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 $\pi = \text{P}(v = 0)$ 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 ith 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

$$O = \sum_{i=1}^{n} \Delta_i$$

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

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

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

Statistical Hypothesis

The null hypothesis is

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

which is tested against one of the following three alternatives

$$H_{1a}: \pi = \pi_0 \text{ and } \lambda = \lambda_1$$
$$H_{1b}: \pi = \pi_1 \text{ and } \lambda = \lambda_0$$
$$H_{1c}: \pi = \pi_1 \text{ and } \lambda = \lambda_1$$

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

$$\omega = v_1 - v_0$$

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

$$\sigma^2 = v_1 - v_1^2 + 2v_{00} - v_0^2 - 2v_{01} + 2v_0v_1$$

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

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

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

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

$$\tau = t_a + t_f$$

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

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

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

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

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

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

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

$$HR = \lambda_1 / \lambda_0$$

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

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

Procedure Options

This section describes the options that are specific to this procedure. These are located on the Design tab. For more information about the options of other tabs, go to the Procedure Window chapter.

Design Tab

The Design tab contains most of the parameters and options that you will be concerned with. This chapter covers four procedures, each of which has different effect size options. However, many of the options are common to all four procedures. These common options will be displayed first, followed by the various effect size options.

Solve For

Solve For

This option specifies the parameter to be solved for from the other parameters. The parameters that may be selected are *Power* or *Sample Size*.

Select *Sample Size* when you want to calculate the sample size needed to achieve a given power and alpha level.

Select *Power* when you want to calculate the power.

Test

Alternative Hypothesis

Specify whether the statistical test is two-sided or one-sided.

Power and Alpha

Power

This option specifies one or more values for power. Power is the probability of rejecting a false null hypothesis, and is equal to one minus Beta. Beta is the probability of a type-II error, which occurs when a false null hypothesis is not rejected. In this procedure, a type-II error occurs when you fail to reject the null hypothesis of equal survival curves when in fact the curves are different.

Values must be between zero and one. Historically, the value of 0.80 was used for power of a phase II trial.

A single value may be entered here or a range of values such as *0.8 to 0.95 by 0.05* may be entered.

Alpha

This option specifies one or more values for the probability of a type-I error. A type-I error occurs when you reject the null hypothesis of equal survival curves when in fact the curves are equal.

Values of alpha must be between zero and one. Historically, the value of 0.05 has been used for a two-sided test and 0.025 has been used for a one-sided test. You should pick a value for alpha that represents the risk of a type-I error you are willing to take in your experimental situation.

You may enter a range of values such as *0.01 0.05 0.10* or *0.01 to 0.10 by 0.01*.

Sample Size

N (Sample Size)

Enter a value for the sample size, *N*. This is the number of subjects in the study. You can enter one or more positive integers greater than or equal to 3. You may also enter a range such as "10 to 100 by 10" or a list of values separated by commas or blanks such as "20 40 60 80."

Ta (Accrual Time)

Enter one or more values for the number of time periods (months, years, etc.) during which subjects are entered into the study. The total duration of the study is equal to the Accrual Time plus the Follow-Up Time.

Accrual times can range from 0 to on up. Enter "0" when all subjects begin the study together.

Tf (Follow-Up Time)

The length of time between the entry of the last individual and the end of the study.

Effect Size

π0 (Proportion Cured – Control)

Specify the cure rate (proportion cured) in the historical control. Since this is a proportion, the value should be from 0 to 1. You may enter a single value or a list of values.

Note that you must have either π_0 and π_1 different or λ_0 and λ_1 different'

π1 (Proportion Cured – New)

Specify the cure rate (proportion cured) in the new group. Since this is a proportion, the value should be from 0 to 1. You may enter a single value or a list of values.

Input Type

Specify which set of parameters you want to use to specify the hazard rates of the historical control (λ_0) and the new group from which the sample is drawn (λ_1). These parameters are functionally related as shown above, so the values of λ_0 and λ_1 are calculated from the items you enter (if necessary).

The possible choices are

- **Hazard Rates (λ0 and λ1)**

   Enter the values of the two hazards rates (λ_0 and λ_1) directly.

- **Hazard Rate and Ratio (λ0 and HR)**

   Enter the hazard rate of the historical control (λ_0) and the hazard ratio $HR = (\lambda_1 / \lambda_0)$.

- **Median Survival Times (M0 and M1)**

    Enter the median survival times of the historical control (M_0) and the new group (M_1). The values of λ_0 and λ_1 are calculated based on the Weibull distribution as shown above.

- **Proportions Surviving (S0 and S1)**

    Enter the proportions surviving for a fixed period of time (T_0) of the historical control (S_0) and the new group (S_1). The values of λ_0 and λ_1 are calculated based on the Weibull distribution as shown above.

λ0 (Hazard Rate – Control)

Enter a value (or range of values) for the hazard rate (event rate or incidence rate) of the distribution of the historical control. This distribution is assumed to be Weibull with a known shape parameter k.

