95 mmHg) of essential hypertension was not as stringent as it is now (DBP > 80 mmHg)… The DBP was measured (mmHg) in the supine position at baseline (i.e., ‘DBP1’) before randomization and monthly thereafter up to 4 months as indicated by ‘DBP2’, ‘DBP3’, ‘DBP4’ and ‘DBP5’. Patients’ age and sex were recorded at baseline and represent potential covariates. The primary objective is to test whether treatment A (new drug) may be effective in lowering DBP as compared to B (placebo).” For this dataset, we will use **d=(DBP5-DBP1)** as the primary endpoint, but ignore patients’ age and sex, and DBP2-DBP4. **Study the treatment effects with both parametric and nonparametric approaches.** **Compare** the results of the two approaches, and discuss your findings (as if you are explaining the analysis results to the investigator who have some but limited knowledge on statistics). In your discussion, clearly specify your **null and alternative hypotheses**, and provide **point and interval estimates of the treatment difference**.

A screenshot of a computer program

Description automatically generated

A close-up of a white background

Description automatically generated

**Parametric method: one- sample t-test**

**Hypothesis**

d(A) = (DBP5 – DBP1), group TRT-A – new drug

d(B) = (DBP5 – DBP1), group TRT-B group – placebo

**H0: d = 0** (There is no difference between baseline DBP and 4 months after treatment with A or B)

**Ha: d ≠ 0** (significant difference in DBP between baselevel dbp and the treatment tested)

**SAS codes:**

**A close-up of a computer code

Description automatically generated**

**Result:**

A screenshot of a computer

Description automatically generated

* d(A) = -15.2 <0 with p<0.0001. The mean reduction in DBP (d) after 4 months of treatment with the new drug (A) is -15.2 mmHg.
* d(B) = -4.8 <0 with p<0.0001. The mean reduction in DBP (d) after 4 months of treatment with placebo (B) is -4.8 mmHg.

**Point Estimate:**

* Treatment A: The mean reduction in DBP is -15.2 mmHg.
* Treatment B: The mean reduction in DBP is -4.8 mmHg.

**Data analysis:**

The t-values for each treatment are significantly different from 0, with p-values less than 0.0001, indicating a statistically significant reduction in DBP from baseline within both treatment groups.

**Parametric method: two-sample t-test**

**Hypothesis**

d = d(A) – d(B)

**H0: d = 0** (There is no difference in mean DBP between treatment A and B 🡺 the new drug and placebo are equally effective in reducing DBP.)

**Ha: d ≠ 0** (There is significant difference in mean reduction of DBP between treatment A and B. If d<0, it suggests that the new drug A is more effective than the treatment B, placebo)

**SAS code:**

A computer code with text

Description automatically generated with medium confidence

**Results:**

A screenshot of a computer

Description automatically generated

* Pooled Method: Assuming equal variances of ‘d’ in the two populations (homoscedasticity), the mean of d is significantly different from zero (d≠0) with p<0.0001. In particular, considering the negative mean value d (=DBP5-DBP1), the data suggests that the new drug (treatment A) is significantly better at lowering DBP than the placebo (treatment B) with P<0.0001.
* Satterthwaite Method: Assuming unequal variances (heteroscedasticity), the mean of d is significantly different from zero (d≠0) with p<0.0001. In particular, considering the negative mean value d (=DBP5-DBP1), the data suggests that the new drug (treatment A) is significantly better at lowering DBP than the placebo (treatment B) with P<0.0001.

**Discussion:**

* Regardless of the assumption about variances, the test results indicate that there is a statistically significant difference in the mean DBP reduction between the two treatment groups with p<0.001.
* With treatment A (new drug), the mean reduction in DBP after 4 months is -15.2 mmHg.

With treatment B (placebo), the mean reduction in DBP after 4 months is -4.8 mmHg.

* Treatment A caused DBP reduction with –15.2 mmHg while the treatment B caused DBP reduction with -4.8 mmHg.
* The mean difference between treatment A and B is (–15.2) – (–4.8) = –10.4 mmHg, indicating that treatment A leads to a greater reduction in DBP by 10.7 mmHg compared to treatment B.
* With p<0.0001, we can conclude that treatment A (the new drug) is significantly more effective in lowering DBP than treatment B (placebo).

**Nonparametric method: Wilcoxon rank-sum test (when not normal)**

**Hypothesis:**

**H0: d = 0** (The median DBP reduction is same for both treatment A and B

**Ha: d ≠ 0** (The median DBP reduction is significantly different between treatments A and B)

**SAS code:**

**A screenshot of a computer code

Description automatically generated**

**Results:**

**A screenshot of a computer

Description automatically generated**

**A screenshot of a graph

Description automatically generated**

**A screenshot of a computer

Description automatically generated**

The Wilcoxon rank-sum test calculates the sum of ranks for each sample. Treatment A has a rank sum of 210.0, and treatment B has a rank sum of 610.0. The mean rank for treatment A is 10.50, and for treatment B, it is 30.50, which suggests that the DBP values for treatment A tend to be lower than those for treatment B.

**Point Estimate:**

The Hodges-Lehmann estimator, which provides a point estimate of the median difference between two treatments, is given as 10.000 mmHg. This means that the median DBP reduction for treatment A is estimated to be 10 mmHg more than the median reduction for treatment B.

**Interval Estimates:**

The 95% confidence interval for the Hodges-Lehmann estimator is provided as [-12.0000, -8.0000] mmHg. This interval estimate tells us that we can be 95% confident that the true median difference in DBP reduction between treatments A and B lies somewhere between -12 and -8 mmHg.

**Conclusion:**

The Wilcoxon rank-sum test provides strong evidence that the median DBP reduction for treatment A is significantly greater than for treatment B, with a median difference estimated at -10 mmHg and a 95% confidence interval of [-12, -8] mmHg.

**Comparison of Parametric and Nonparametric Methods:**

* Both tests indicate that there is a statistically significant difference in DBP reduction between treatment A and treatment B, with treatment A showing more effectiveness.
* The parametric method provided a mean difference of -10.4 mmHg, while the nonparametric method provided a median difference estimate of 10.000 mmHg with a 95% confidence interval of [8.0000, 12.0000] mmHg.
* Both the parametric and nonparametric tests yield consistent results, confirming that treatment A (new drug) is more effective at reducing diastolic blood pressure (DBP) than treatment B (placebo).

**Conclusion for the investigator:**

Our analysis has examined the effectiveness of two treatments on lowering diastolic blood pressure (DBP). Treatment A is a new drug, while treatment B is a placebo. We looked at the data using two different types of statistical methods: one that assumes the data is normally distributed (parametric) and one that does not (nonparametric).

The findings from both methods are telling us the same story: the new drug (treatment A) is doing a better job at reducing DBP than the placebo (treatment B).

On average, patients taking the new drug saw their DBP drop by about 15.2 mmHg over 4 months. On the other hand, those on the placebo had a smaller average drop of about 4.8 mmHg. When we look at *the difference in average reductions between the two groups,* we see that the new drug is about 10.4 mmHg more effective than the placebo.

The nonparametric method, which is less sensitive to the specific distribution of the data, provides a *median treatment difference* of 10 mmHg, with a range (95% confidence interval) of 8 to 12 mmHg. This means we can be quite sure that the true effectiveness of the new drug over the placebo lies somewhere in that range.

With a very high level of statistical confidence (p<0.0001), we can say that the new drug is significantly better at reducing DBP compared to the placebo.