Exam: sample questions

2016

Course contents

- During the 8 lectures of the course, we have covered the following topics

  - Introduction to clinical trials
  - Basic statistical methods for clinical trials
  - Basic Designs and Randomization
  - Designs for Clinical Trials
  - Safety Data
  - Classification of Clinical Trials
  - Cancer Trials
  - Continuous Data
  - Non-continuous Data
  - Longitudinal Data
  - Survival Analysis
  - Multiplicity and Sample size determination

Course details:

- Chapters 1-12 in the book plus the material in the handouts.
- For Chapters 1-7, reading instructions are included in the lecture notes.
- For the technical chapters you should learn the content of the following chapters
  - Chapter 8: 8.1-8.5,
  - Chapter 9: 9.1-9.6,
  - Chapter 10: 10.1-10.4 and 10.6,
  - Chapter 11: 11.1-11.4 (until example 11.4.1) and 11.5-11.7 (until example 11.7.2),
  - Chapter 12: 12.6 as well as the lectures notes distributed as handouts.

Examination:

- Closed book written exam and
- Compulsory computer project
- The written exam is worth 30 scores (pass (G) = 15 scores, excellent (VG) = 24 scores).
- No material is allowed at the exam other than a simple pocket calculator

1 For the following questions, please indicate which answer is correct. Just one of the four alternatives is correct.

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:

- Only drug X.
- Drug X and drug Y.
- Drug X and placebo.
- Drug X, drug Y and placebo. (1p)

For the following questions, please indicate which answer is correct. Just one of the four alternatives is correct.

Typically, the main requirements for FDA to approve a new drug for marketing are

A) Proven efficacy in at least one trial (p-value<5%) AND an estimated rate of severe adverse events (SAE) of at most 0.5%.

B) Proven cost-effectiveness (p-value<5%) where one saved life is equated to 2.4 million US dollars.

C) Proven efficacy in at least two trials (p-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)

For the following questions, please indicate which answer is correct. Just one of the four alternatives is correct.

- 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)

For the following questions, please indicate which answer is correct. Just one of the four alternatives is correct.

- 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)

- 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

- A clinical study is comparing active treatment (drug A) with placebo for the treatment of symptoms of heartburn. Patients are included if they have had symptoms of heartburn during at least 5 out of the 7 days prior to enrolment into the study. Further they are randomised to receive either drug A or placebo during 6 weeks. The primary objective of the study is:

- To compare the effect of drug A versus placebo on symptoms of heartburn.

- Suggest two different possible primary variables.

- “With 260 evaluable subjects the power is 80% to detect a 7 mmHg change in DBP from baseline to week 8 at the significance level 5%, assuming a standard deviation of 20 mmHg.”
-
- When determining the sample size for a clinical study one of the important considerations is to decide for which specific effect size we are going to power the study.
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- Suggest two different ways of thinking when chosing this effect size.

- When an investigator randomise a patient to a clinical study it is important that he/she is blinded to which treatment the patient is assigned.

- Mention one potential risk with the investigator not being blinded, and the statistical implication of that risk.

- In a clinical study comparing an active treatment with placebo for treatment of hypertension, the conlusion from the statistical analysis is that the active treatment gives a statistically significantly greater reduction of the blood pressure as compared to placebo.
-
- How can we be sure that it is the drug that causes the difference in response between the groups and not something else?

- 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)

- 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. (2)

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

- 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 where 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

- 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. Which patients would you include/exclude from the different analyses in this specific example? (2)

- 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

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

- 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)

- 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? (2p)

- Assume you are given data from a two period crossover trial to investigate the effects of two treatments A (standard) and B (new) for cirrhosis in the lever. The endpoint is maximal rate of urea synthesis over a short period and high values are desirable. Patients were randomly allocated to two treatment groups with 8 subjects receiving treatments AB and 13 subjects BA. Specify a suitable model for the data which includes treatment, period and carryover effects.
  - How would you assess the evidence that there is a carryover effect from period 1 to period 2? (1p)
  - How would you assess the evidence that there is a difference in average response between periods 1 to period 2? (1p)
  - How would you assess the treatment effect taking into account carryover and period effects? (2p)