LECTURE FOUR: Measuring Outcomes and Adverse Effects

Reading Assignment for Lecture 4

Required Reading:

- Designing Clinical Research (4th Edition), Chapter 10, pages 140-142, Chapter 11 page 162.
- Psaty BM, Lumley T. Surrogate end points and FDA approval: a tale of 2 lipid-altering drugs. JAMA. 2008 Mar 26;299(12):1474-6.
- Bent S, et al. Brief communication: Better ways to question patients about adverse medical events: a randomized, controlled trial. Ann Intern Med. 2006 Feb 21;144(4):257-61.

Homework Assignment for Lecture 4
Total points = 13

Assignment file: AssignL4_2014
Assignment due:

- email to Carolyn Seib & Jesus Valdez (clinicaltrials2014@gmail.com) by February 10, 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_AssignL4
    - Subject Line of email: SmithJohn_L4
- bring a copy of homework to Section II on February 13, 2014

Please answer the following questions.

1. Breast density is the proportion of breast that is comprised of fibrous and cellular tissue rather than fat. A high 75% density means the breast is mostly fibrous and cellular tissue while a low 10% density means the breast is almost entirely composed of fat. On average, women with breast cancer have higher breast density than women without breast cancer.

   Companies developing drugs to reduce the risk of breast cancer would like to use breast density as a surrogate marker for their trials to gain FDA approval to market new treatments to prevent breast cancer. Specifically, one company has a new (fictitious) SERM (Alloxifene) that they would like to have approved for prevention of breast cancer.

   a. Briefly list 3 examples of results from hypothetical clinical studies that might support the use of breast density as a surrogate marker for the effect of Alloxifene on risk for breast cancer. (4 points)

2. Arterene is a fictional new drug that has been shown in early phase trials to reduce markers of inflammation (CRP by 50% and IL-6 by 80%), decrease platelet aggregation, and increase HDL cholesterol levels by 30%. You are asked to consult on plans for a phase III trial of the effect of Arterene to gain approval from the FDA to market the drug. In pooled results from small early phase trials, Arterene reduced risk of stroke by 60% (95% C.I. 0.20 to 1.25). It also reduced the risk of MI 33% (95% C.I. 0.45 to 1.15). There was also a trend toward reduction in revascularizations (20% decrease) and sudden death (15% decrease) with very wide confidence intervals. CHD events (MI, revascularization, sudden death) were 3 times more common than strokes. In addition, there were non-statistically significant increases in risk of breast cancer (RR 1.75; 95% CI 0.4-2.9) and dementia (RR 2.4; 95% CI 0.3-3.5) and statistically significant increases in rates of headache, diarrhea, and cough.

   A debate has broken out about what should be the primary outcome of the Arterene Trial. Here are the alternatives and the respective sample size and budget needed for a trial with that endpoint, assuming that the effect sizes are the same as the trends observed in early studies.

   - Stroke (fatal and nonfatal): Sample size = 12,000 participants; $280M. CHD events would be a secondary outcome.
   - CHD events (CHD death, MI + coronary revascularization): Sample size = 9,000 participants; $200M.
   - Combined CV Disease (CHD events, stroke): Sample size = 5,000 participants; $130M.

   a. List the pros and cons of each of the three potential primary outcomes mentioned above (at least one pro and con for each). (6 points)

   b. Write out the question(s) you would ask patients to assess the potential adverse effects of Arterene in this trial. Then briefly (2 or 3 short sentences) describe the advantages and disadvantages of the approach you took to assessing the safety of Arterene. (3 points)