Chapter 713

One-Sample Cure Model Tests

Introduction

This module computes the sample size and power of the one-sample parametric cure model proposed by Wu (2015). This technique is useful when working with survival data in phase II clinical trials when a substantial portion of the subjects are cured of the disease or ailment, and you are comparing the results of a new treatment to a historical control.

Technical Details

One-Sample Cure Model Test Statistic

Following Wu (2015), suppose the failure time, T^*, is assumed to be $T^* = v\,T + (1 - v)\,\infty$, where v indicates whether the subject will experience failure and T denotes failure time of the subjects not cured. Let $S(t)$ be the *latency distribution* of T which in this procedure is assumed to be the Weibull distribution with shape parameter k known and scale parameter λ. The survival distribution of T^* is a mixture of a cure rate π = P(v = 0) and $S(t)$ given by

$$S^*(t) = \pi + (1 - \pi)S(t)$$

Suppose N subjects are enrolled in a study during the accrual period of length t_a and then observed during a follow-up period of length t_f. Let t_i and C_i denote the failure time and censoring time of the i^{th} subject. The observed failure time is $X_i = T^*_i \wedge C_i$ and the observed failure indicator is $\Delta_i = I(T^*_i \le C_i)$. The test L is defined in terms of the number of observed failures O and the number of expected events E, as follows

$$L = \frac{O - E}{\sqrt{(O + E)/2}}$$

The test statistic L is asymptotically standard normal distributed under the null, where

$$O = \sum_{i=1}^{n} \Delta_\mathrm{i}$$

$$E = \sum_{i=1}^{n} \Lambda_0^*(\mathrm{X_i})$$

$$\Lambda_0^*(\mathrm{t}) = -\ln S_0^*(t)$$

Note that $\Lambda_0^*(\mathrm{t})$ is the cumulative hazard function of $S_0^*(t)$ under the null hypothesis.

Statistical Hypothesis

The null hypothesis is

$$H_0: \pi = \pi_0 \quad \text{and} \quad \lambda = \lambda_0$$

which is tested against one of the following three alternatives

$$H_{1a}: \pi = \pi_0 \quad \text{and} \quad \lambda = \lambda_1$$

$$H_{1b}: \pi = \pi_1 \quad \text{and} \quad \lambda = \lambda_0$$

$$H_{1c}: \pi = \pi_1 \quad \text{and} \quad \lambda = \lambda_1$$

Power Calculation

Wu (2015) gives the following power and sample size formulas for a one-sided hypothesis test based on *L* for the Weibull distribution with known shape parameter *k*. The power of a two-sided test is found by substituting α/2 for α. Note that we use the subscript 0 to represent the historic control and the subscript 1 to represent the new treatment group.

$$Power \cong \Phi\left(-\frac{\bar{\sigma}}{\sigma} z_{1-\alpha} - \frac{\omega\sqrt{n}}{\sigma}\right)$$

$$n = \frac{(\bar{\sigma} z_{1-\alpha} + \sigma z_{Power})^2}{\omega^2}$$

where

$$\omega = v_1 - v_0$$

$$\bar{\sigma}^2 = (v_1 + v_0)/2$$

$$\sigma^2 = v_1 - v_1^2 + 2v_{00} - v_0^2 - 2v_{01} + 2v_0 v_1$$

$$v_0 = \int_0^\tau G(t) S_1^*(t) h_0(t) dt$$

$$v_1 = \int_0^\tau G(t) S_1^*(t) h_1(t) dt$$

$$v_{00} = \int_0^\tau G(t) S_1^*(t) h_0(t) \lambda_0^*(t) dt$$

$$v_{01} = \int_0^\tau G(t) S_1^*(t) h_1(t) \lambda_0^*(t) dt$$

$$\tau = t_a + t_f$$

$$S_0^*(t) = \pi_0 + (1 - \pi_0)\exp\left(-\lambda_0 t^k\right)$$

$$S_1^*(t) = \pi_1 + (1 - \pi_1)\exp\left(-\lambda_1 t^k\right)$$

$$\lambda_0^*(t) = -\ln\left(S_0^*(t)\right)$$

$$h_0(t) = \lambda_0 k t^{k-1} \frac{(1 - \pi_0)\exp\left(-\lambda_0 t^k\right)}{\pi_0 + (1 - \pi_0)\exp(-\lambda_0 t^k)}$$

$$h_1(t) = \lambda_1 k t^{k-1} \frac{(1 - \pi_1)\exp\left(-\lambda_1 t^k\right)}{\pi_1 + (1 - \pi_1)\exp(-\lambda_1 t^k)}$$

$$G(t) = \begin{cases} 1 & \text{if } t \leq t_f \\ \dfrac{\tau - t}{t_a} & \text{if } t_f \leq t \leq \tau \\ 0 & \text{otherwise} \end{cases}$$

Note that t_a represents the accrual time and t_f represents the follow-up time.

