

## Chapter 698

# One-Sample Tests of Weibull Hazard Rates

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## Introduction

This module computes the sample size and power of a parametric, one-sample chi-square test of the Weibull scale parameter which is used to compare the hazard rate of a single treatment group to that of a historical control. Such is often the case in clinical phase-II trials with survival endpoints. Accrual time, follow-up time, and hazard rates are parameters that can be set.

Wu (2015) presented sample size formulas for the one-sample logrank test which is based on the assumption that the data follow a Weibull distribution with known shape parameter. This test is available in another **PASS** procedure. In this procedure, we implement the work of Phadnis (2019) which provides an exact, small sample parametric test comparing hazard rates. Because the test is exact, not asymptotic, it allows for power and significance requirements to be achieved with a significant reduction in sample size. Such a reduction is important when investigating a somewhat rare disease which is associated with a small accrual rate.

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## Technical Details

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### One-Sample Chi-Square Test

We received the following from Milind Phadnis as an explanation of why he pursued a replacement to the logrank test.

“The logrank test became very popular after its discovery in the late 1960s and has been the main method for comparing two survival curves (Treatment vs Control) from then till now. Its nonparametric nature is found to be very useful by researchers. However, the calculations are based on the asymptotic normality of the test statistic. As we know, two-arm randomized clinical trials are the gold standard in research and it is only recently that survival endpoints such as progression-free survival (PFS) and overall survival (OS) are being considered for Phase II single-arm trials. The idea is that sometimes two-arm trials are simply not possible owing to some practical constraints (such as low accrual rate in oncology trials) and so single-arm trials are getting the go-ahead as a way of finding “initial signals” in small sized Phase II studies.”

## One-Sample Tests of Weibull Hazard Rates

### Test Statistic

The Weibull distribution may be parameterized in several ways. Phadnis (2019) adopts the following pdf

$$f(t) = \frac{\beta}{\theta^\beta} t^{\beta-1} \exp\left\{-\left(\frac{t}{\theta}\right)^\beta\right\}, \quad \theta, \beta, t > 0$$

In the following, we use  $k = \beta$  (because beta is commonly used in power analysis) and  $\lambda = \theta^{-\beta}$  to remain consistent with our documentation of the one-sample logrank test.

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  $t_i$  denote the event time of the  $i^{\text{th}}$  subject that experiences the event. Let the number of events be  $E$ .

Under the null hypothesis that  $\lambda = \lambda_0$ , the quantity

$$2\lambda_0 \sum_{i=1}^E t_i^k$$

is distributed as a chi-square random variable with  $2E$  degrees of freedom.

Under the alternative hypothesis that  $\lambda = \lambda_1$ , the quantity

$$2\lambda_1 \sum_{i=1}^E t_i^k$$

is also distributed as a chi-square random variable with  $2E$  degrees of freedom.

### Sample Size Calculation

Phadnis (2019) gives the following formula based on the above test statistic that can be used to iteratively solve for the number of required events.

$$(HR)^{1/k} = \frac{\chi_{\beta, 2E}^2}{\chi_{1-\alpha, 2E}^2}$$

where  $HR = \lambda_1/\lambda_0$  and  $\chi_{\gamma, V}^2$  is the  $\gamma$  quantile of a chi-square random variable with  $V$  degrees of freedom.

The required sample size can be found by adjusting the required number of events for administrative censoring using

$$N = E/d$$

where  $d$ , the probability of an event, is given by

$$d = \int_0^\infty G(t)f(t, \lambda_1)dt$$

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

The value of  $d$  may be found by numerical integration.

## One-Sample Tests of Weibull Hazard Rates

Assuming that failure times follow a two-parameter Weibull distribution, the cumulative survival function  $S(t)$  under null and alternative is given by

$$S_0(t) = \exp(-\lambda_0 t^k)$$

$$S_1(t) = \exp(-\lambda_1 t^k)$$

The hazard and cumulative hazard functions are given as

$$\lambda_0(t) = k\lambda_0 t^{k-1}$$

$$\lambda_1(t) = k\lambda_1 t^{k-1}$$

$$\Lambda_0(t) = \lambda_0 t^k$$

The hazard rates  $\lambda_0$  and  $\lambda_1$  can be given in terms of the hazard ratio  $HR$ , the median survival times  $M_0$  and  $M_1$ , the survival proportions  $S_0$  and  $S_1$  at time  $t_0$ , or  $\theta_0$  and  $\theta_1$ . These parameters are defined as

$$HR = \lambda_1/\lambda_0$$

$$\lambda_0 = \frac{\log 2}{M_0^k} = \frac{-\log S_0(t_0)}{t_0^k} = \theta_0^{-k}$$

$$\lambda_1 = \frac{\log 2}{M_1^k} = \frac{-\log S_1(t_0)}{t_0^k} = \theta_1^{-k}$$

