Homework 5: Noninferiority Trials

Read the following articles.

> Pocock SJ (2003) The pros and cons of noninferiority trials. Fundamental & Clinical Pharmacology, 17: 483–490.
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> Stone GW, Lansky AJ, Pocock SJ, Gersh BJ, Dangas G, Wong SC, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Möckel M, Ochala A, Kellock A, Parise H, Mehran R, HORIZONS-AMI Trial Investigators. (2009) Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. New England Journal of Medicine, 360:1946-59.

Regarding the trial reported by Stone et al (2009):

1. Interventions & Outcomes:

   - What was the control treatment in this trial? What was the rationale for selection of the control treatment(s)?
   - What was the experimental intervention?
   - What protocol procedures were used (i) to ensure that and (ii) to track whether participants were exposed to interventions at the levels planned?
   - Did study follow-up end if/when intervention exposures ended? Why?
   - What allocation ratio, where $\gamma = n_E / n_C$, did they use? Based on your reading of the paper, why did the investigators choose this allocation ratio?
   - What was the primary efficacy outcome studied? What variable type is it (see Lecture 3)? How frequently was it assessed per participant? Cite the within-arm summaries reported at the end of the trial, if any (eg, mean; CI)?
   - What was the primary safety outcome studied? What variable type is it? How frequently was it assessed per participant? Cite the within-arm summaries reported at the end of the trial, if any?

2. Noninferiority design: The authors study the primary (safety) outcome using a NI design.

   - Was the experimental intervention expected to increase or to decrease the (safety) outcome?
   - What noninferiority margin, δ_0, was selected?
   - Express the null and alternative hypotheses in terms of δ_0.
   - Sketch the relationships between between δ_0 and δ_A using a diagram as on page 4 of Lecture 5. Give the actual values of these parameters, not just the symbols, and draw the

diagrams to scale. *(If sketches are made with pen/pencil, please scan and include with HW5.)*

- Based on the analysis at the end of the trial, the authors present the mean and 95% CIs for the primary outcome on the difference scale. Add this to your plot. Is this estimate consistent with H_0?
- For the control event rate π_C, how did the observed value (analysis stage, based on sample) compare with the expected value (design stage; hypothesized)? Did authors provide info you need to answer this?

3. Pocock (2003) states: "First it is essential to realize that failure to demonstrate a statistically significant difference between two treatments does not allow one to assert that the two treatments are equivalent, or even similar, in their efficacy. … Obviously, the fewer patients there are in a trial the less power to detect any meaningful difference so that nonsignificance in a conventional test of a null hypothesis is a hopeless criterion for inferring noninferiority."

   - What does Pocock mean by "conventional trial?"
   - Can you illustrate Pocock's point using a diagram as on page 4 of Lecture 5, with one or more 95% CIs added?
   - Is it possible to design a superiority trial and then use it to infer noninferiority? Vice versa?