Assignment 3: Designing Clinical Trials
2018 Spring

Background Knowledge

0.1 Proportional Data

You're testing two flu drugs A and B. If drug A works on 41 patients out of 195, while drug B works on 351 patients out of 605. Are the two drugs comparable? Set $\alpha = 0.05$.

0.2 χ-squared test for two proportions

0.3 Z-test for two proportions

- Null hypothesis H_0 : two proportions are the same
- The working proportion for drug A: $p_A = 41/195 = 0.21$
- The working proportion for drug B: $p_B = 351/605 = 0.58$
- The overall proportion: $\bar{p} = (41 + 351)/(195 + 605) = 0.49$
- Compute the Z-statistic:

$$Z = \frac{p_A - p_B}{\sqrt{\bar{p}(1-\bar{p})(1/n_A + 1/n_B)}} = \frac{0.21 - 0.58}{\sqrt{0.49 \times 0.51 \times (1/195 + 1/605)}} = -8.99$$

- The absolute value of Z is larger than the critical z value, hence we reject the null hypothesis.
- There is significant difference in treatment effect of the two drugs, A and B.

Exercises

1. (30 points) Answer the following questions.

   (1) Can we draw a conclusion of equivalence based on the insignificance result of superiority trial? If not, then outline the statistical testing on how to prove that a treatment T is equivalent to B in a parallel trial?

   > **Solution:** No, equivalence trial should be conducted using two null hypothesis. Or we can just use the confidence interval to prove equivalence.

   (2) Which test requires a larger sample size for the same δ_0, α, power, equivalence trial or non-inferiority trial?

   > **Solution:** Equivalence trial.

(3) How to deal with the non-compliance of the participants in a clinical trial?

Solution:

- Intention-to-treat (ITT) analysis
- Per-protocol (PP) analysis
- As-treated (AT) analysis

(4) When aren't the double-blindings feasible in a clinical trial?

Solution:

- Technical issues
- Safety issues
- Ethical issues

(5) As we have talked about selection bias in the observational study, it is a more severe issue in a randomized controlled trial. Can you use some example to illustrate what is selection bias in an RCT.

Solution: In a clinical trial, selection bias can occur as the result of systematic difference between baseline characteristics of the groups that are compared. This can arise in several situations:

- The assignment of patients into a group is influenced by knowledge of which treatment they will receive.
- The decision to recruit a patient is influenced by knowledge of which treatment the patient will receive.
- The decision to adhere to the assigned treatment is influenced by the prognostic factors.

Randomization or other similar methods abolishes selection bias.

(6) Illustrate how block randomization could be used to randomly allocate treatments to 30 patients with an allocation ratio of 1:2 using a block size of 6.

Solution: The number of different permuted block of size 6 with an allocation ratio of 1:2 is $\binom{6}{2} = 15$; then we choose five of the blocks, finally randomize the individuals to these blocks one by one.

Data analysis of continuous outcome

2. (40 points) An RCT was conducted to compare two therapies for pain relief after the wisdom tooth extraction surgery. A dual-therapy (Acetaminophen+Ibuprofen) was compared againt a mono-therapy (Ibuprofen only). The primary outcome is the post-surgery pain measure at an interval of 15 minutes within a follow-up of 120 minutes. The pain was measured in a scal of 0 (no pain) to 100 (worst pain).

Table 1: The follow-up pain data after wisdom-tooth extraction surgery

	Ibuprofen			Acetaminophen+Ibuprofen		
Time (min)	Mean (mm)	S.D. (mm)	N	Mean (mm)	S.D. (mm)	N
15	27.9	14.8	24	18.2	13.1	24
30	32.6	24.4	25	25.3	20.9	25
45	35.5	23.2	22	28.7	23.3	20
60	31.3	18.9	19	25.1	22.8	23
75	29.9	18.8	24	14.9	13.8	24
90	23.8	17.9	22	15	14.2	24
105	22.7	16.4	21	13.7	12.8	19
120	20.9	17.2	24	15.2	14.4	23

(1) Conduct a t-test to compare the treatment effects of the two therapies at each time point. Give also the 95% confidence interval.

Solution: Use Welch's t-test with unequal variances:

$$t = \frac{\bar{y}_1 - \bar{y}_2}{\sqrt{s_1^2/n_1 + s_2^2/n_2}} \overset{a}{\sim} t_\nu$$

where the degrees of freedom is

$$\nu = \left[\frac{c}{n_1 - 1} + \frac{(1-c)^2}{n_2 - 1}\right]^{-1}$$

and

$$c = \frac{s_1^2/n_1}{s_1^2/n_1 + s_2^2/n_2}$$

therefore, we can write down the R code:

```
ttest <- function(x1,s1,n1,x2,s2,n2){
        t <- (x1-x2)/sqrt(s1^2/n1+s2^2/n2)
        c <- s1^2/n1/(s1^2/n1+s2^2/n2)
        nu <- 1/(c/(n1-1) + (1-c)^2/(n2-1))
        pv <- 2*(1- pt(t, df=nu))
        return(list(statistic=t, df=nu, pval=pv))
}
```

(2) What kind of assumptions should we make when we conduct a t-test? So, is it plausible to use t-test here? Should we use a nonparametic approach, instead?