### Iterative Search

This section will explain the steps taken in the iterative search for the required number of events and associated sample size.

1. Solve the HR equation for the required number of events, E. This step will usually result in a decimal value for E, such as 53.17.
2. Round the value of E up to the next integer. Call this E'. For example, E = 53.17 is rounded up to 54. This guarantees that the power specification will be achieved.
3. Divide E' by PE, the proportion of subjects having an event (failure). Obtain N = E'/PE.
4. Do not round up N on the report. Note, however, that the value of N is rounded off in the report. However, you can increase the number of decimal places shown for N to see what the exact value was.

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### Estimation of the Weibull Shape Parameter

The above results assume that the Weibull shape parameter,  $k$ , is known. Since a value for this parameter must be provided, it will be important to determine how sensitive the calculated sample size is to small changes in this value.

Phadnis (2020) provides a discussion of estimating  $k$  from historical controls using simulation. In a personal communication, he explained that government review committee's always want to know how the estimated value of  $k$  was obtained.

If no other information is available, you can set  $k$  equal to one and assume that the data are exponentially distributed.

## One-Sample Tests of Weibull Hazard Rates

## 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. The current population of responses 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 and 0.8 or less at a 5% significance level for a two-sided, one-sample chi-squared test. The accrual period will be 1 year. The researcher would like to compare the sample requirements if the follow-up period is 1, 2, or 3 years.

### Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the procedure. 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**.

<u>Option</u>	<u>Value</u>
<b>Design Tab</b>	
Solve For .....	<b>Sample Size</b>
Alternative Hypothesis .....	<b>Two-Sided</b>
Power .....	<b>0.90</b>
Alpha .....	<b>0.05</b>
Ta (Accrual Time) .....	<b>1</b>
Tf (Follow-Up Time) .....	<b>1 2 3</b>
Input Type .....	<b>M0, HR (Median Survival, Hazard Ratio)</b>
M0 (Median Survival - Control) .....	<b>1.54</b>
HR (Hazard Ratio) .....	<b>0.7 0.8</b>
k (Weibull Shape Parameter) .....	<b>1.67</b>

### Annotated Output

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

### Numeric Results

#### Numeric Results

Alternate Hypothesis: Two-Sided

Power	N	Events E	Time		Weibull Parameters				Median Survival		Prob of an Event PE	Alpha
			Accrual Ta	Follow Up Tf	Hazard Rates		Hazard Ratio HR	Weibull Shape k	Time			
					Hist Cntl $\lambda_0$	Trt $\lambda_1$			Hist Cntl M0	Trt M1		
0.9001	219	81	1	1	0.337	0.236	0.7	1.67	1.54	1.907	0.371	0.05
0.9011	510	209	1	1	0.337	0.270	0.8	1.67	1.54	1.760	0.410	0.05
0.9001	123	81	1	2	0.337	0.236	0.7	1.67	1.54	1.907	0.659	0.05
0.9011	296	209	1	2	0.337	0.270	0.8	1.67	1.54	1.760	0.707	0.05
0.9001	96	81	1	3	0.337	0.236	0.7	1.67	1.54	1.907	0.848	0.05
0.9011	237	209	1	3	0.337	0.270	0.8	1.67	1.54	1.760	0.883	0.05

## One-Sample Tests of Weibull Hazard Rates

### References

- Phadnis, Milind A. 2019. 'Sample size calculation for small sample single-arm trials for time-to-event data', Contemporary Clinical Trials Communications, Volume 15, 100360. <https://doi.org/10.1016/j.conctc.2019.100360>.
- Phadnis, M. A., Sharma, P., Thewarapperuma, N., Chalise, P. 2020. 'Assessing accuracy of Weibull shape parameter estimate from historical studies for subsequent sample size calculation in clinical trials with time-to-event outcome', Contemporary Clinical Trials Communications, Volume 17, 100548. <https://doi.org/10.1016/j.conctc.2020.100548>.
- Narula, S.C. and Franz, S.L. 1975. 'Sample size calculations in Exponential Life Testing', Technometrics, Vol 17, No. 2, pages 229-231.
- Wu, Jianrong. 2015. 'Sample size calculation for the one-sample log-rank test', Pharmaceutical Statistics, Volume 14, pages 26-33.

