

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

**Date and place:** 2014-03-29 in V

**Questions:** Ziad Taib 0707655471 eller Stefan Franzén 0702524340 eller David Bock 0317762925

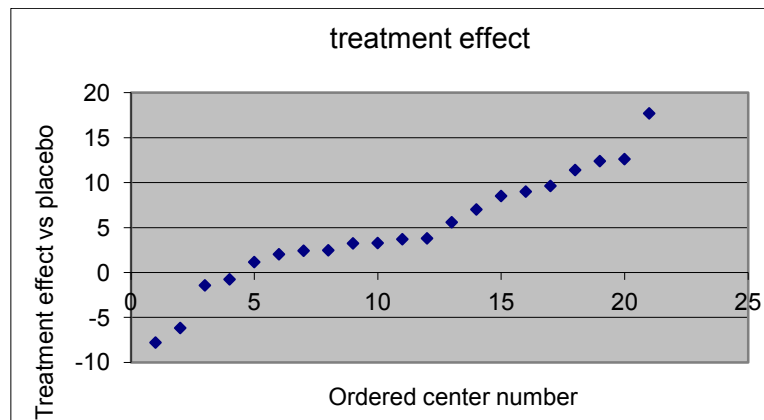
**Rules:** This is a closed book exam. No material is allowed other than a simple pocket calculator and statistical tables.

**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.

### DEL 1 Stefan Franzén

1. Consider a large phase III trial with 1629 patients comparing a novel treatment to placebo in patients diagnosed with acute bipolar depression. The level of symptoms are assessed using a validated questionnaire, HAMD17, and the analysis is performed by fitting a linear model including fixed effects of treatment, center and a treatment by center interaction.

The statistical analysis reveals an estimated treatment effect of 4.75 with a 95% confidence interval [2.55, 6.93] and p-value  $< 0.0001$ . The center by treatment interaction is statistically significant with  $p=0.0073$ . Use the figure below showing treatment effect vs. center to answer the following questions: (i) What can be said about the treatment effect? (ii) How can we proceed with the analysis? (3p)



2. We would like to compare the efficacy of a new pain killer drug to placebo in healthy volunteers. An electrode emitting low current electricity through the skin, is attached to the index finger on the left hand (right hand for left-handed subjects). The current causes a small amount of pain and the response variable is time the current is switched off by the subject.

Your task is to suggest three designs that would be suitable to compare the treatments and describe in brief the advantage of those three designs.

3. 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 and one water based oral solution. Due to the large between subject variability the study is designed as a crossover design in 24 healthy volunteers. Two design have been proposed:

Design1:

ABC – BCA – CAB – ACB – BAC - CBA

Design2:

ABC – BCA - CAB

- (i) Which of the two designs is superior and why?
  - (ii) If you felt compelled to investigate the advantages of the two designs further, how would you proceed? (3p)
4. You are a part of a clinical development team designing a phase I cancer trial evaluating a new cytotoxic agent that is being developed for treatment of Pancreas cancer. Your objective is to estimate the probability of observing dose limiting toxicity.

Discuss three design options and how you plan to estimate the probability of observing dose limiting toxicity. (3p)

**DEL 2 David Bock**

5. Phase IIa single centre parallel study of lung function in asthmatics. The objective is to assess whether a drug is able to improve lung function as measures by an increase in Forced Expiratory Volume in 1 second (FEV1) compared to placebo. The unit of the measurements is in litres. In the study design FEV1 is measured at baseline and at the end of the treatment period. Address the following questions:
- (i) What is an appropriate statistical model for analysis in light of assumptions about FEV1 and at what scale (e.g. number of litres or percentage improvement over placebo) we're interested in addressing the effect on lung function.
  - (ii) Discuss different approaches for utilizing the baseline measurements in the analysis. What are the advantages of accounting for baseline information? When are the advantages most pronounced? (3p)
6. Discuss the objective of the following:
- (i) Pre-specifying objectives and analysis methods in the Clinical Study Protocol
  - (ii) Randomization
  - (iii) Blinding
- (3p)

**DEL 3 Ziad Taib**

7. A new toothpaste additive has been developed to reduce plaque levels. You have been asked to design a study to compare toothpaste with and without the additive. The patients will come from two randomly selected groups. Plaque scores will be measured on a continuous scale from 0 to 5 and you can assume that they are normally distributed. The difference in plaque score you want to detect is 0.4, the standard deviation of the plaque scores is

0.8. A t-test will be carried out at a significance level of 5% and you want to have power of 90%. How many patients will you need? (3 p)

8. 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. (3p)

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

9. 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. (3P)

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

10. 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 4 or not. The proportional hazard model corresponding to this can be written in the following form:

$$h(t|Z) = h_0(t) \exp (\beta_1 Z_1 + \beta_{12} Z_{12} + \beta_{13} Z_3)$$

The maximum likelihood estimates of the parameters are

$$\beta_1 = 0.066$$

$$\beta_2 = 0.612$$

$$\beta_3 = 1.172$$

- 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:

$$\beta_1 = 1.38(0.462)$$

$$\beta_2 = 0.638(0.356)$$

$$\beta_3 = 1.693(0.422)$$

$$\beta_{34} = 0.019(0.014)$$

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? (3p)

Formelsamling:

$$h_d(t) = h_c(t)e^{\beta^T Z},$$

$$h_d(t) = h_c(t)e^{\beta},$$

$$n = \frac{Z\left(\frac{\alpha}{2}\right)^2 \sigma^2}{E^2}$$

$$n_1 = \frac{(Z_\alpha + Z_\beta)^2 \sigma^2}{\Delta^2}$$

$$n = \frac{[Z(\alpha) + Z(\beta)]^2 (\sigma_1^2 + \sigma_2^2)}{\Delta^2}$$

$$n = \frac{2\sigma^2 \left[ t_K \left( \frac{\alpha}{2} \right) + Z(\beta) \right]^2}{\Delta^2}, \quad Z(\beta) = t_K \left( \frac{\alpha}{2} \right) - \frac{\Delta}{\sigma \sqrt{\frac{2}{n}}}$$