

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

Date and place: 2010-03-22 in V, **Questions:** Malin Östensson (+46 31 772 53 16)

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.

1. The aim of a confirmative phase III study of a treatment for lung cancer is to show efficacy compared to placebo with respect to all cause mortality. A double blind balanced randomized parallel group study including 1400 patients is planned and submitted to the ethical committé. The response is that it is unethical to randomize patients to placebo as there already are treatments with proved effect on the market and they ask you to redesign the study. What do you propose? (3p)
2. We would like to compare the bioavailability in terms of the area under the plasma concentration vs. time curve (AUC) of a novel drug using two tablet formulations A and B with the objective to show that the formulations are practically equal. A crossover design in 24 healthy volunteers has been proposed.

A	→	B
B	→	A

- a) How would you set up a hypothesis test to meet the objective?
 - b) The drug has very long half life, suggest a design where the carry over effect and treatment effect can be estimated independently. (3p)
3. Consider a phase III study that is designed to compare a new lipid lowering treatment with placebo for the prevention of CV death. Low-density lipoprotein (LDL) is used as a surrogate endpoint and it is assumed that a lower LDL level implies a lower risk of CV death. The sample size is calculated in order to have 90% power to detect a difference in mean percent change from baseline in LDL of 50% between the active treatment and placebo. This effect size is chosen based on observed effects on LDL of the active treatment in the phase I and phase II studies.

This is one way to power the study. Suggest three other possible approaches for choice of the effect size for which the study is powered. (3p)

4. Consider a large phase III study with the two primary objectives
 - To evaluate the effect of gastrozole 20 mg versus placebo for the prevention of gastric ulcers
 - To evaluate the effect of gastrozole 20 mg versus placebo for the prevention of lesions in the oesophagus

Which condition has to be fulfilled in order for the primary objectives to also be confirmatory?

A long list of secondary objectives follows the primary ones. The very last objective is

- To evaluate safety and tolerability of treatment with gastrozole 20 mg.

How could this objective be evaluated? Suggest assessments/variables, as many as you think are necessary and give brief suggestions on how to analyze the different variables.

What would be the implication if the clinical study fails to meet this objective? (3p)

5. For the following questions, please indicate which answer is correct. Just one of the four alternatives is correct.
 - a. A certain type of breast cancer has a 1-year mortality rate of 25% when untreated. The standard treatment (drug Y) has a relative risk reduction of 10%. A new drug under

development (drug X) is likely to have a relative risk reduction between 10% and 40%. You are to design a trial with 1 year treatment duration and total sample size 2,000. Which treatment arms would you include:

- A) Only drug X.
 - B) Drug X and drug Y.
 - C) Drug X and placebo.
 - D) Drug X, drug Y and placebo. (1p)
- b. Typically, the main requirements for FDA to approve a new drug for marketing are
- A) Proven efficacy in at least one trial ($p\text{-value} < 5\%$) AND an estimated rate of severe adverse events (SAE) of at most 0.5%.
 - B) Proven cost-effectiveness ($p\text{-value} < 5\%$) where one saved life is equated to 2.4 million US dollars.
 - C) Proven efficacy in at least two trials ($p\text{-value} < 5\%$) AND benefit/risk judged to be beneficial
 - D) Positive point estimate for cost-effectiveness where one saved life is equated to 1.2 million US dollars AND proven efficacy ($p < 0.1\%$) based on a meta-analysis. (1p)
- c. For a single-center clinical trial comparing 1-month treatment with a new obesity drug with placebo, two different designs are considered. Design 1 is a randomized parallel-group design with 200 patients. Design 2 is a cross-over design with 100 patients, each receiving both treatments in a randomized order. What can be expected:
- A) The power for demonstrating a positive treatment effect is larger in Design 1, as the sample size is larger.
 - B) There is no risk of carry-over effects in Design 2, as one of the treatment arms is placebo.
 - C) The total trial time is radically shorter for Design 1, as it only incorporates one treatment period.
 - D) The residual variance is smaller in Design 2, as the inter-individual variance is eliminated. (1p)
- d. What is true about observational studies? A) They are almost always randomized. B) They are the only valid basis for scientific inference. C) They often have problems with confounded effects. D) They require that the patients are in the clinical center during the whole study. (1p)
- e. What is true about the Clinical Study Protocol (CSP) and the Clinical Study Report (CSR)? A) the CSR has to be approved by an ethics committee. B) the primary analysis in the CSR cannot be determined before an explanatory analysis of data. C) the CSR should describe deviations from the CSP. D) the CSP is commonly publicized in a peer-reviewed scientific journal. (1p)

