SA_Hw9

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Problem 1

Key information of the background:

1:1 ratio, Two Sample; 20 months for the median survival time in the standard of care; The expected median survival time in the new treatment arm is 28 months; The enrollment period is 18 months; The minimum follow-up time for each subject is 24 months.

How many events will be needed to reach 90% power at the 1-sided significant level of 0.025?

To achieve 90% power at the 1-sided significant level of 0.025 to detect a 40% increase in median survival time from 20 months in the standard of care to 28 months.

1. Assuming exponential distribution
2. $\lambda = \frac{20}{28} = \frac{5}{7}$
3. $$d = 4\frac{(z_{1-\alpha} - z_{\beta})^2}{(log\lambda)^2} = 4\frac{(1.96 + 1.28)^2}{(log0.71)^2} = 371$$

So, 371 events are needed to reach 90% power at the 1-sided significant level of 0.025.

How many subjects should be planned?

4. Hazard function :
$$h = \frac{-log(0.5)}{28} = 0.0248$$
5. Expected event rate:
$$\tau = 24, \tau_a = 18$$
$$Pr = 1 - e^{-h\tau}(1 - e^{-h\tau_a})/h\tau_a = 1 - e^{-0.0248*24}(1 - e^{-0.0248*18})/(0.0248*18) = 0.555$$
6. Subjects enrolled:
$$N = \frac{371}{0.555} = 669$$

So, 669 subjects should be planned.

What is the number of subjects if more investigate sites are available and the enrollment period is shortened to 12 months?

When enrollment period is shortened to 12 months, the $\tau = 12$.

$$Pr = 1 - e^{-h\tau}(1 - e^{-h\tau_a})/h\tau_a = 1 - e^{-0.0248*24}(1 - e^{-0.0248*12})/(0.0248 * 12) = 0.523$$

Subjects enrolled:

$$N = \frac{371}{0.523} = 710$$

So, 710 subjects should be planned.

What do you think of the power loss if the hazard ratio is 1 during the first 4 months of treatment? What strategies would you like to recommend to the study team?

1. Assuming a piecewise exponential distribution for the hazard function is strongly suggested.

Suggestions:

2. **Increase the sample size:** The study team could consider increasing the sample size to ensure that the study has sufficient power to detect a difference between the two treatment arms. A larger sample size would also increase the precision of the estimated treatment effect.
3. **Extend the follow-up period:** Since the minimum follow-up time for each subject is 24 months, the study team could consider extending the follow-up period to capture more events and improve the accuracy of the estimated survival curves.
4. **Adjust the randomization ratio:** The study team could consider adjusting the randomization ratio to increase the number of subjects in the new treatment arm. This would increase the power of the study to detect a difference between the two treatment arms.

Please add your own assumption on the rates of loss of follow-up and re-answer the questions above.

If the rate of loss of follow-up is 20%

Total events:

371/(1-20%) = 464

Planned subjects:

669/(1-20%) = 837

Planned subjects when the enrollment period is shortened to 12 months:

710/(1-20%) = 888

Problem 2

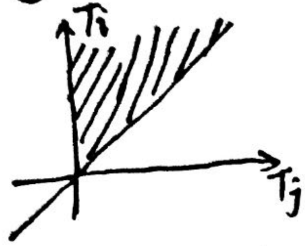
A smaller sample size may result in lower statistical power to detect a difference between the two treatment arms, while a shorter follow-up period may limit the ability to assess long-term outcomes.

Problem 3

① The joint p.d.f of T_i and T_j is:

$$f_{T_i,T_j}(t_i,t_j)=\begin{cases} h_i h_j e^{-h_i t_i} e^{-h_j t_j}, & t_i \geq 0,\ t_j \geq 0 \\ 0, & o/w. \end{cases}$$

② The domains of T_i and T_j for $P(T_i \geq T_j)$:



$$\begin{cases} 0 \leq T_i < \infty \\ 0 \leq T_j \leq T_i \end{cases}$$

③ The integration:

$$P(T_i \geq T_j)=\int_0^\infty \int_0^{t_i} h_i h_j e^{-h_i t_i} e^{-h_j t_j}\, dt_j\, dt_i$$

$$=\int_0^\infty -h_i e^{-h_i t_i} \left(e^{-h_j t_j}\right)\Big|_0^{t_i} dt_i$$

$$=\int_0^\infty (1-e^{-h_j t_i}) h_i e^{-h_i t_i}\, dt_i$$

$$=\left(-e^{-h_i t_i}+\frac{h_i}{h_j+h_i} e^{-(h_j+h_i)t_i}\right)\Big|_0^\infty$$

$$=1-\frac{h_i}{h_j+h_i}$$

$$=\frac{h_j}{h_j+h_i}$$