BI476: Biostatistics - Case Studies

Exercise 03 - Designing Clinical Trials

Spring, 2018

1 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?

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

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

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

(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 the types of selection biases in an RCT.

(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.

2 Data analysis of continuous outcome

An RCT was conducted to compare two therapies for pain relief after the wisdom tooth extraction surgery. A dual-therapy (Acetaminophen+Ibuprofen) was compared

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

	lbuprofen			Acetaminophen+lbuprofen		
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

againt a mono-therapy (lbuprofen 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).

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

(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?

(3) We can also calcualte 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

	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

to compare the treatment effect.

(4) 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.

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

(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: $\alpha = 0.05$)

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

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

(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?

3 Clinical trial design

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:

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

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

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

4 Case study

Read this article, and answer the following questions.

> Petter Quist-Paulsen. Randomised controlledtrial 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.

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

(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.

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

5 Case study

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 $\alpha = 0.05$.