Designing Clinical Trials for Testing Overall Survival in the Presence of Crossover at Progression

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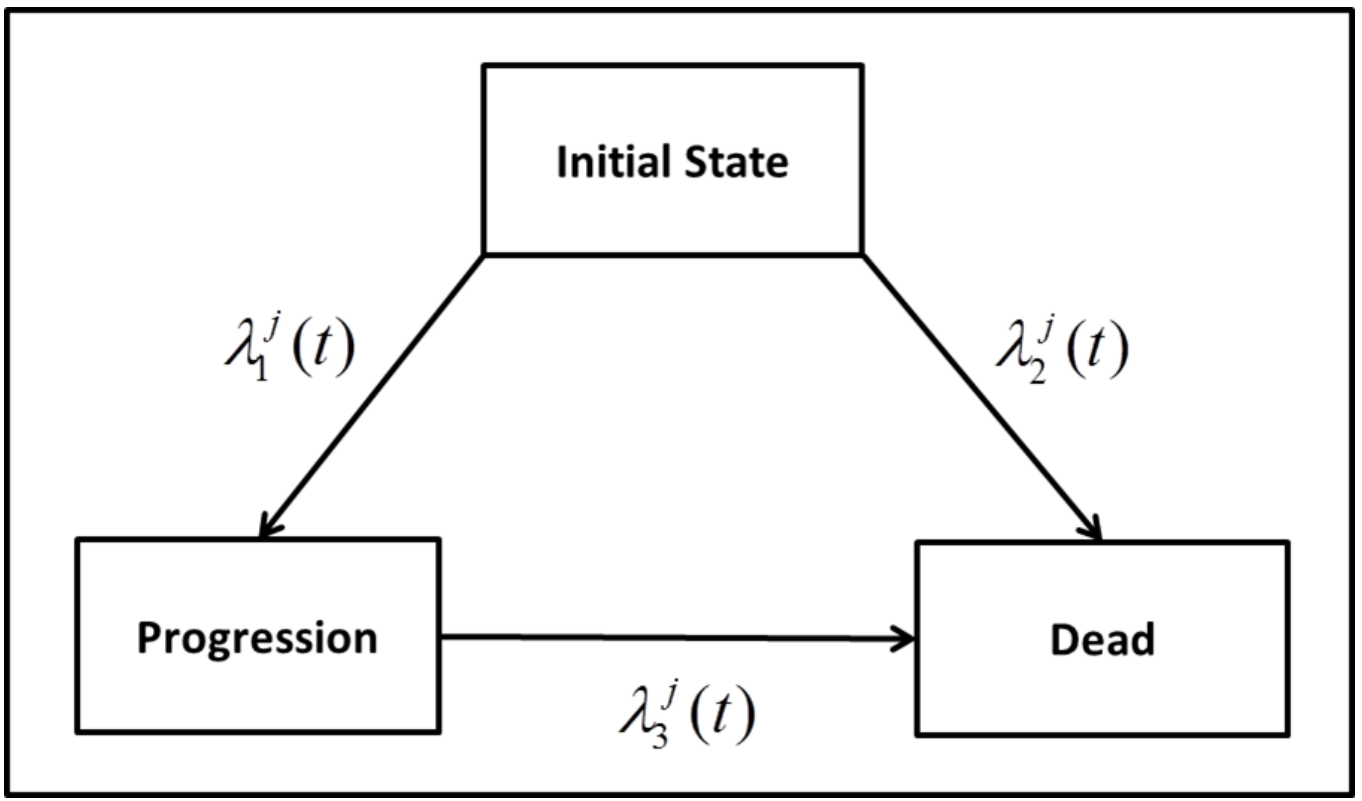
Objective

- To present a design tool to assess the power for OS in the presence of treatment switching or crossover after progression from the control treatment to the experimental treatment

Multi-state Model

Figure 1 : A simple multi-state model.