This rate is compared to λ_1 by the one-sample logrank test. The ratio of these rates, HR = λ_1 / λ_0, is the amount that this design can detect.

The value must be greater than zero.

Example of Estimating λ0

If 200 control patients were followed for 1 year and 40 experienced the event of interest and there is no censoring, the hazard rate would be

$\lambda_0 = 40/(200*1) = 0.2$ per patient-year.

Note that this estimate does not consider the censoring. For censored survival data, it is often estimated from a survival distribution fitted from historical data. For example,

$$\lambda_0 = -\frac{\ln S(t_0)}{t_0^k}$$

λ1 (Hazard Rate – New)

Enter a value (or range of values) for the hazard rate (event rate or incidence rate) of the distribution of the response values in the new group. This distribution is assumed to be Weibull with a known shape parameter k.

This rate is compared to λ_1 by the one-sample logrank test. The ratio of these rates, $HR = \lambda_1 / \lambda_0$, is the amount that this design can detect.

The value must be greater than zero.

Example of Estimating λ_1

Once we have λ_0 and HR, λ_1 is obtained as follows

$$\lambda_1 = HR(\lambda_0)$$

HR (Hazard Rate – New)

Enter one or more values for HR, the hazard ratio λ_1 / λ_0. This value is used with λ0 to calculate a value for λ_1.

HR can be any number greater than zero and unequal to one. You may enter a single value or a range of values.

M0 (Median Survival - Control)

Specify a single value, or set of values, for the median survival time in the historical control group. Assuming a Weibull distribution with shape parameter k, the value of λ_0 is calculated as given in the technical details above.

This value must be a number greater than zero.

M1 (Median Survival - New)

Specify a single value, or set of values, for the median survival time in the new (treatment) group. Assuming a Weibull distribution with shape parameter k, the value of λ_1 is calculated as given in the technical details above.

This value must be a number greater than zero.

S0 (Proportion Surviving - Control)

Enter the proportion surviving (S_0) for a fixed period of time (t_0) in the historical control group. The value of λ_0 is calculated as given in the technical details above.

Since this is a proportion, it must be a value between (but not including) zero and one. You may enter a single value or a range of values.

S1 (Median Survival - New)

Specify a single value, or set of values, for the median survival time in the new (treatment) group. Assuming a Weibull distribution with shape parameter k, the value of λ_1 is calculated as given in the technical details above.

This value must be a number greater than zero.

T0 (Time of S0 and S1)

When S_0 and S_1 are selected as the *Input Type*, this value is needed to give the amount of time that S_0 and S_1 are related to. Since this value is a time period, it must be a positive value.

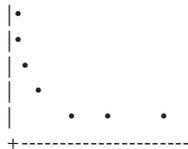## k (Weibull Shape Parameter)

This is the (assumed to be known) value of Weibull shape parameter. Usually, you will need to estimate k from the historical controls. If you don't have any information, you can set k to one which results in the exponential distribution.

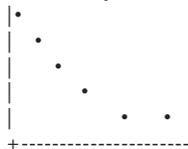The parameter k must be a number greater than zero. Usually it is greater than zero and less than or equal to 5.

Examples

The shape of the Weibull distribution probability distribution function is quite different depending on the value of k. Here are some examples. Note that *elapsed time* is shown on the horizontal axis.
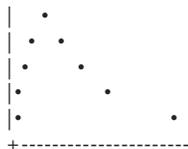
```
k = 0.5
|•
|•
| •
|   •
|     •  •   •
+---------------------

k = 1 (Exponential)
|•
|  •
|    •
|      •
|        •  •
+---------------------

k = 2
|   •
| • •
|•   •
|•     •
|•         •
+---------------------

k = 5 (approx. normal)
|     •
|   • •
|  •   •
| •     •
|•         •
+------------------------
```

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

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **One-Sample Cure Model Tests** procedure window by expanding **Survival**, then **One Survival Curve**, and then clicking on **One-Sample Cure Model Tests**. You may then make the appropriate entries as listed below, or open **Example 1** by going to the **File** menu and choosing **Open Example Template**.

Option	**Value**
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)	**0.7 0.75 0.8**
k (Weibull Shape Parameter)	**1.67**

Annotated Output

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

Numeric Results

Numeric Results for the Two-Sided, One-Sample Cure Model Test

Power	N	Evnt Cnt E	Accr Time Ta	Folw Up Time Tf	Cntl Cure Rate π0	New Cure Rate π1	λ1/λ0 Haz Ratio HR	Cntl Med Surv M0	New Med Surv M1	Wei-bull Shape k	Alpha
0.9006	370	157	3.0	1.0	0.32	0.32	0.700	1.54	1.91	1.67	0.050
0.9000	576	253	3.0	1.0	0.32	0.32	0.750	1.54	1.83	1.67	0.050
0.9001	972	441	3.0	1.0	0.32	0.32	0.800	1.54	1.76	1.67	0.050