### Report Definitions

- Power is the probability of rejecting a false null hypothesis.
- N is the sample size of the treatment group. It is found by adjusting the required number of events.
- E is the expected number of events (positive or negative) in the treatment group during the study.
- Ta is the accrual time during which subjects are added to the study. Uniform accrual is assumed.
- Tf is the follow-up time after the last subject is added to the study.
- $\lambda_0$  is the hazard rate of the historical controls (standard).
- $\lambda_1$  is the hazard rate of the treatment (new) group.
- HR is the hazard ratio ( $\lambda_1/\lambda_0$ ). It is the ratio of the treatment and the control hazard rates.
- k is the shape parameter of the Weibull distribution. It is used for both groups.
- M0 is the median survival time of the historical controls (standard).
- M1 is the median survival time of the treatment (new) group.
- PE is the probability that a subject experiences a failure (event) during the study.
- Alpha is the probability of rejecting a true null hypothesis.

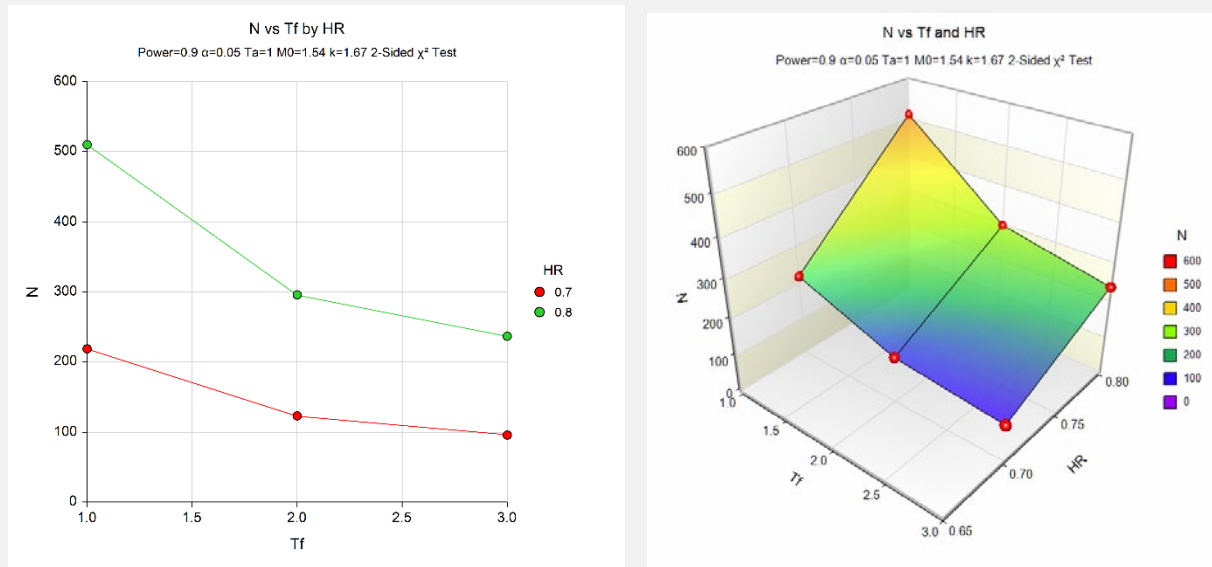
### Summary Statements

A two-sided, one-sample chi-squared test comparing a test group to a historical control group calculated from a sample of 219 subjects achieves 90% power at a 0.05 significance level to detect a hazard ratio of 0.7 when the median survival time of the historic control group is 1.54. Subjects are accrued for a period of 1. Follow-up continues for a period of 1 after the last subject is added. The probability that a subject experiences an event during the study is 0.371. The expected number of events during the study is 81. It is assumed that the survival time distribution is approximated reasonably 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.

