**Assignment Topics # 6 & 7**

**The assignment is due Friday, March 19th at 10am. Please submit an electronic copy of your assignment through the blackboard. Out of 100 points.**

*Please present all answers and output in the order the questions are asked and include your SAS code as part of the answer.*

**Topic 6: Multiple testing**

A Phase III dose-finding clinical trial in patients with pancreatic cancer was conducted to determine if at least one of two doses of a new experimental treatment has a beneficial effect on 1-year mortality. Occasionally, for serious illnesses such as pancreatic cancer, the FDA allows the sponsor to skip Phase II and go directly to a Phase III dose-finding study in order to expedite product testing and get the product on the market as soon as possible, especially when there is no current treatment for the disease being studied. However, the usual appropriate statistical rigor required for Phase III (i.e., control the probability of a false positive study at 0.05) needs to be applied.

The following table summarizes the results of the study:

|  |  |  |
| --- | --- | --- |
|  | *Died within 1 year of randomization* | |
| *Treatment group* | ***Yes*** | ***No*** |
| ***Control*** | 30 | 16 |
| ***Low dose*** | 23 | 22 |
| ***High dose*** | 13 | 31 |

1. The goal of the trial is to detect if at least one of the doses of the experimental treatment is significantly more effective than the control at reducing mortality of pancreatic cancer patients. State the pairwise (null and alternative) hypotheses of interest in both words and notation, and the Bonferroni comparison-wise error rates that will control the family-wise error rate (probability of a false positive study) at the 0.05 level of significance.
2. Use PROC FREQ to set up a formal contingency table relating treatment to mortality. Please highlight the risk of death within 1 year for each treatment group. Report the Bonferroni-adjusted chi-square p-values for the comparison of each dose versus control.
3. Calculate the risk difference for death between (a) the low dose group and the control group; and (b) the high dose and the control group. Calculate the Bonferroni-adjusted 2-sided 95% confidence interval for the risk difference in each case, appropriately controlling the family-wise error rate at the 0.05 level of significance.
4. Repeat 3 above, but for the risk ratio for each dose versus control. Present the estimates and Bonferroni-adjusted 2-sided 95% confidence interval.
5. Explain whether or not the study is a success based on the definition of success in question #1 and the results you generated; please state the dose(s), if any, that you feel should be marketed and why (include just a brief write-up here).

**Topic 7: Sample size and power calculations in clinical trials**

Persons who inject drugs (PWID) often experience stigma, which is defined as the social exclusion and dehumanization of individuals in an undesirable social category. A randomized controlled trial will be conducted to assess the effect of a stigma intervention targeted to help PWID cope with stigma. Patients will be recruited at 3 treatment addition clinics. They will be randomized 1:1 to either i) stigma intervention consisting of three 2-hour group sessions (stigma intervention), or ii) standard of care (control intervention). The primary outcome is overdose during the 12 month study period. The investigators expect that 15% of patients in the control group will experience an overdose in the 12 months following the intervention, but they hope that only 5% of patients in the stigma intervention group will experience an overdose event.

1. State the null hypothesis and the alternative hypothesis in both words and notation for the primary analysis. What is the clinically meaningful effect the investigators are hoping to detect?
2. Please compute and report the required total sample size to achieve 80% power for assessing superiority of the stigma intervention over the control intervention at the two-sided 0.05 level of significance. Adjust your sample size to account for potential loss to follow-up which is expected in 15% of the patients.
3. Repeat the computation from question 7 with a 2:1 allocation ratio: report the total number of patients required to achieve 80% power. Adjust for an expected 15% loss to follow-up and report this total number of patients as well. Using question 7, report how many additional patients are required for a 2:1 compared with a 1:1 ratio (under expected 15% loss to follow-up).
4. A secondary study outcome is change in stigma score from baseline to 12 months. Stigma score is measured in a scale ranging from 0 to 52 with higher scores being indicative of higher level of internalized stigma and lower self-esteem. Stigma score at baseline is expected to be 10 units with standard deviation of 8 units.

We expect to observe an average change in stigma score from baseline to 12 months of 1 in the control group. The study team thinks a clinically relevant difference in stigma score between the treatment and control groups is at least 3 units. State the null hypothesis that will be tested in this secondary analysis. Compute the power to reject the null hypothesis for the sample using the size you used in question 8 (2:1 allocation ratio, accounting for loss to follow-up) at two-sided alpha=0.05. You may assume equal variability in the treatment groups (standard deviation of 8).