Biostatistics 699 Project #4

The purpose of this project is to introduce you to the analytic tools and simulation techniques that may be useful for the design of medical and epidemiological studies. You will learn how to simulate data from statistical models, basic concepts behind sample size and power calculation, and how to summarize simulation results. **You must turn in your complete computer code as an appendix for this project.** There are two design questions listed on the following two pages. You are to do **one** of questions as follows:

(a) Those with an interim or final presentation with a number of 1, 2, 3, or 4 are to do Design Question 1;
(b) Those with an interim or final presentation with a number of 5, 6, 7, or 8 are to do Design Question 2.

You are welcome to use any existing sample size formulas or sample size programs that you find. However, these formulas and programs should only be used as a comparison to judge to your simulation results.

Design Question 1

Pain is a common problem in Medicare End-Stage Renal Disease (ESRD) Hemodialysis (HD) patients, but its prevalence varies widely by geography, dialysis unit, and possibly, ethnicity. Perception of pain has been linked to decreased quality of life, lack of social support, depressed mood and other mental health disorders. Chronic opioid prescription has been identified in approximately 20% of US ESRD HD patients, far higher than the rate in Medicare comparison populations. Opioid doses prescribed to HD patients exceed Centers for Disease Control and Prevention (CDC) recommendations. Prescription and dose level have been associated with increased hospitalizations and mortality in this population.

Behavioral modification interventions such as Cognitive Behavioral Therapy (CBT) have not been employed to reduce the rate of opioid prescription and opioid use, as well as addressing comorbid related issues such as depression, anxiety and pain in the HD population. Medical interventions such as use of naloxone and buprenorphine have not been evaluated by randomized controlled trials in HD patients who use opioids. The ESRD HD population, because of its continuous longitudinal participation in monitored treatment and the availability of data resources is an ideal population in which to launch and monitor interventions.

This project will include five to seven (5-7) geographically-distinct centers, and each center will be required to enroll and follow 120 patients in the study. The primary endpoint measured in each patient is complete elimination of opioid dependence, i.e. opioid-free. A patient will be defined as opioid-free if they do not take a prescribed opioid for 90 consecutive days during one-year of follow-up. Historically, in the absence of any interventions, approximately 10% of patients taking opioids at the beginning of their follow-up are able to become opioid-free.

Information pertinent to the design:

(a) Due to differential patient characteristics among centers, the historical rate of opioid independence at a center can be as low as 5% and as high as 20%.
(b) Approximately 1% of patients will become eligible for transplant before completing a year of follow-up, and approximately 8% of patients will die before completing a year of follow-up.
(c) Investigators hypothesize that patients currently taking 30-60 morphine milligram equivalents (MME) of opioids are 25% more likely to quit than patients currently taking more than 60 MME.

Specific questions to address:

(1) If a two-arm study of (i) CBT alone versus (ii) CBT + buprenorphrine is designed to have 0.80 power, what differential proportions of opioid independence can be detected between the two arms? Assume a Type I error rate of 0.05.
(2) If a three-arm study of (i) standard of care versus (ii) CBT alone versus (iii) CBT + buprenorphrine is designed to have 0.80 power, what differential proportions of opioid independence can be detected between the three arms? Assume a Type I error rate of 0.05.
(3) What is the differential power of the two-arm and three-arm designs between using only five centers as compared to using all seven centers?

Design Question 2

Cancers of the blood, such as leukemia and multiple myeloma, that are unresponsive to other forms of treatment, can be treated with an allogeneic hematopoietic stem cell transplant (alloHSCT), in which the stem cells come from a genetically-matched donor, usually a sibling.

However, the percentage of matching is often imperfect, leading to the immune system (T cells) in the alloHSCT (graft) and the remaining immune system in the recipient (host) to fight each other. Acute graft-versus-host disease (aGVHD) is the name of this immune reaction if it occurs within 100 days of alloHSCT. Acute GVHD occurs in 40-50% of alloHSCT recipients, and the skin, gut, and liver are the organ systems most affected. Acute GVHD is one of the leading causes of early death in HSCT recipients and few approaches are available to either prevent or treat aGVHD. The most common approach for treatment is heavy-dose steroids, which present patients with other serious side effects even if the aGVHD is eliminated.

The process of alloHSCT has been shown to result in alteration of the intestinal microbiome, the bacterial community that lives in the human intestine that is believed to be central to gut health. Thus, it is hoped that treatments that directly work to maintain the intestinal microbiome will thereby lead to a reduced incidence of aGVHD in alloHSCT patients.

It is hypothesized that increased consumption of potato starch will work to increase or maintain levels of butyrate, which is a short-chain fatty acid that plays numerous roles in the intestinal microbiome. You are asked to help design a one-arm clinical trial, in which all enrolled alloHSCT patients will ingest 40g of starch each day for up to 100 days in hopes of preventing aGVHD from developing.

Information pertinent to the design:

(a) Historically, the median time-to-onset of aGVHD is 28 days, with an interquartile range of [7, 56] days.
(b) Approximately 15% of patients will experience graft failure, relapse of cancer, or death by Day 100 and will not be observable for aGVHD. Assume that dietary starch has no impact on any of these outcomes.
(c) Approximately 20% of patients will discontinue taking starch for a variety of reasons unrelated to aGVHD.

Specific questions to address:

(1) How many patients need to be enrolled to reduce the 50% historical rate of aGVHD to each of 40%, 35%, and 30%? Assume power of 0.80 and a Type I error rate of 0.05.
(2) It is possible that the study should be terminated early because the treatment is appearing to be ineffective. Assume that a rate of 50% would be evidence of ineffectiveness. How would you design the study to include one interim analysis of futility, and how does this affect the sample size you found in (1) if no interim analysis were used?