## Chart Section

### Chart Section



This plot shows the relationship between sample size, follow-up time, and HR.

## Example 2 – Validation using Phadnis (2019)

Phadnis (2019) Table 1 gives an example in which the power is 0.80, alpha = 0.05 for a one-sided test, k = 0.5, Ta = 3 and Tf = 1, M0 = 2.5, and M1 = 3.75. The required events are reported as 148 and N as 350.

### Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the procedure. 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**.

<u>Option</u>	<u>Value</u>
<b>Design Tab</b>	
Solve For .....	<b>Sample Size</b>
Alternative Hypothesis .....	<b>One-Sided</b>
Power .....	<b>0.8</b>
Alpha .....	<b>0.05</b>
Ta (Accrual Time) .....	<b>3</b>
Tf (Follow-Up Time) .....	<b>1</b>
Input Type .....	<b>M0, M1 (Median Survival Times)</b>
M0 (Median Survival - Control) .....	<b>2.5</b>
M1 (Median Survival - New) .....	<b>3.75</b>
k (Weibull Shape Parameter) .....	<b>0.5</b>

### Output

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

<b>Numeric Results</b>													
Alternate Hypothesis: One-Sided													
Power	N	Events E	Accrual Ta	Follow Up Tf	Weibull Parameters Hazard Rates			Weibull Shape k	Median Survival Time		Prob of an Event PE	Alpha	
					Hist Cntl λ0	Trt λ1	Hazard Ratio HR		Hist Cntl M0	Trt M1			
0.8011	349.1	148	3	1	0.438	0.358	0.8165	0.5	2.5	3.75	0.424	0.05	

PASS has also calculated E as 148. Note that N is 349.1 which rounds up to the 350 reported in the table.

## Example 3 – Investigating the Impact of the Shape Parameter

This example will investigate the impact of the shape parameter on required sample size. For this example, power is 0.90, alpha is 0.05 for a one-sided test  $T_a = 2$ ,  $T_f = 1$ ,  $M_0 = 2.5$ , and  $M_1 = 3.75$ . The value of  $k$  will vary from 0.5 to 1.5. The sample size will be investigated.

### Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the procedure. You may then make the appropriate entries as listed below, or open **Example 3** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
<b>Design Tab</b>	
Solve For .....	<b>Sample Size</b>
Alternative Hypothesis .....	<b>One-Sided</b>
Power .....	<b>0.90</b>
Alpha .....	<b>0.05</b>
$T_a$ (Accrual Time) .....	<b>2</b>
$T_f$ (Follow-Up Time) .....	<b>1</b>
Input Type .....	<b>M0, M1 (Median Survival Times)</b>
$M_0$ (Median Survival - Control) .....	<b>2.5</b>
$M_1$ (Median Survival - New) .....	<b>3.75</b>
$k$ (Weibull Shape Parameter) .....	<b>0.5 0.75 1 1.25 1.5</b>

### Annotated Output

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

### Numeric Results

Numeric Results														
Alternate Hypothesis: One-Sided														
Power	N	Events E	Time		Weibull Parameters				Median Survival Time		Prob of an Event PE	Alpha		
			Accrual $T_a$	Follow Up $T_f$	Hist Rates Cntl $\lambda_0$	Trt $\lambda_1$	Hazard Ratio HR	Weibull Shape k	Hist Cntl M0	Trt M1				
0.9012	530	208	2	1	0.438	0.358	0.81650	0.50	2.5	3.75	0.392	0.05		
0.9004	266	92	2	1	0.349	0.257	0.73779	0.75	2.5	3.75	0.346	0.05		
0.9018	170	52	2	1	0.277	0.185	0.66667	1.00	2.5	3.75	0.305	0.05		
0.9067	126	34	2	1	0.220	0.133	0.60240	1.25	2.5	3.75	0.269	0.05		
0.9003	97	23	2	1	0.175	0.095	0.54433	1.50	2.5	3.75	0.238	0.05		

