Name

Final Exam

CPH 675: Clinical Trials and Intervention Studies

Dr Melanie Bell, Spring 2015

Instructions

This exam is due, printed out, at my office, by 5:00pm 11 May 2015. Please show relevant code and output within your solution (i.e., not in an appendix). Your exam will be graded both on correctness and conciseness. You can receive no help on this exam.

Academic Integrity

I agree to abide by all rules of academic integrity while working on this final exam. I agree that all the work contained herein is my own, and I did not consult with anyone, except possibly Dr Bell for clarification, on this exam. This includes asking classmates or others about statistical software.

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Signature Date

Question 1

a) [8 pts] You are part of a research team that is going to carry out a 2x2 factorial study investigating Tai Chi and meditation to reduce anxiety in cancer survivors. Create a randomization list for this trial which is based on simple randomization, but is equally balanced across the arms. Start from first principles by using a statistical distribution. The total sample size is 400. Show your code and appropriate table(s) that demonstrate that you have achieved balance.

b) [2 pts] The above randomization is neither stratified nor blocked. Discuss the implications of this.

c) [4 pts] Discuss some of the issues (both positive and negative) that arise due to this design and intervention structure (do not discuss the likelihood of the intervention being effective or not).

d) [8pts] Anxiety is measured as a binary variable, and is measured once only (post-intervention). The primary objective is to compare both the active interventions to control. A secondary hypothesis is that men and women may respond differently to the intervention. Write a brief statistical analysis plan for this study.

Question 2

a) [8 pts] Find the sample size required for a three armed trial where allocation ratio is 2:1 for each of the two active interventions compared to the control (2:2:1). Assume 80% power, type I error rate of 0.05, two-sided tests. The researchers aim to find a standardized difference between the two active arms of 0.3, and a standardized difference of at least 0.5 between the control group and either of the active arms.

b) [4 pts] A secondary outcome is binary. Do they have enough power (≥ 80%) to detect a relative risk of 1.5 or greater between the control group and either of the active arms? State all the assumptions you are making.

Question 3

Download the data RCT\_wide from D2L to answer the following questions.

a) [3 pts] This is a longitudinal study, which means that the data are not independent. What are three methods which could account for the lack of independence of the data?

b) [3 pts] Create an informative table of missing data

c) [2 pts] You should note that the missing data rates differ by group. Does this give evidence that the data are MCAR, MAR, or MNAR? Explain briefly.

For problems d) and e), use a means mixed model, assuming a compound symmetric variance-covariance matrix.

d) [2 pts] Is there a difference in the pattern of change over time by arm? Explain.

e) [6 pts] Use a contrast within your mixed model to find the difference between groups in the change from baseline at each post-baseline timepoint, and the associated 95% confidence intervals. Use a table to display your results, and show your code.

f) [6 pts] Suppose that the primary outcome was the comparison of groups in their change from baseline at the final timepoint. Write your results in a few sentences that would be appropriate for a journal.

g) [2 pts] A secondary objective was to investigate whether the difference between groups in the patterns of change over time was modified by sex. Test this hypothesis.

h) [2 pts] How could you improve the precision of your results?

Question 4: Short answer, 2 pts each

a) What method should be used to test the difference in overall survival between two arms in an RCT?

b) A two-arm parallel RCT found a hazard ratio of 1.14 ( 95%CI, 1.10-1.17) for the outcome of survival when comparing a new intervention to usual care. Explain what this means.

c) State two of the functions of a data safety monitoring board.

d) Suppose a trial uses a block size of 8 during randomization. What is the largest sample size imbalance between the arms that could occur during the trial?

e) During an interim analysis for a trial that was half way through recruitment, it was found that sex, which was thought to be highly prognostic of outcome, was imbalanced between the arms. What are two approaches that could be used to handle this imbalance?

f) Suppose a cluster randomized trial does not take between cluster variation into account. Will this affect bias, type I error rate, both or neither?

g) The following is output from an individual level analysis of a cluster randomized trial. There were 50 hospitals randomized, with 20 patients at each hospital.

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| **Stata**  ------------------------------------------------------------------------------  Random-effects Parameters | Estimate Std. Err. [95% Conf. Interval]  -----------------------------+------------------------------------------------  hospital: Identity |  sd(\_cons) | .3889497 .0667754 .2778164 .5445389  -----------------------------+------------------------------------------------  sd(Residual) | 2.274258 .0217349 2.232055 2.317259 |
| SAS  Covariance Parameter Estimates  Cov Parm Subject Estimate  Intercept hospital 0.1775  Residual 5.1612 |

h) What was the empirical (observed) ICC?

i) What was the empirical design effect?

j) Suppose you are planning a group sequential trial with 2 intermediate looks. Using the O’Brien-Fleming alpha spending function, find the alpha required to stop the trial early at both stages.

k) Briefly explain the concept of stopping for futility

l) suppose you are carrying out a non-inferiority trial, where lower scores are better and the non-inferiority margin is 4. The confidence interval is (-3.2, 1.9). Do you reject or fail to reject the null hypothesis?