MATH 654-102: Design and Analysis of Clinical Trials

MID-TERM EXAM

Spring, 2011

(Time allowed: TWO AND HALF HOURS)

INSTRUCTIONS TO STUDENTS:

1. This test contains **FIVE** questions and comprises **SIX** printed pages.
2. Answer **ALL** questions for a total of 100 marks.
3. This is a **open-book**, **open-note** test; you can use any materials you have.
4. Write your name on the front of your answer booklet and on any additional sheets you write on.

1. You are asked to help design a phase II clinical trial using Simon's two-stage design to evaluate a new treatment. The investigator decides that if the true response rate $\pi \leq \pi_0 = 0.2$ then the treatment is definitely ineffective and if $\pi \geq \pi_1 = 0.4$ then the treatment will be declared effective and considered for further investigation in a phase III clinical trial. The investigator wants to control the probability of falsely declaring the treatment effective when in fact it is ineffective at the level of 0.05 and to have high probability (0.9) to declare the treatment effective when in fact it is effective. Using the tables provided in our lecture slides or lecture note, set up an optimal two-stage design by answering the following questions:

   (a) How many patients will be need in the first stage?

   (b) When will you declare the treatment a failure?

   (c) When will you stop the trial at the first stage?

   (d) What is the early termination probability if the true response rate $\pi = \pi_0$?

   (e) What is the expected sample size if the true response rate $\pi = \pi_0$?

2. We are to conduct a randomized clinical trial to compare treatment A to treatment B. We are going to use permuted block randomization with varying block sizes to assign treatments. The block sizes that will be used for the patients are 4, 2, 6, 4, 4, 6, 4. Using the following uniform random numbers to fill out these blocks (you may not need all the numbers).

   0.53 0.71 0.72 0.50 0.83 0.07 0.76 0.69 0.47 0.79 0.36 0.75 0.90 0.08
   0.74 0.84 0.00 0.54 0.88 0.57 0.74 0.87 0.69 0.49 0.33 0.58 0.95 0.74
   0.71 0.47 0.53 0.97 0.47 0.97 0.14 0.74 0.30 0.91 0.32 0.74

3. A clinical trial is to be conducted to compare a generic drug to a brand name drug. The response rate of the brand name drug can be accurately assumed to be 30%. The generic drug is considered non-inferior to the brand name drug if the response rate of the generic drug is not 4% worse than the response rate of the brand name drug. Suppose we would like to control at 0.05 the probability of claiming non-inferiority of the drug when in fact it is inferior to the brand name drug, and would like to detect with power 90% if the generic drug is the same as the brand name drug (in terms of having the same response rate).

   (a) Assume equal treatment groups, how large should the sample size be in order to claim non-inferiority?

   (b) Assume the brand name drug costs 4 times as much per subject as the generic drug, what is the optimal sample size for each group if the goal is to minimize the cost of the trial while still controlling type I and type II errors?

4. The following data is from a traditional design comparing two treatments where the outcome is whether or not a patient responds to the treatment. The data is re-arranged in groups with every 40 patient increment (for a total of 4 groups):

	time 1		time 2		time 3		time 4	
	n	Y	n	Y	n	Y	n	Y
treatment 1	20	13	40	26	60	43	80	58
treatment 0	20	7	40	16	60	23	80	25

where n is the total sample size available at each time point, Y is the total number of complete responses at the corresponding time point. Do the following:

(a) Use the (two-sided) two-sample proportion test at the last time point to test at the significance level 0.05 whether or not the response rates for these two treatments are the same.

(b) Conduct (two-sided) group sequential tests using Pocock boundaries at significance level $\alpha = 0.05$. What is your conclusion?

(c) Conduct (two-sided) group sequential tests using O'Brien-Fleming boundaries at significance level $\alpha = 0.05$. What is your conclusion?

5. Suppose the dose-toxicity relationship is given by the following equation

$$\pi(x) = P[\text{toxicity}|x] = \frac{e^{-4+x}}{1+e^{-4+x}},\ 0 < x < \infty,$$

where x is a dose level and $\pi(x)$ is the probability of having serious (but reversible) adverse events. You are going to use the traditional design to conduct a phase I trial to search for the maximum tolerated dose (MTD).

(a) Find the true MTD. That is, find a dose level x^* such that $P[\text{toxicity}|x^*] = 1/3$.

(b) Starting with an initial dose level of $x_1 = 1$, prepare a dose sequence of length 6 using the modified Fibonacci sequence.

(c) Define B_i to be the event that the trial will reach the ith dose level x_i, and A_i to be the event that the trial will stop at x_i (if the trial reaches the last dose level, the trial will stop there). Find the relationship between B_i's and A_i's (for example, $B_2 = \overline{A}_1$).

(d) Assume that the dose level at which the trial stops is claimed to the (estimated) MTD (when the trial reaches the last dose level, that dose level is claimed to be the MTD). Define a random variable $X =$ dose level claimed to be the MTD. Find the distribution of X (Hint: $P[X = x_i] = P[A_iB_i] = P[A_i|B_i]P[B_i]$).

(e) Find $E(X)$ for the dose schedule. Is this expectation close the true MTD? What is $var(X)$?