The values of the v_0, v_1, v_{00}, and v_{01} can be calculated by numeric integration.

The hazard rates λ_0 and λ_1 can be given in terms of the hazard ratio HR, the median survival times M_0 and M_1, or the survival proportions S_0 and S_1 at time t_0 of the latency distribution. These parameters are defined as

$$HR = \frac{\lambda_1}{\lambda_0}$$

$$\lambda_0 = \frac{\ln(2)}{M_0^k} = \frac{-\ln[S_0]}{t_0^k}$$

$$\lambda_1 = \frac{\ln(2)}{M_1^k} = \frac{-\ln[S_1]}{t_0^k}$$

Example 1 – Finding the Sample Size

A researcher is planning a clinical trial to compare the response of a new treatment to that of the current treatment. The median survival time in the current population is 1.54 and the cure rate is 0.32. Failures in the current population exhibits a Weibull distribution with a shape parameter of 1.67. The researcher wants a sample size large enough to detect hazard ratios of 0.7, 0.75, and 0.8 at a 5% significance level for a two-sided test. They assume that the cure rate stays the same. The accrual period will be 3 years. The follow-up period will be 1 year.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 1** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab

Solve For	**Sample Size**
Alternative Hypothesis	**Two-Sided**
Power	**0.90**
Alpha	**0.05**
Ta (Accrual Time)	**3**
Tf (Follow-Up Time)	**1**
π0 (Proportion Cured - Control)	**0.32**
π1 (Proportion Cured - New)	**0.32**
Input Type	**M0, HR (Median Survival, Hazard Ratio)**
M0 (Median Survival - Control)	**1.54**
HR (Hazard Ratio - λ1/λ0)	**0.7 0.75 0.8**
k (Weibull Shape Parameter)	**1.67**

Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Reports

Numeric Results

Solve For: Sample Size
Groups: 0 = Historic Control, 1 = New or Treatment
Alternative Hypothesis: Two-Sided

	Sample	Number of	Time		Cure Rate		Hazard	Median Survival Time		Weibull	
	Size	Events	Accrual	Follow-Up			Ratio			Shape	
Power	N	E	Ta	Tf	π0	π1	HR	M0	M1	k	Alpha
0.9006	370	157	3	1	0.32	0.32	0.70	1.54	1.91	1.67	0.05
0.9000	576	253	3	1	0.32	0.32	0.75	1.54	1.83	1.67	0.05
0.9001	972	441	3	1	0.32	0.32	0.80	1.54	1.76	1.67	0.05

Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N The sample size of the new group, assuming no subject lost to dropout or follow-up during the study.
E The expected number of events (failures) in the new group during the study.
Ta The length of the accrual time during which subjects are added to the study. Subjects are added uniformly.
Tf The length of the follow-up time after the last subject is added to the study.
π0 The cure rate (proportion cured) of the historic control group.
π1 The anticipated cure rate (proportion cured) of the new group. The difference between π1 and π0 may be one of the statistics that you want to test.
HR The hazard ratio is the new group's hazard rate divided by the hazard rate of the historic control. HR = λ1 / λ0.
M0 The median survival time of the historic control group.
M1 The median survival time of the new (treatment) group.
k The shape parameter of the Weibull distribution used for both groups.
Alpha The probability of rejecting a true null hypothesis.

Summary Statements

A single-group design will be used to test whether a new treatment cure rate and/or hazard rate is different from that of a historical control. The comparison will be made using a two-sided, one-sample cure model test, with a Type I error rate (α) of 0.05. It is assumed that the survival time distribution is approximated reasonably well by the Weibull distribution with a shape parameter value of 1.67. The accrual time will be 3 and the follow-up time (time after complete accrual) will be 1. To detect a cure rate of 0.32 in the new treatment group when the cure rate in the historical control group is 0.32 and/or detect a hazard ratio of 0.7 when the median survival time of the historical control group is 1.54, with 90% power, the number of needed subjects will be 370. The expected number of events during the study is 157.