Multi-state Model

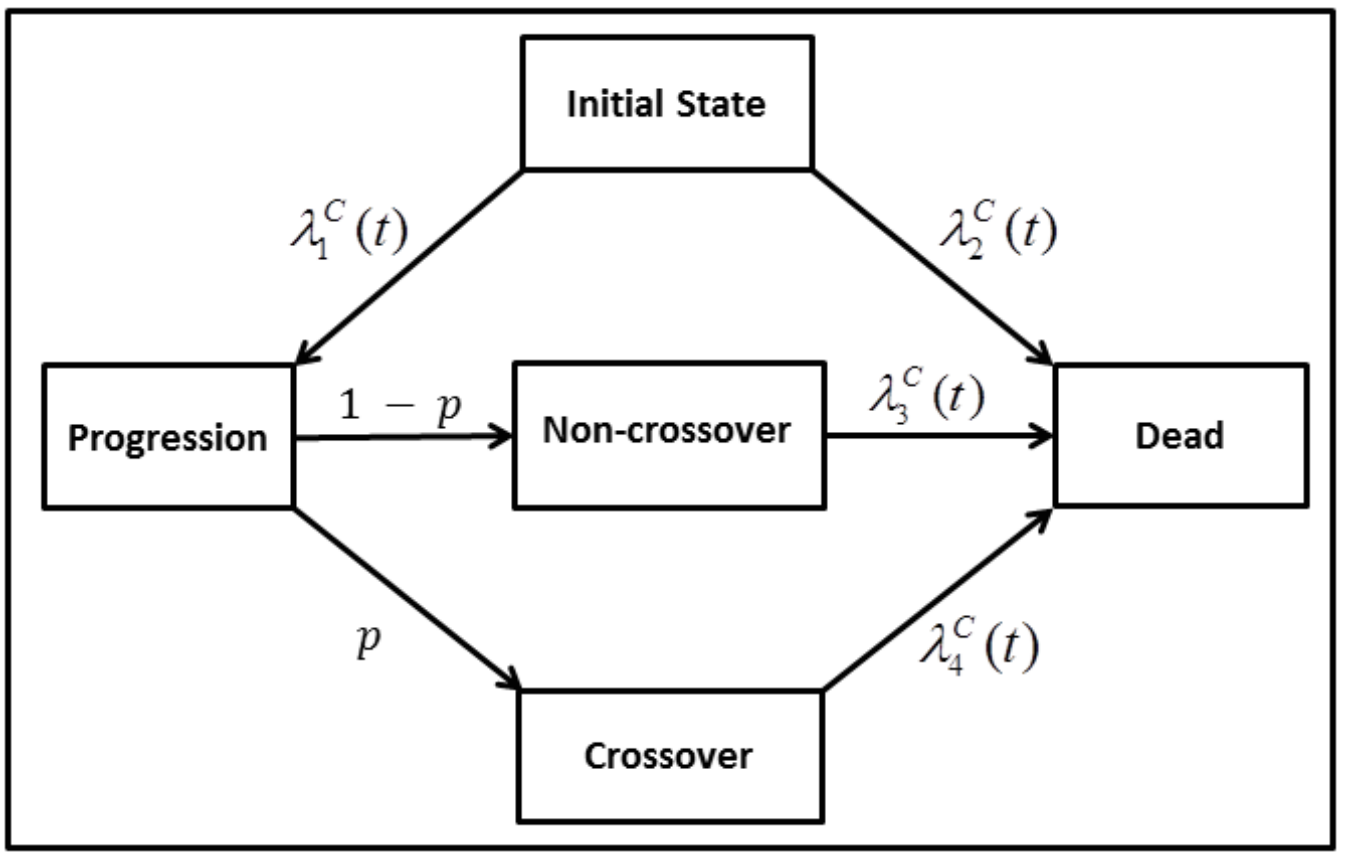
- Notation from Fleisher *et al* (2009)
  - TTP: time to progression
  - X: time to death without progression
  - OS': time until death after progression (also noted as SPP)
- $PFS = min(TTP, X)$

$$OS = \begin{cases} TTP + OS' & \text{if } TTP < X \\ PFS & \text{otherwise} \end{cases}$$

Multi-state Model with Crossover

- p: the probability of crossover for control patients
- $\lambda_3^C(t)$: the hazard function for non-crossover control patients
- $\lambda_4^C(t)$: the hazard function for control patients who crossover

Figure 2 : Multi-state model for control arm with crossover to experimental treatment after progression.



Relationship between PFS and OS

- Assumption
  - The time in each state is exponentially distributed
  - *TTP*, *X* and *OS'* are independent
- Then
  - $PFS = min\{TTP, X\} \sim Exp(\lambda_1 + \lambda_2)$
  - Probability of death before progression: $\omega = \frac{\lambda_2}{\lambda_1 + \lambda_2}$
- The distribution function of *OS* can be derived by extending the results of Fleisher *et al* (2009) to the case of crossovers

Design Parameter Required

- Logrank tests are used to compare the treatments

Table 1 : Items to be Specified in the Design

α_1	Type I error rate for PFS
α_2	Type I error rate for OS
$1-\beta_1$	Power for PFS
$1-\beta_2$	Power for OS
N_{max}	Maximum feasible sample size
T_{max}	Maximum study duration
a	Accural rate
M_{PFS}	Median PFS
$M_{OS'}$	Median OS' (control-no crossover/crossover; experimental)
ω	Probability of death before progression
p	Probability of crossover (control)

