

Written Examination for Design and Analysis of Clinical Trials (MSA620)

Date and place: 2011-10-04, **Teacher:** Ziad Taib (+46 31 772 53 73/ 0707655471)

Rules: This is a closed book exam. No material is allowed other than a simple pocket calculator and statistical tables.

Scores: The written exam is worth 30 scores. There are three possible grades: Excellent (VG) (at least 24 scores), pass (G) (at least 15 cores) and do not pass (U) (less than 15 scores). In addition to the written exam, the computer assignments are compulsory.

- Consider a clinical study with N patients in a parallel group design, comparing a test drug (T) and placebo (P) with equally sized groups. The statistician who is going to produce the randomization list is considering either complete randomization or permuted-block randomization for the study. Below are two test sequences for the 24 first treatment allocations.

Sequence 1

T	P	P	T	P	T	T	T	T	P	P	P	T	P	P	T	P	T	P	P	T	T	T	P
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Sequence 2

T	P	T	P	T	T	P	P	P	P	T	P	T	T	P	P	T	T	T	T	T	T	T	T
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Which sequence is generated with complete randomization and which one with permuted-block randomization and what is the block size?

Describe the different methods and discuss pros and cons of the methods in relation to small studies ($N \leq 30$) and large studies ($N \geq 500$). (3)

- In the development of the antihypertensive drug hypersartan a clinical study is performed. The study is a 2-arm, parallel group, placebo-controlled study with the primary objective to compare the sitting diastolic blood pressure (DBP) lowering effect of hypersartan with that of placebo. In the table below 4 different scenarios of outcome of the study are presented.

Scenario	Difference in change (mmHg)		p-value
	LS Mean	95% confidence interval	
1	0.8	[-0.2, 1.8]	>0.05
2	0.9	[0.3, 1.5]	<0.05
3	0.5	[-10, 11]	>0.05
4	6	[1, 11]	<0.05

Discuss the statistical significance, the clinical relevance and strategies for the further development of the drug in each of the 4 scenarios. (3)

- Consider a clinical study comparing surgical therapy with medical therapy in treatment of gastric ulcers; with the objective to compare the two treatments with regard to the risk of a gastric ulcer bleed. The study enrolled 234 patients, 132 were randomized to the surgical group and 102 to the medical group. 22 of the randomized patients had a gastric ulcer bleed shortly after they had been randomized, before they had started the medical treatment or had the surgical therapy. 20 out of these 22 patients were randomized to the surgical group. Of the patients who were treated 10 and 15 patients experienced a gastric ulcer bleed in the surgical and medical group respectively.

It is decided to perform both a Per-Protocol analysis and an Intention-to-Treat analysis of the study. Explain these two different principles.

Which patients would you include/exclude from the different analyses in this specific example? Discuss potential biases in the different approaches. (3 scores)

4. In a trial aiming at comparing 3 different dietary regimes, the endpoint response variable (Y) measured is weight at the end of the trial. In this case it is obvious that individuals differ with respect to age and initial weight. Therefore it is desirable to formulate a model capable of taking the baseline weight X into account. How does such a model look like? How should it be analyzed? (3)
5. In a clinical trial we want to compare an old therapy with 2 years survival rate of 25% with a new one and hope that the survival rate of the new therapy is 40%. We perform a two sided test with $\alpha=0.05$ and want to achieve 90% power of discovering a risk ratio that corresponds to the above survival rates. Moreover we assume that $p=q=0.5$. Discuss how to find the number of events needed to achieve this goal. (4)
6. A new treatment is believed to stabilize calcium concentration in the body. 9 patients were treated for 30 days and calcium concentration was measured before and after the treatment. The following data was obtained. How would you analyze such data? What is the hypothesis to be tested and what other assumptions are needed. (4)

Patient	1	2	3	4	5	6	7	8	9	mean	sdv
Before	3.57	2.33	4.13	4.29	2.85	5.19	5.18	3.96	4.33	3.97	0.94
After	5.63	7.45	4.82	10.37	5.73	6.22	8.13	6.12	5.8	6.7	1.6

7. Discuss how the score test for Cox regression can be arrived at, at least in principle. I.e. what is the exact inference problem and what inference principle is used and in what way? (4)
8. Assume we perform $N=5$ tests of hypothesis simultaneously and want the result to be significant at the level 0.05. The p-values obtained are as in table below. Use these to decide whether to reject or accept the individual hypothesis using the three approaches Bonferroni's, Holm's and Hochberg's. Compare and discuss the results. (3)

p(1)	p(2)	p(3)	p(4)	p(5)
0.004	0.002	0.04	0.052	0.1

9. The neurological state "stiff person syndrome" is characterized by stiffness of the muscles, painful spasms and sometimes unprovoked muscle contractions. We want to investigate if this syndrome is related to prevalence of anti-GAD-auto antibodies (GAD = glutamic acid decarboxylase). A total of 550 persons were considered, 370 of which had the syndrome. Is there a significant relationship between the syndrome and prevalence of anti-GAD-auto antibodies? (3)

	Has anti-GAD-auto antibodies	Lacks anti-GAD-auto antibodies
Normal	55	125
Stiff person syndrome	220	150