6. For the following question, please indicate which answer is not correct. Just one of the four alternatives is incorrect.

- A) Randomization eliminates systematic biases.
- B) Randomization is the only valid basis for scientific inference.
- C) Randomization can be a valid basis for inference even if the distribution is not assumed to belong to the exponential family.
- D) Randomization is often performed within blocks of consecutive patients. (1p)

7. Assume we performed $n=5$ tests of hypothesis simultaneously and want the result to be at the level 0.05. The p-values obtained were as in the following table. Compute adjusted p-values according to Bonferroni, Holm and Hochberg. (2p)

p(1)	p(2)	p(3)	p(4)	p(5)
0.00012	0.0091	0.012	0.0534	0.0812

8. We want to know if regular intake of vitamin C can protect against catching a cold. For that purpose 30 twins of the same sex are chosen in the age interval 10–13 years. These are subject to a

randomized trial where one twin within each pair gets real vitamin C while the other one gets ineffective pills. We keep track of the number of subjects who did catch cold at least once during the subsequent 6 months. The results for the $2 \cdot 30 = 60$ children were as in the table below. Moreover it was noticed that in 9 of the twin pairs no one suffered a cold during the study period, regardless of intake of vitamin C. Discuss different analysis alternatives. (3 p)

Caught a Cold	Vitamin C	Placebo
Yes	12	14
No	18	16

9. A study of the effect of a certain treatment on bone marrow cancer was performed on 90 male patients diagnosed with the disease. The outcome variable was “the time from the first treatment until either death or the end of the study”. In addition to this variable other independent variables were also recorded: the patients’ age at the time of diagnosis, and the stage of the patients’ cancer. Let $Z_1=1/0$ when the patient is in stage II or not, $Z_2=1/0$ when the patient is in stage III or not and $Z_3=1/0$ when the patient is in stage IV or not. The proportional hazard model corresponding to this can be written in the following form:

$$h(t|Z) = h_0(t) \exp(\beta_1 Z_1 + \beta_2 Z_2 + \beta_3 Z_3)$$

The maximum likelihood estimates of the parameters are

$$\hat{\beta}_1 = 0.066$$

$$\hat{\beta}_2 = 0.612$$

$$\hat{\beta}_3 = 1.172$$

- Calculate the estimated relative risk of dying for patients with stage III disease relative to patients with stage II disease. (1p)
- If we introduce the age covariate Z_4 , in addition to the stage indicator variables, we get the following estimates of the parameters:

$$\hat{\beta}_1 = 0.138 (0.462)$$

$$\hat{\beta}_2 = 0.638 (0.356)$$

$$\hat{\beta}_3 = 1.693 (0.422)$$

$$\hat{\beta}_4 = 0.019 (0.014)$$

The partial log likelihood is -188.179. The values in parenthesis are standard errors. Calculate the relative risk for 50-years old patients compared to 40-years old patients with stage IV disease. How can you interpret the relative risk? (2p)

- Assume the model with all the covariates (i.e. as in b.). We would like to test the hypothesis that there is no difference in survival between patients in the different stages of the disease adjusting for the ages of the patients. We can formulate that hypothesis as $\beta_1 = \beta_2 = \beta_3 = 0$. Assume that the estimate of β_4 is 0.023 and the partial log likelihood is -195.906. How can this be used to test the above hypothesis? (2p)
- Discuss how we can calculate a 95% confidence interval for the risk of death for patients in stage IV relative to the risk of death for patients in stage I in the model with four covariates. Do as much as you can. Comment the result. (2p)