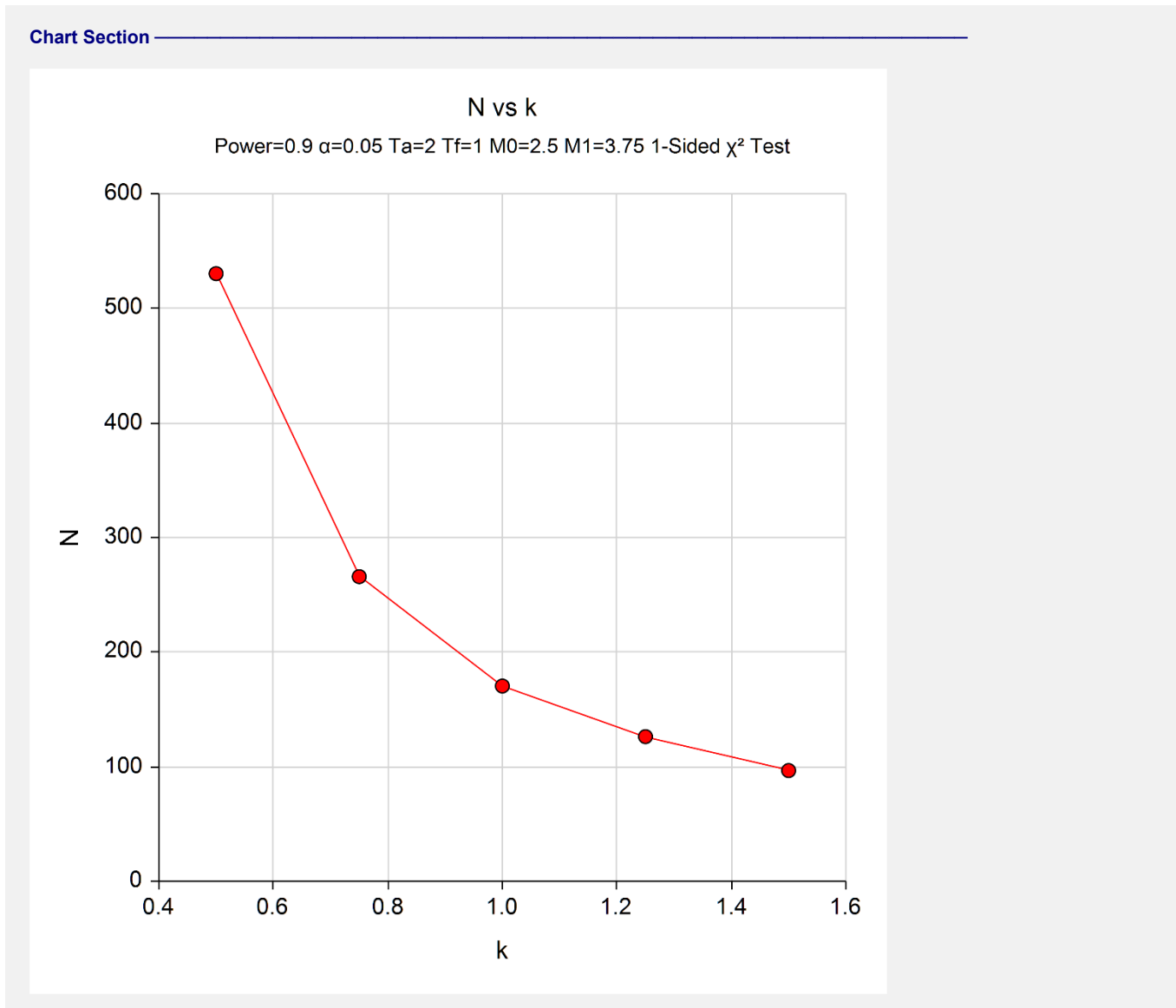
This report shows the substantial impact of the value of the shape parameter on the sample size. In fact, the sample size decreases dramatically as  $k$  increases from 530 at  $k = 0.5$  to 97 at  $k = 1.5$ .

The decrease in the required number of events is even more dramatic. The number of events falls from 208 at  $k = 0.5$  to 23 at  $k = 1.5$ !

Clearly, an accurate estimate of  $k$  is very import.

## One-Sample Tests of Weibull Hazard Rates

## Chart Section



This plot shows the substantial impact of the value of the shape parameter on the sample size. In fact, the sample size decreases dramatically as  $k$  increases from 0.5 to 1. After that, the change in the required sample size is less dramatic.