**BS851 Assignment Topic 10 – Interim Analyses**

**Due by 10am on Wednesday, April 21. Please submit an electronic copy of your assignment through 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.*

A randomized trial for Hepatitis C is planned with 1:1 randomization to a new treatment versus a standard of care treatment (control). The initial goal is to enroll 1500 patients in both treatments combined. The primary outcome is sustained virological response (“SVR”) at 6 months after randomization (meaning hepatitis C virus is not detected in the blood). The investigators plan to carry out 4 interim analyses (***plus*** the final analysis) and will consider stopping the study at an interim analysis if there is a significant difference in SVR at 6 months between the two treatments using O’Brien-Fleming two-sided significance levels. Suppose we are at the design stage of the study, and we are *planning* on enrolling 1500 patients. Suppose that the first interim analysis is *scheduled* after the first 600 patients (300 per group) are treated and followed for 6 months, the second interim analysis is *scheduled* after the first 750 patients (375 per group) are treated and followed for 6 months, the third interim analysis is *scheduled* after the first 1000 patients (500 per group) are treated and followed for 6 months, the fourth interim analysis is *scheduled* after the first 1200 (600 per group) are treated and followed for 6 months, and the final analysis is *planned* after all 1500 patients have been treated and followed.

* 1. Find the O’Brien-Fleming two-sided significance levels for the 5 analyses (the 4 interim analyses, plus the final). Use SAS PROC SEQDESIGN, and use it at an overall two-sided 0.05 level of significance. In a nicely formatted table, please provide the alpha spent, critical values, significance levels at each interim stage and the final stage. Explain *briefly* the general difference between a significance level (at a given interim analysis) versus “alpha-spent” (at a given interim analysis).
  2. It’s now time for the first interim analysis comparing treatments. It turns out there are 560 total patients in this first analysis (280 per group) instead of the planned 600. Revise the O’Brien-Fleming two-sided significance levels to use for this first analysis and subsequent analyses 2 through 5, still assuming a planned total of 1500 patients and still planning for the remaining interim analyses to be carried out at the planned sample sizes discussed above (750, 1000, and 1200). In a nicely formatted table, please provide the alpha spent, critical values, significance levels at each interim stage and the final stage.
     + 1. After the first but before the second interim analysis, the authors decided to increase the total sample size for the Primary Efficacy Population from 1500 to 1800 (900 per group). Re-calculate the two-sided significance levels to use for analyses 2 through 5, keeping in mind that one interim analysis has already been done on 560 patients at a given significance level, and that this first significance level and the corresponding alpha that was spent cannot be changed. Also, when calculating the revised significance level values for the remaining analyses, please do it under these assumptions:

(1) Despite the increase in sample size, the analyses will still be carried out on the first 750, 1000, and 1200 total patients, respectively, but that the final analysis will, again, be conducted on the 1800 total patients.

(2) At the time of each interim analysis, we would like to only spend the same amount of alpha that we spent at each interim analysis in Part B (e.g., the alpha-spent by the second interim analysis under this new total sample size of 1800 should match the alpha-spent by the second interim analysis under the old total sample size of 1500 in Part B, and similarly for analyses 3-5).

* + - 1. Suppose the study is re-designed as in Part C, and now it is the time for the second interim analysis (again, the first interim analysis is already completed with a total sample size of 560). There are 822 total patients in this second interim analysis (411 in per group) instead of the planned 750. Re-calculate the significance levels to be used for this second interim analysis and in analyses 3-5, assuming analyses 3-5 will still be performed on 1000, 1200 and 1800 patients, respectively, and that the alpha-spent at the interim analyses should match what we calculated in Parts B & C.
      2. The authors present the results of the second interim analysis comparing SVR at 6 months on 822 patients. In the control group, 122 of the 411 patients had an SVR. In the new treatment group, 160 of the 411 patients had an SVR. Use a chi-square test to determine the p-value for the test of:

H0: pnew\_treatment = pcontrol vs. HA: pnew\_treatment ≠ pcontrol

Based on the significance levels you calculated in Part D, should the DSMB recommend stopping the study for overwhelming efficacy of the new treatment? Explain briefly.