Required Number of Events and Duration of Study for PFS

- $D_{PFS} = \frac{4(Z_{\alpha_1/2} + Z_{\beta_1})^2}{(ln\Delta)^2}$, where $\Delta = \frac{\lambda_1^E + \lambda_2^E}{\lambda_1^C + \lambda_2^C} = \frac{\lambda_E}{\lambda_C}$
- The expected time to achieve D_{PFS} events can be derived as in George and Desu (1974) by solving the following equation for t

$$D_{PFS} = \frac{at^*}{2}[(1 - \frac{exp^{-\lambda_C t(exp^{\lambda_C t^*})}}{\lambda_C t^*}) + (1 - \frac{exp^{-\lambda_E t(exp^{\lambda_E t^*})}}{\lambda_E t^*})]$$

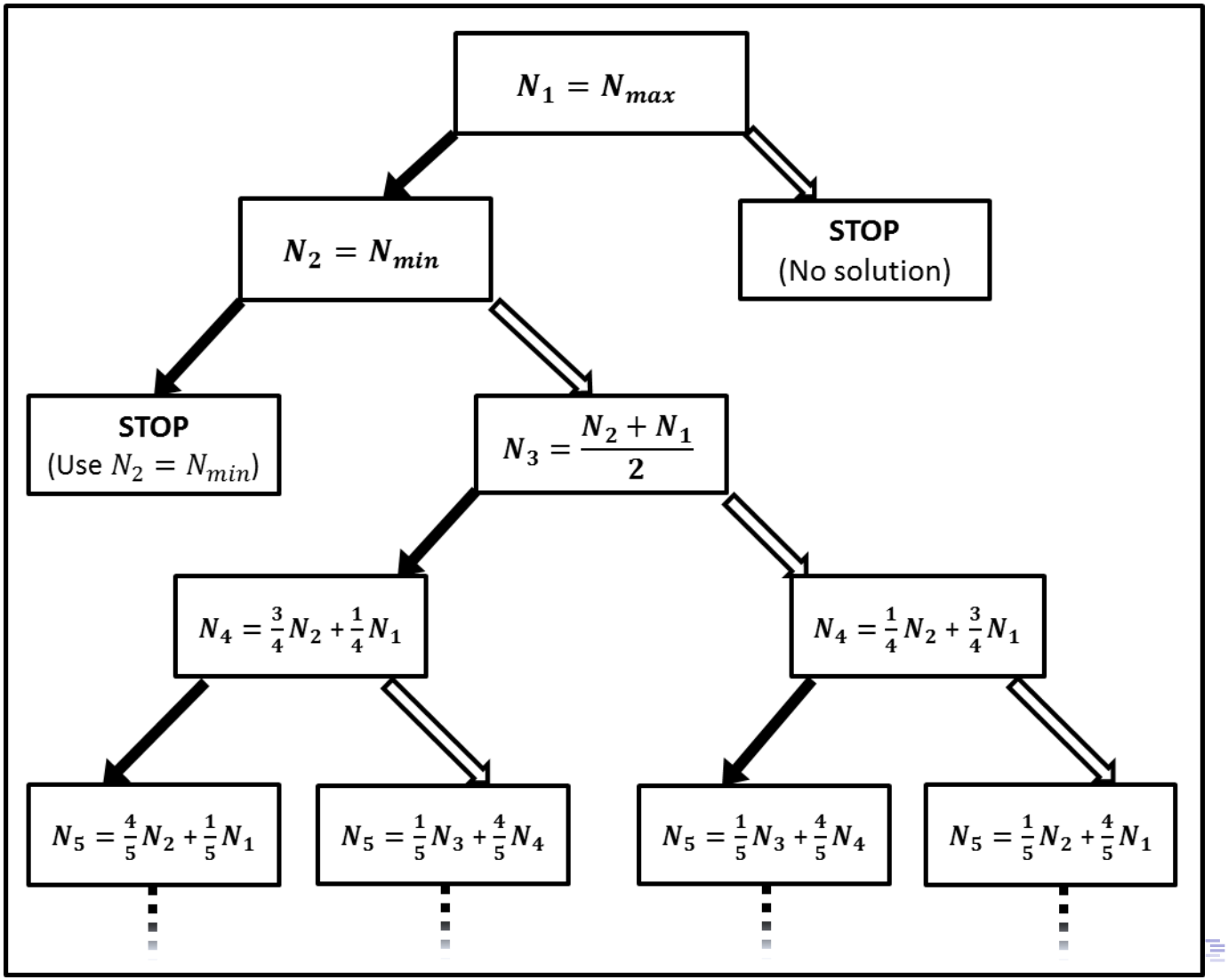
where t^* is the minimum of t and the accural time T.