References

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

Report Definitions
Power is the probability of rejecting a false null hypothesis.
N is the sample size of the New group, assuming no subject lost to dropout or follow-up during the study.
E is the expected number of events (failures) in the new group during the study.
Ta is the length of the accrual time during which subjects are added to the study. Subjects are added
    uniformly.
Tf is the length of the follow-up time after the last subject is added to the study.
$\pi0$ is the cure rate of the historic control group.
$\pi1$ is the anticipated cure rate of the new group. The difference between $\pi1$ and $\pi0$ may be one of the
    statistics that you want to test.
HR is the hazard ratio ($\lambda1/\lambda0$) is the new group's hazard rate divided by the hazard rate of the historic
    control.
M0 is the median survival time of the historic control group.
M1 is the median survival time of the new (treatment) group.
k is the shape parameter of the Weibull distribution used for both groups.
Alpha is the probability of rejecting a true null hypothesis.

Summary Statements
A two-sided, one-sample cure model test calculated from a sample of 370 subjects achieves 90.1%
power at a 0.050 significance level to detect a cure rate of 0.320 in the new group when the
cure rate in the historic control group is 0.320 and/or detect a hazard ratio of 0.700 when the
median survival time of the historic control group is 1.54. Subjects are accrued for a period
of 3.0. Follow-up continues for a period of 1.0 after the last subject is added. The expected
number of events during the study is 157. It is assumed that the survival time distributions of
both groups are approximated reasonable well by the Weibull distribution with a shape parameter
of 1.67.

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

Plots Section
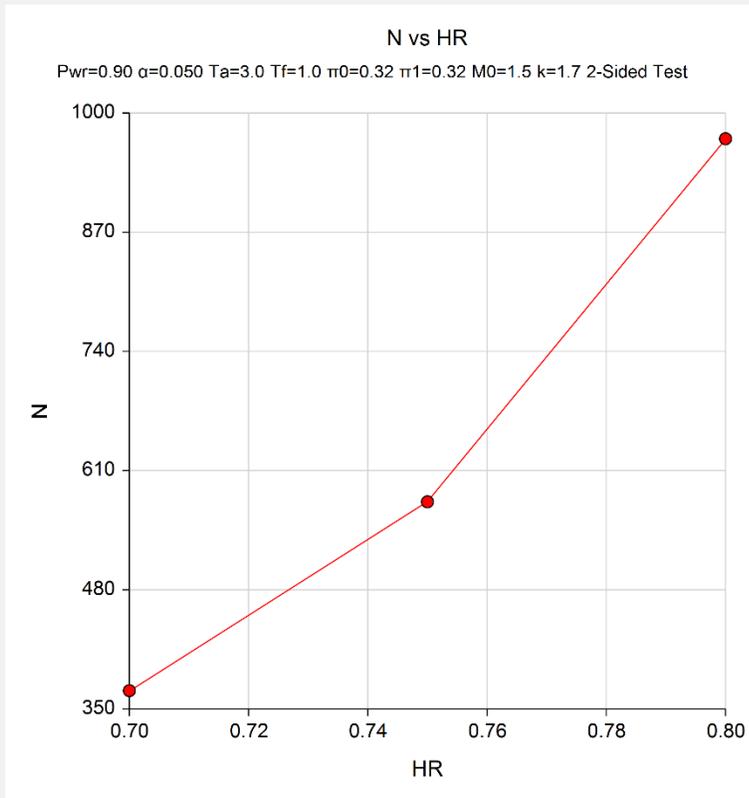
This plot shows the relationship between sample size and HR.

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, $\lambda 0$ = 0.836, HR = 1/1.75 = 0.57143, and $\pi 0$ = 0.35. Wu calculates N to be 93.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **One-Sample Cure Model Tests** procedure window by expanding **Survival**, then **One Survival Curve**, and then clicking on **One-Sample Cure Model Tests**. You may then make the appropriate entries as listed below, or open **Example 2** by going to the **File** menu and choosing **Open Example Template**.

Option   **Value**

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**

$\pi 0$ (Proportion Cured – Control)............. **0.35**

$\pi 1$ (Proportion Cured – New) **0.35**

Input Type... **$\lambda 0$, HR (Hazard Rate, Hazard Ratio)**

$\lambda 0$ (Hazard Rate – Control) **0.836**

HR (Hazard Ratio) **0.57143**

k (Weibull Shape Parameter) **1.018**

Output

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

Numeric Results

Numeric Results for the Two-Sided, One-Sample Cure Model Test

Power	N	Evnt Cnt E	Accr Time Ta	Folw Up Time Tf	Cntl Cure Rate $\pi 0$	New Cure Rate $\pi 1$	$\lambda 1/\lambda 0$ Haz Ratio HR	Cntl Haz Rate $\lambda 0$	New Haz Rate $\lambda 1$	Wei-bull Shape k	Alpha
0.8022	93	41	3.0	1.0	0.35	0.35	0.571	0.836	0.478	1.02	0.050

PASS has also calculated N as 93.