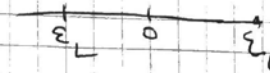
2010-03-22

1. Unrealistic example. BC trials are often open label (unethical with placebo) due to short survival times of patients. Putting that apart, when redesigning the study, one should think about the fact that the effect vs. placebo is higher than vs. comparators, and therefore a higher sample size would be required.

2. We use e.g. an equivalence test for $\delta = \mu_A - \mu_B$
(a) and H_0: δ is outside $[\varepsilon_L, \varepsilon_U]$ vs
H_1: δ is in $[\varepsilon_L, \varepsilon_U]$



(b) Long half life imply a carry over effect. The 2 periode two sequence design does not work if not (i) allow very long washout period (ii) extend the design to eg. ABB / BAA so the carry over effect is estimable.

3. (i) Number of subjects achieving a certain reduction in LDL-C.
(ii) Time to achievement of a certain reduction in LDL-C
(iii) Change of baseline measured in absolute change.

4. To be confirmatory the hypothesis should be stated in advance and there should be prior evidence from earlier trials. Estimate effect with enough precision to assess clinical relevance on top of statistical significance. Other issues: Adherence to protocal, SOPs etc results generalizable to wider population - relaxed inclusion criteria - Multiplicity issues dealt with.

To evaluate safety and tolerability: AE - Lab data - vital signs - ECG - physical exams - etc. Use e.g. relative risks between arms, association tests, time to event etc. Failing to demonstrate safety would be a stopper for the project.

5. a. Right answer is B (Drug X and drug Y)
   b. Right answer is C (proven efficacy in two trials and benefit/risk judged beneficial)
   c. Right answer is C (Parallel design is shorter since only one period)
   d. Right answer is C. (often problems with confounding).
   e. Right answer is C. (The CSR should describe deviations from the CSP).

6. The wrong statement is A (Randomization eliminates bias)

7. Compute adjusted p-values

P(i)	K	K P(i)	Holm	Bonf.
0.00012	5	0.0006	0.0006*	0.0006*
0.0091	4	0.0364	0.0364*	0.0455*
0.012	3	0.0360	0.0364*	0.06
0.0534	2	0.1068	0.1068	0.2670
0.0812	1	0.0812	0.1068	0.4060

8. Let P_1 = P(cold in Vitamin group) and P_2 = P(cold in non vitamin group)
   (a) Difference in proportions (b) An association test e.g. X^2 (c) Logistic regression are 3 possible analysis methods.

9. $h(t|\underline{z}) = h_0(t)\exp(\beta_1 z_1 + \beta_2 z_2 + \beta_3 z_3)$

z_1 = stage II cancer – z_2 = stage III cancer
z_3 = stage IV cancer. Estimates $\hat{\beta}_i$, $i=1,2,3$ are available.

(a) Estimate RR of stage III vs. stage II

$$\frac{h(t|z_2=1)}{h(t|z_1=1)} = \frac{h_0(t)\exp(\hat{\beta}_2)}{h_0(t)\exp(\hat{\beta}_1)} = \frac{1.0682}{1.0631} = 0.995$$

(b) A new covariate z_4 added representing age. Calculate the relative risk for 50 years vs. 40 years for Stag IV cancer

$$\frac{h(t|z_3=1, z_4=50)}{h(t|z_3=1, z_4=40)} = \frac{\exp(\hat{\beta}_3 + 50\hat{\beta}_4)}{\exp(\hat{\beta}_3 + 40\hat{\beta}_4)} =$$

$$= \frac{2.158}{2.1383} = 1.209 \quad \therefore 20\% \text{ higher risk}$$

Remaining questions not applicable in this year's version of the course (did not go thru partial likelihood).