Required Number of Events and Duration of Study for OS

- The situation for OS is more complicated because the hazard functions and hazard ratios are not constant
- Want to determine the required OS events D_{OS} and the optimal sample size N^*
  - N^*: the smallest sample size N that achieves the appropriate statistical power for OS within the maximum allowable expected study duration T_{max}
- N_{min}: $1.25 * D_{PFS}$
- N_{max}: the pre-specified maximum sample size allowed

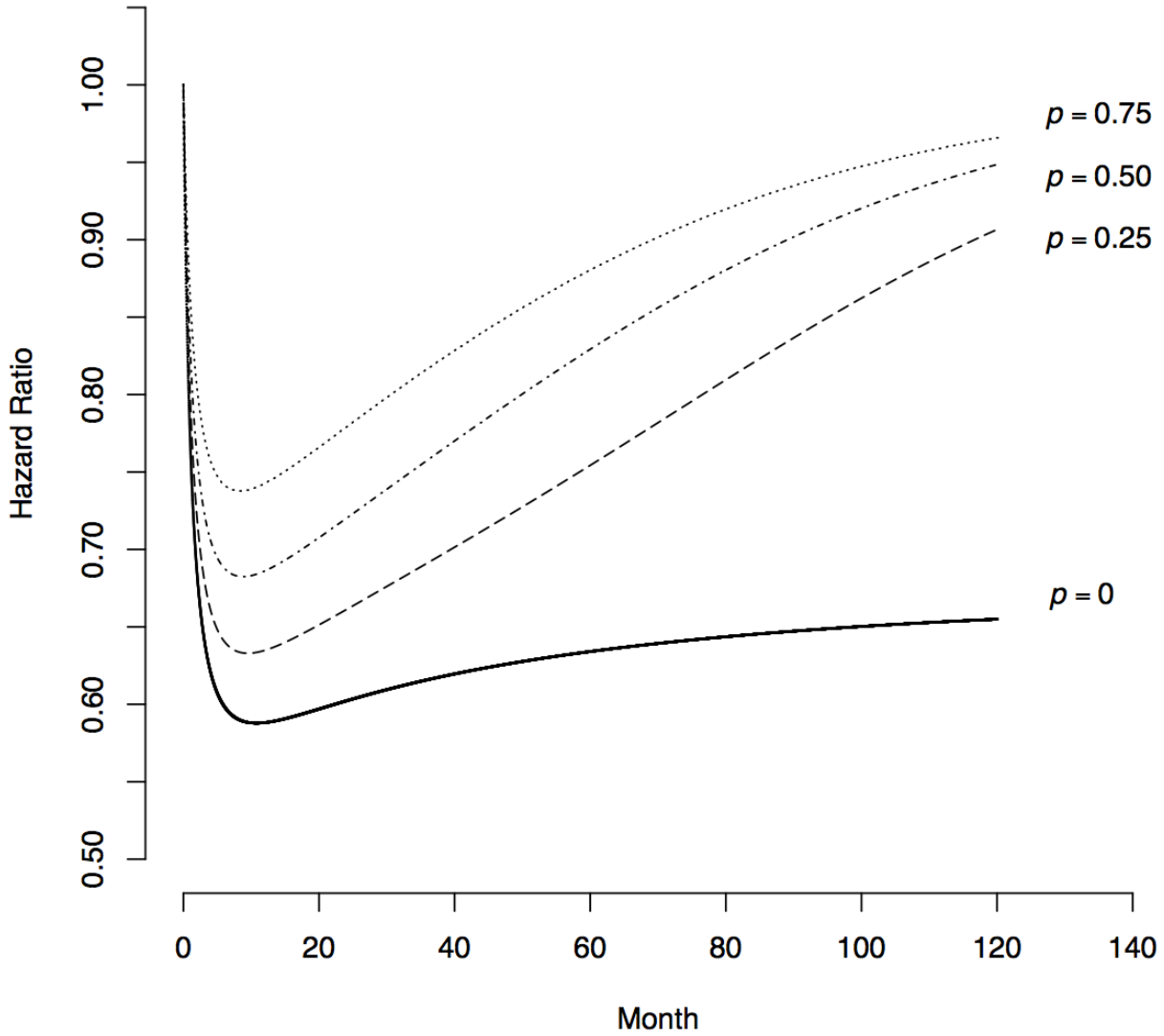
Required Number of Events and Duration of Study for OS

Figure 3 : Tree diagram for determining the optimal sample size.



Simulation Example: Hazard Ratios for OS

Figure 4 : Hazard Ratios for OS



Discussion

- We present a design tool to assess the power for testing OS in the presence of treatment switching or crossover after progression from the control treatment to the experimental treatment
- The approach taken here enables one to assess the power for testing OS under various realistic scenarios and to check the sensitivity of the power to changes in the assumed model parameters in the model
- Possible to further develop the process to include prognostic factors, loss to follow up, time-varying intensity functions for the multi-state model etc.

References

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Thank you.