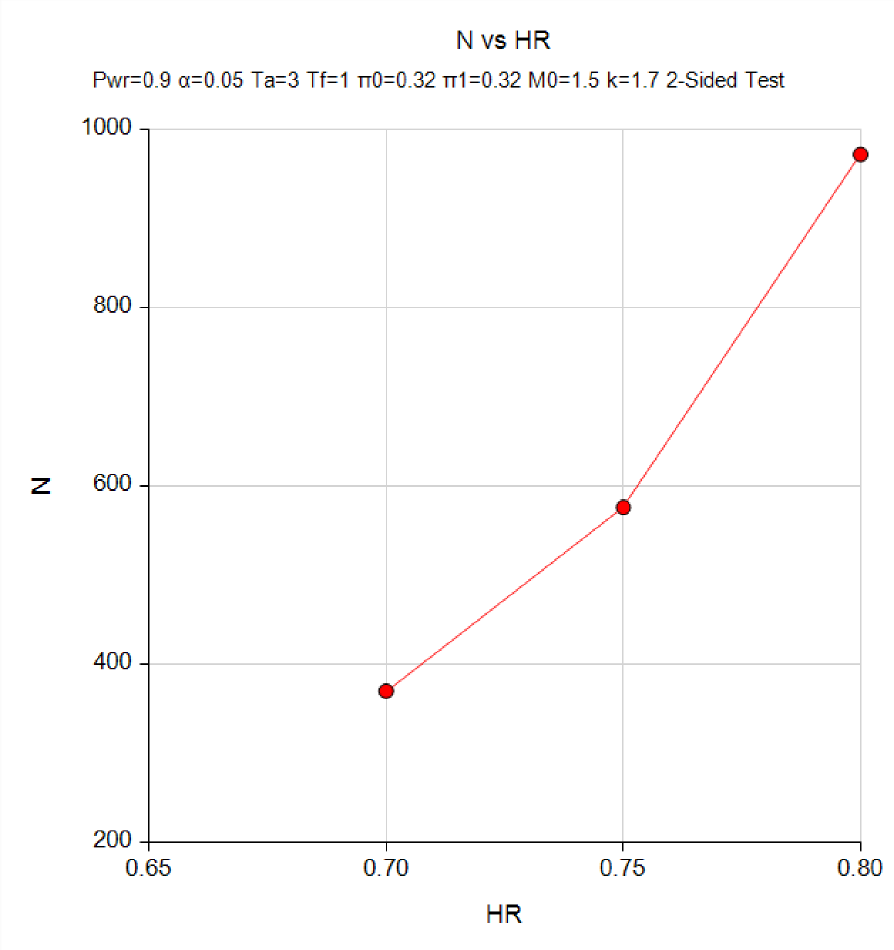
References

Wu, Jianrong. 2015. 'Single-arm phase II trial design under parametric cure models', Pharmaceutical Statistics, wileyonlinelibrary.com, DOI: 10.1002/pst.1678.

This report presents the calculated sample sizes for each scenario as well as the values of the other parameters.

Plots Section

Plots



This plot shows the relationship between sample size and HR.

Example 2 – Validation using Wu (2015)

Wu (2015) gives an example in which the power if 0.80, alpha = 0.05 for a one-sided test, k = 1.018, Ta = 3 and Tf = 1, λ0 = 0.836, HR = 1/1.75 = 0.57143, and π0 = 0.35. Wu calculates N to be 93.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 2** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab

Solve For	**Sample Size**
Alternative Hypothesis	**One-Sided**
Power	**0.80**
Alpha	**0.05**
Ta (Accrual Time)	**3**
Tf (Follow-Up Time)	**1**
π0 (Proportion Cured - Control)	**0.35**
π1 (Proportion Cured - New)	**0.35**
Input Type	**λ0, HR (Hazard Rate, Hazard Ratio)**
λ0 (Hazard Rate - Control)	**0.836**
HR (Hazard Ratio - λ1/λ0)	**0.57143**
k (Weibull Shape Parameter)	**1.018**

Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Results

Solve For: Sample Size
Groups: 0 = Historic Control, 1 = New or Treatment
Alternative Hypothesis: One-Sided

			Time		Cure Rate		Hazard	Hazard Rate		Weibull	
Power	Sample Size N	Number of Events E	Accrual Ta	Follow-Up Tf	π0	π1	Ratio HR	λ0	λ1	Shape k	Alpha
0.8022	93	41	3	1	0.35	0.35	0.571	0.836	0.478	1.02	0.05

PASS has also calculated N as 93.