Lecture twenty-two: Sample Size Determination

1. **The courses on design of clinical trials in the department**
   (a) PQHS450: Clinical Trials and Intervention Studies.
   (b) EPBI446: Experimental Design for Biomedical Sciences
2. **Software for Power Analysis and Sample Size Determination**
   (a) Free one: http://stattools.crab.org (SWOG).
   (b) Commecial ones: nQuery Advisor; Power and Precision, etc.
   (c) SAS (version 9 and up): PROC POWER; PROC GLMPOWER.
   (d) Group sequential inference: EaSt @www.cytel.com.
   (e) https://www.trialdesign.org/ (Yuan & Lee from MD Anderson).
3. The Aspects of the Design of a Clinical Trial
   (a) Primary/secondary questions
   (b) Study population: Eligibility, inclusion/exclusion criteria
   (c) Study designs:
      i. Fundamental strategies in design:
      Randomization, blocking, stratification, balancing, and replication.
      ii. Special designs:
      Latin square; factorial design; longitudinal studies with repeated measurements; cross-over trials, etc;
      iii. Observational studies
   (d) Randomization
   (e) Blindness
   (f) Power and sample size
   (g) Design based on fixed sample size vs a (group) sequential design
   (h) Interim analysis and early stopping rules
4. **Why power analysis and sample size (SS) calculation?**

5. **SS requirement for a survival study with fixed SS**

(a) **Recall**: factors to determine the sample size of two group t-test of equal means: Significance level, α, 1 or 2 sided test, means μ_1 and μ_2 (the difference between the two means), common standard error σ, power $1 - \beta$.

(b) Distinguishing between two treatment groups

Assuming PH model for the survival times

$$h_N(t) = \psi h_S(t),$$

where ψ is unknown hazard ratio. Let $\theta = log\, \psi$ be the log-hazard ratio, then

survival is longer under new treatment if $\theta < 0$

survival is longer under standard treatment if $\theta > 0$

no treatment difference if $\theta = 0$.

In order to test the null hypothesis $H_0 : \theta = 0$, we have to choose a test statistic, for example, log-rank, test from Cox model, a test from parametric model (eg. exponential distribution), which are valid under certain assumptions.

(c) The required number of deaths:

Since we usually can not measure the acual survival times of censored observations, it is the number of acual deaths that is important, rather than the total number of subjects. *What does the KM estimate look like if there is no event*?

i. The number of deaths depends on
   A. The *reference value of* θ: θ_R, which reflects the magnitude of the treatment difference to be detected.
   B. Type I error α: the probability of rejecting H_0 when H_0 is true (false positive).
   C. Type II error β: the probability of not rejecting H_0 when H_0 is false (false negative).
   D. $1 - \beta$: Power (probability to reject H_0 when H_0 is not true) to detect the difference.
   E. The test statistic chosen

ii. The total required number of deaths for the two arms is

$$d = \frac{4(z_{\alpha/2} + z_\beta)^2}{\theta_R^2},$$

where $z_{\alpha/2}$, z_β are the upper $\alpha/2$, and upper β points, respectively of the standard normal distribution, N(0,1). If we define $c(\alpha, \beta) = (z_{\alpha/2} + z_\beta)^2$, then

$$d = 4c(\alpha, \beta)/\theta_R^2.$$

If the two treatment arms have unequal number of patients, say, with proportion $\pi, (1-\pi)$ in each group, then the formula becomes

$$d = \frac{c(\alpha, \beta)}{\pi(1-\pi)\theta_R^2}.$$

iii. The derivation of the required number of deaths (section 15.2.1)
   A. based on log-rank test
   B. Use several approximations
   C. The estimate of the number of deaths based on the formula derived tends to be underestimated.

iv. Example 15.1: Survival from chronic active hepatitis
   A. The KM estimate of survival of patients under standard treatment:
   $Median = 3.3$ years
   $S(2) = 0.7$, $S(4) = 0.45$
   $S(5) = 0.41$, $S(6) = 0.25$
   B. For similar population (eg. age, sex, race, disease status, ect), the expected survival rate at 5 years is 0.60 under the new treatment.
   C. Assume proportional hazard, then

$$S_N(t) = [S_S(t)]^\psi,$$

thus,

$$\psi_R = \frac{log(0.6)}{log(0.41)} = 0.57,$$

and $\theta_R = log\, \psi_R = log(0.57) = -0.563$.

D. given $\alpha = 0.05$, $\beta = 0.1$, $c(\alpha, \beta) = 10.51$. Therefore the required number of deaths is

$$d = \frac{4 \times 10.51}{0.563^2} = 133$$

E. $S_N(t)$ can be estimated under PH assumption

(d) The required number of patients

i. The required number of patients depends on

A. The accrual period: say, length a

B. follow-up period: say length f

C. the total duration of a study is $a + f$

D. The death rate, $p(death)$,

ii. Thus, the total required number of patients is

$$n = \frac{d}{p(death)},$$

iii. The death rate can be estimated by

$$p(death) = 1 - \frac{1}{6}\{\bar{S}(f) + 4\bar{S}(0.5a + f) + \bar{S}(a + f)\},$$

where

$$\bar{S}(t) = \frac{S_S(t) + S_N(t)}{2},$$

The death rate formula is for equal number of patients in the two treatment arms.

iv. The derivation of the probability of death $p(death)$: section 15.3.1.

v. Example 15.2: Survival from chronic active hepatitis (cont.)

A. Accrual period: 18 months ($a = 18$)

B. (subsequent) Fellow-up period: 24 months ($f = 24$)

C. The death rate:

$$p(death) = 1 - \frac{1}{6}\{\bar{S}(24) + 4\bar{S}(33) + \bar{S}(42)\},$$

D. Based on estimated survival functions

$$\bar{S}(24) = \frac{S_S(24) + S_N(24)}{2} = \frac{0.7 + 0.82}{2} = 0.76,$$

$$\bar{S}(33) = \frac{S_S(33) + S_N(33)}{2} = \frac{0.57 + 0.73}{2} = 0.65,$$

$$\bar{S}(42) = \frac{S_S(42) + S_N(42)}{2} = \frac{0.45 + 0.63}{2} = 0.54,$$

E. $P(death) = 0.35$, and the required number of patients is $n = 133/0.35 = 380$

F. what if accrual period: 18 months ($a = 18$) and ($f = 0$), then $P(death) = 0.155$, and the required number of patients is $n = 133/0.155 = 858$

vi. An approximate procedure

A. The average probability of survival beyond τ is $\frac{S_S(\tau)+S_N(\tau)}{2}$.

B. The probability of death, in the period from the time origin to τ, can be approximated by

$$1 - \frac{S_S(\tau) + S_N(\tau)}{2}.$$

C. The required number of patients is

$$n = \frac{2d}{2 - S_S(\tau) - S_N(\tau)},$$

D. The choice of τ: The average length of the follow-up: $f + a/2$.

E. Example 15.3: