Using Z-Scores of the Log-Rank Test to Assess Probability of Success at Planned Interim in Survival Analysis Using Correlated Secondary Endpoints

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Introduction

By consideration of the joint distribution of the Z-scores of the log-rank test for the primary endpoint and a correlated secondary endpoint, and the resulting conditional distribution of these, this poster shows that secondary endpoints can provide an assessment of the probability of trial success (TS) or clinical success (CS), under the assumption of proportional hazards in both endpoints. This method requires information on the expected Z-scores and their correlation, which may be provided through a meta-analysis of similar trials.

Method

Consider the two upper-sided hypothesis tests for secondary $(k = 1)$ and primary $(k = 2)$ endpoints

$$H_{0_k}: \theta_k \leq \psi_k \; vs \; H_{1_k}: \theta_k \geq \psi_k,$$

where $\theta_k = -\log(\lambda_k)$ for hazard ratio λ_k. ψ_k is set the respective target values for TS or CS.

The asymptotic joint distribution of the Z-scores, under the assumption of proportion hazards for both survival endpoints [a], is

$$\begin{bmatrix} Z_1 \\ Z_2 \end{bmatrix} \sim MVN\left(\begin{bmatrix} \theta_1\sqrt{I_1} \\ \theta_2\sqrt{I_2} \end{bmatrix}, \begin{bmatrix} 1 & \rho \\ \rho & 1 \end{bmatrix}\right),$$

where

- $I_k = n_k p_k d(1-d)$
- $n_k =$ total number of evaluable participants
- $p_k =$ expected proportion of events
- $d =$ proportion allocated to control arm.

Note $n_k p_k$ is the expected number of events under the asymptotic normal approximation of a binomial random variable.

Therefore, applying the theory on conditional distributions of bivariate normal random variables, $Z_2|Z_1 = z_1$ is distributed as a univariate normal with the following properties under the primary alternate hypothesis:

- $E[Z_2|Z_1 = z_1] = \mu_2 + \rho\sigma_2\left(\frac{z_1-\mu_1}{\sigma_1}\right) = \psi_2\sqrt{I_2} + \rho\left(z_1 - \theta_1\sqrt{I_1}\right)$
- $V[Z_2|Z_1 = z_1] = \sigma_2^2(1-\rho^2) = (1-\rho^2)$

And the resulting conditional power is

$$CP_\theta(t) = \Phi\left(\frac{E[Z_2|Z_1 = z_1] - z_{1-\alpha/2}}{\sqrt{V[Z_2|Z_1 = z_1]}}\right) = \Phi\left(\frac{\psi_2\sqrt{I_2}+\rho\left(z_1-\theta_1\sqrt{I_1}\right)-z_{1-\alpha/2}}{\sqrt{(1-\rho^2)}}\right).$$

Note $\lim_{\rho\to 0} CP_\theta(t) = \Phi\left(\psi_2\sqrt{I_2} - z_{1-\alpha/2}\right)$, i.e.. unconditional power.

Example

Table I considers the situation where an early evaluation of progression free survival (PFS) is made early in the study, and how this can inform of the probability of overall survival at a later timepoint.

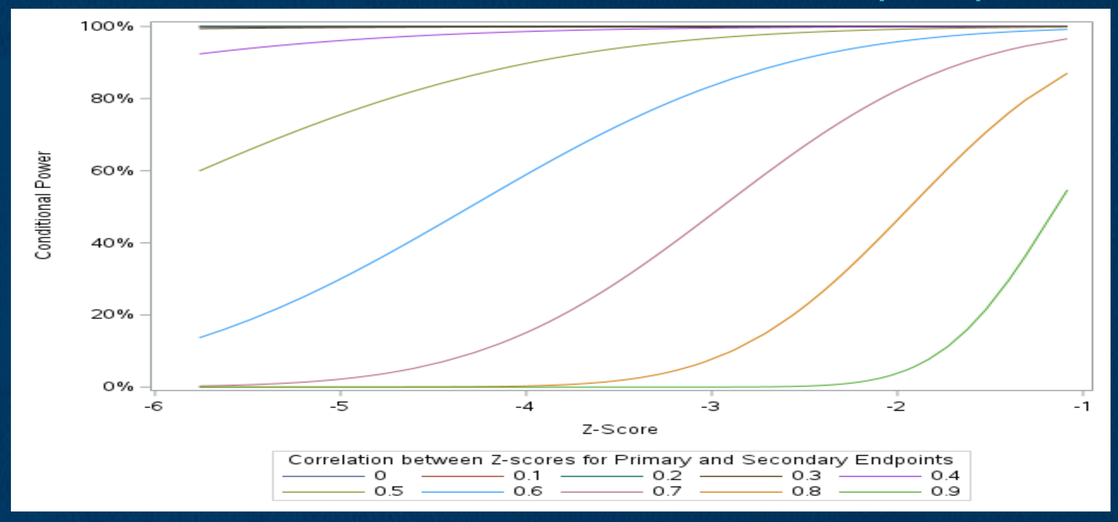
Using information about the expected median time-to-event (MTTE) for each endpoint, and assuming event times follow an exponential distribution with rate parameter equal to $\log(2)/MTTE$ to evaluate the expected number of events, it is shown that the conditional probability of CS for improvement in survival can be evaluated.

Table 1 – Scenario

	Experimental	Control
Number of evaluable participants	500	500
Accrual rate (per day)	20	
Accrual time (days)	50	
Secondary: PFS at 3 months		
Expected MTTE (months)	24	12
Hazard Ratio	0.5	
Expected number of events[1]	30.29	58.58
Primary: Survival at 12 months		
Expected MTTE (months)	60	20
Hazard Ratio for CS	$1/3$	
Expected number of events[1]	75.39	193.93

1: Simulated trial mean, assuming event times exponentially distribution.

Figure 1 – Conditional power for CS under assumed correlations and observed Z-scores for secondary endpoint.



For a range of correlations and the resulting Z-score from a set of scenarios within a range of ± 4 months for the observed MTTE for the secondary endpoint in each arm, the conditional power is plotted in Figure I.

Lower correlations result in higher power in this scenario, as the conditional power tends to the unconditional power of the primary endpoint, where $\psi_2\sqrt{I_2} - z_{1-\frac{\alpha}{2}} \approx 9.01$, i.e., $CP_\theta(t) \approx 1$.

Higher Z-scores correspond to the scenarios where a smaller (larger) MTTE is experienced in the control (experimental) arm, and vice versa.

Conclusion

Through assessment of the MTTE for survival endpoints, assuming exponentially distributed event times, and conducting a meta-analysis to quantify correlation between Z-scores, the probability of meeting the alternative hypothesis can be evaluated between correlated survival endpoints. However, caution should be exercised due to multiplicity.

References
[a] Jennison and Turnbull *Handbook of Survival Analysis* 2013

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