LECTURE FIVE: Follow-up, Adherence to the Protocol, Post-randomization and Sample Size Planning

Reading Assignment for Lecture 5

Required Reading:

- Designing Clinical Research (4th Edition), Chapter 6, pages 55-59 and Chapter 11, pages 160-162.
- Fundamentals of Clinical Trials (4th Edition), Chapter 14.
- Hollis and Campbell. What is meant by intention to treat analysis? Survey of published randomized controlled trials. BMJ 1999:319;670-4.

Homework Assignment for Lecture 5
Total Points: 19 (+2 extra credit)

Assignment file: AssignL5_2014.doc
Assignment due:

- email to Carolyn Seib & Jesus Valdez (clinicaltrials2014@gmail.com) by February 24, 2014; 5pm.
    - Make sure that your NAME is on the top of the document
    - Use this format to name your homework documents: LastnameFirstname_L#, for example: SmithJohn_AssignL5
    - Subject Line of email: SmithJohn_L5
- bring a copy of homework to Section III on March 6, 2014

Please answer the following questions

A study of an antihypertensive medication was done in which 1000 persons with mild hypertension were randomized to a new drug (500) or placebo (500) with planned treatment and follow-up for one year. The primary endpoint of the study was change in diastolic blood pressure from baseline until the last measurement in the study. By some miracle, everyone took their pills every day until they stopped taking them and then they never took another pill. Participants measured their own blood pressure at home daily for the entire year and continued this measurement daily whether or not they continued to take study pills. By one last miracle, all participants also reported adverse events (AE's) for the entire year whether or not they continued to take study pills. The number of days before stopping study medications and the proportion of participants who stopped medication at each time point in study is tabulated below. For example, 100 participants (10%) took their first 10 pills and then stopped; 200 (20%) took their pills for the first 50 days and then stopped. All participants had blood pressure measurements for all 365 days (another miracle).

Days before stopping study meds	% of participants
10	10%
50	20%
100	10%
365	60%

1. What statistical test would you use to compare the mean blood pressure change from baseline until the last measurement on study drug? (1 point)

2. Since adherence to study drug was rather low and some participants stopped study medication after only 10 days of use, you might want to consider some alternative ways to analyze the data. Let's assume that for any analysis that you perform, the outcome will be the change from baseline to the last available measurement (i.e., no values will be 'carried forward' or imputed).

Answer questions 2a through 2h with respect to assessing efficacy:

2a. What analytic approach would you recommend that the study investigators use with respect to which patients and which data are included in the analysis? (2 points + 1 extra point possible)

2b. Does this approach qualify as an intent-to-treat (ITT) analysis? (Yes or No). Why or why not? (1 point + 1 extra point possible)

2c. What are the advantages to ITT for this study? (2 points)

2d. Describe one alternative *per protocol or as-treated* analysis that the investigators could do. (1 point)

2e. Describe one advantage of this proposed alternative analysis. (1 point)

2f. Is this alternative protocol you described ITT? (1 point)

2g. What might you conclude if the results of these alternative analyses agree with your primary analyses? (1 point)

2h. What might you conclude if they disagree? (1 point)

Answer questions 2i through 2j with respect to assessing safety:

2i. Suggest at least 2 different analytic approaches that you recommend that the study investigators use with respect to which patients and which data are included in the analysis? Include one ITT and another non-ITT approach. (2 points)

2j. List at least one advantage to each of your approaches. Which would you prefer? (2 points)

3. Drawing upon the lecture, please list as many concrete steps as you can that can be taken during the trial to increase participants' adherence? (bulleted list is fine) (4 points)