Solution: Since t-test is robust to deviation from the assumption of normality, we don't need to use a nonparametric approach.

(3) You can count the number of the tests for all the time points with p-value less than 0.05, and then arrive at the final conclusion.

Solution:

(4) We can also calculate the weighted average of the pain scores across the time points for every patient: Can you conduct the t-test only on the weighted mean to compare the

	lbuprofen			Acetaminophen+lbuprofen		
	Mean (mm)	S.D. (mm)	N	Mean (mm)	S.D. (mm)	N
summary	27.9	13.6	25	19.5	12.3	26

treatment effect.

(5) The other approach is to only use the weighted average to reach the conclusion. Which one do you prefer? Why?

Solution: The former, since it takes into consideration the changing curve across time.

(6) If the pain reduction $\delta = -8$ is clinically significant, can the sample size in this trial achieve a power of 0.90 to detect such reduction? (Hint: $\alpha = 0.05$)

Solution: Use superiority test.

(7) Can you find some flaws for the above study design? Comment.

Solution: Because each patient has a different tolerance over the pain, we should take this factor (between-subject variation) into consideration.

(8) Try to figure out a method to give the best estimate of the effect of Acetaminophen in pain relief following the wisdom-tooth extraction?

Solution: Use a placebo-group as one of the reference, and lbuprofen as another reference.

Clinical trial design

3. (10 points) An RCT was comparing the psychological treatment (**CBT**) with the exercise program (**EX**) for patient suffering from moderate to severe anxiety. Patients are randomized to treatment using **deterministic minimization** controlling for gender and severity. After 65 patients have entered the trial. The number of patients with each characteristic is summarized in the following table:

Table 2: Number of patients for each characteristic

Characteristics		Treatment CBT	EX
Gender	Male	18	15
	Female	15	17
Severity	Moderate	22	21
	Severe	11	11

(1) How many patients have been allocated to each treatment?

Solution: Thirty-three and thirty-two patients have been allocated to CBT and EX group, respectively.

(2) If the 66^{th} is a male and moderately severe patient, which treatment would he be allocated?

Solution:

	Treatment CBT	EX	Summary
Male	18	15	3+
Moderate	22	21	1+

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therefore, the 66-th patient should be assigned to EX group.

(3) The 67^{th} is a female and moderately severe patient, which treatment would she be allocated?

Solution: After the assignment of 66-th patient, the summary table becomes

	Treatment CBT	EX	Summary
Female	15	17	2-
Moderate	22	22	0

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Therefore, the 67-th patient should be assigned to the CBT-group.

Case study

4. (20 points) Read this article, and answer the following questions.

Petter Quist-Paulsen. Randomised controlled trial of smoking cessation intervention after admission for coronary heart disease. BMJ 2003;327:1254.

(1) Using a z-test of proportions, check the analysis for Table 2 of the paper to compare the smoking cessation rates in intervention group and control group at 12 months. Report also the 95% confidence interval of the treatment effect.

Solution:

(2) Summarize the results of the above analysis in your own words.

Solution:

(3) How does the author deal with the missing data? Since we have talked about intention-to-treat analysis, how does it deal with the missing data? Compare the results with the article.

Solution:

(4) Comparing the lost-to-follow-up rates between the intervention and control group, what conclusion can you draw from this analysis?

Solution:

Case study

5. (10 points) A randomized controlled equivalence trial is conducted to test whether a new **generic drug** is of equal efficacy to the current **standard drug**. Here is the partial result:

```
         | Obs   Mean   Std. Err. Std. Dev. [90% Conf. Interval]
---------+--------------------------------------------------------
Standard | 42   35.2    2.79289   18.1      30.49991    39.90009
Generic  | 41   34.1    2.79551   17.9      29.39278    38.80722
---------+--------------------------------------------------------
```

The investigators suggest that a difference of 5 is clinically significant. Using the above data, tell whether the new generic drug is equivalent to the current standard drug under the significance level of $\alpha = 0.05$.

Solution: Equivalence is established at the α significance level if a $(1´2\alpha) \times 100\%$ confidence interval for the difference in efficacies between new and current treatment is contained within the interval $(-\delta, \delta)$. The reason the confidence interval is $(1-2\alpha)\times 100\%$ and not the usual $(1-\alpha)100\%$ is because this method is tantamount to performing two one-sided tests. Thus, using a 90% confidence interval yields a 0.05 significance level for testing equivalence.

In this example, the generic drug has a 90% confidence interval of $(29.393, 38.807)$, which is crossing with the equivalence margin interval $(35.2 - 5.0, 35.2 + 5.0) = (30.2, 40.2)$. Therefore, we can not draw a conclusion of equivalence between these two drugs.